Structured cardiac assessment and treatment following exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Introduction Heart disease is common in COPD, yet is inadequately managed due to systemic deficiencies in both diagnosis and treatment. Through a systematic review and meta-analysis of published studies, it is estimated that 10-20% of patients have undiagnosed left ventricular systolic dysfunction. During exacerbations of COPD (ECOPD), cardiac risk is temporally elevated.

In view of these problems, a pilot randomised controlled trial, examining the feasibility and effect of inpatient structured cardiac assessment (SCA) to diagnose and prompt guideline-recommended treatment of heart disease, was conducted.

Methods: 115 inpatients with ECOPD were randomised 1:1 to receive usual care (UC, n=58) or SCA (n=57), comprising transthoracic echocardiography, CT coronary artery calcium scoring, 24-hour ECG, blood pressure and diabetes assessment. Follow-up was for 12 months. The prevalence of underdiagnosis and undertreatment of heart disease were captured, and potential outcome measures for future trials assessed. An economic analysis was also rehearsed.

Results: Among patients undergoing SCA, 42/57 (73.7%) received a new cardiac diagnosis compared with 11/58 (19.0%; p<0.001) in UC. When heart disease was diagnosed, the proportion receiving optimal treatment at discharge was significantly higher in SCA (35/47 (74%) vs 4/11 (34%); p=0.029). There was no difference in days alive outside hospital between the arms. Survival curves for both adverse cardiovascular and cardiopulmonary events separated throughout follow-up, with ACE occurring in 17.2% in usual care vs. 10.5% in SCA in one year. The economic analysis suggested a low probability of cost-effectiveness, but estimates were very broad.

Conclusions: A structured cardiac assessment during ECOPD significantly improved diagnosis and treatment of heart disease. Further research is needed in order to establish how to deliver SCA with the greatest clinical and economic effectiveness. Future interventional trials should use time to first adverse cardiovascular or cardiopulmonary event as the primary outcome.

Dedication

This work is dedicated to the person who helped me the most: my wife, Carrie.

Acknowledgements

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Finally, I wish to thank the patients who participated in this study. If they gave a reason for doing so, it was overwhelmingly because they wanted to help others with COPD have a better quality of life. I hope I have gone some way to honouring their selflessness and generosity.

Declaration

I declare that this thesis has been written solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgment, the work presented is entirely my own.

Joseph Kibbler, June 2025

Word count of main body of thesis: 76355

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List of abbreviations

4MGS	4-metre gait speed
ABG	Arterial blood gas
ACE	Adverse cardiovascular event
ACEi	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
(AU)ROC	(Area under the) receiver-operator curve
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
bpm	Beats per minute
BP	Blood pressure
BSE	British Society of Echocardiography
CABG	Coronary artery bypass graft
CAC(S)	Coronary artery calcium (score)
CAD	Coronary artery disease
CCB	Calcium channel blocker
CCI	Charlson comorbidity index
CFS	Rockwood clinical frailty score
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
CV(D)	Cardiovascular (disease)
CXR	Chest radiograph
DAOH	Days alive outside hospital
DAPT	Dual antiplatelet therapy

DECAF	Dyspnoea, Eosinopenia, Consolidation, Acidaemia, Fibrillation
ECG	Electrocardiogram
ECOPD	Exacerbation of chronic obstructive pulmonary disease
eGFR	Estimated glomerular filtration rate
eMRCD	Extended MRC dyspnoea score
EQ-5D-5L	5-level EQ-5D instrument
ESC	European Society of Cardiology
FAC	Fractional area change
FEV1	Forced expiratory volume in 1 second
FiO_2	Fraction of inspired oxygen
(F)VC	(Forced) vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HbA_{1C}	Haemoglobin A_{1C}
HDL	High density lipoprotein
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HOT	Home oxygen therapy
HR	Hazard ratio
HRUQ	Healthcare resource questionnaire
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IQR	Interquartile range
IRR	Incident rate ratio
kPA	Kilopascals
LA	Left atrium
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LDL	Low density lipoprotein
LTOT	Long term oxygen therapy
LV	Left ventricle

LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MCID	Minimum clinically-important difference
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MWU	Mann-Whitney U test
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
(N)STEMI	(Non-) ST-segment elevation myocardial infaction
NSVT	Non-sustained ventricular tachycardia
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
$PaCO_2$	Partial pressure of carbon dioxide
PA:A	Pulmonary artery to aorta ratio
PAF	Population attributable fraction
PAD	Peripheral arterial disease
PaO_2	Partial pressure of oxygen
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
PEARL	PEARL prognostic score
PH	Pulmonary hypertension
PYH	Pack year history
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Right atrium
RCT	Randomised controlled trial
ROX	Respiratory rate-Oxygenation index
RR	Relative risk
RV	Right ventricle

SCA	Structured cardiac assessment
SD	Standard deviation
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
SGRQ-C	St. George's Respiratory Questionnaire for COPD
SVT	Supraventricular tachycardia
TAPSE	Tricuspid annular plane systolic excursion
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiogram
UC	Usual care
UI	EQ-5D-5L Utility index
VBG	Venous blood gas

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Chapter 1: Chronic Obstructive Pulmonary Disease

1.1 Chapter introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide[1] and is associated with the worst quality of life scores amongst common chronic diseases.[2] Two hallmarks of the disease are progressive, gradual decline in lung function and therefore functional capacity, and transient, significant worsening of symptoms and lung function termed COPD exacerbation (ECOPD). COPD is a multi-system condition associated with extra-pulmonary organ dysfunction[3]; virtually all patients with COPD have other chronic conditions and more commonly die as a result of these rather than their COPD.[4,5] Consequently, if clinicians and commissioners desire to improve the lives of patients with COPD, it is vital that COPD care involves the identification and management of disease beyond the lungs.

Heart disease is highly prevalent in COPD, beyond the rate expected due to the common risk factors of tobacco smoking, advanced age and socioeconomic deprivation.[6] When present, it is associated with a higher risk of mortality and hospitalisation,[7] and a lower quality of life.[8,9]

Therefore, identification and treatment of heart disease in patients with COPD should be a priority. However, heart disease often goes undiagnosed – more than 1/3 of patients with COPD identified to have left ventricular systolic dysfunction (LVSD) had no known heart disease diagnosis.[10] Even when identified, heart disease is not treated optimally, with COPD a significant predictor of beta-blocker non-use after myocardial infarction (MI) with an odds ratio of 1.86 (95% confidence interval [CI] 1.76-1.97).[11] Despite this, current UK guidance recommends pursuing a diagnosis of comorbid heart disease at the time of COPD diagnosis or symptomatic deterioration only if it is suggested by clinical examination findings or standard investigations.[12] Clearly, this approach is not sufficient, and novel approaches are needed.

An exacerbation of COPD (ECOPD) is characterised, and defined, by a deterioration in respiratory symptoms that require an increase in respiratory treatments. Whilst episodes of ECOPD result in a substantial, and often only partially reversible, deterioration in respiratory function, they also prefigure a time period during which there is a markedly increased risk of cardiovascular events such as myocardial infarction and stroke . A succinct illustration of this was provided in an analysis of the UPLIFT trial of tiotropium in 4000 moderate to severe COPD, in which only 1 patient had a myocardial infarction in the 30 days prior to an exacerbation, and 13 had one in the 30 days after an exacerbation.[13] Further evidence for increased risk in the post-exacerbation period compared with baseline is provided by a meta-analysis on over half a million patients that reported risk ratios of

2.43 and 1.68 for MI and stroke respectively, over a period up to 3 months post-exacerbation.[14] More recently, observational evidence from the EXACOS-CV cohorts has expanded the definition of post-exacerbation cardiovascular events to include acute coronary syndromes, heart failure decompensation, cerebral ischaemia (both stroke and transient ischaemic attack [TIA]) and arrhythmias. Results from these studies demonstrated a particularly large increase in risk in the first week after a severe exacerbation (defined as an exacerbation leading to hospital admission), compared with the pre-exacerbation period, as well as suggesting that the increased risk persists for at least a year (in the case of cardiovascular events including death after a severe exacerbation (see Figure 1).[15]

The time of hospitalisation with ECOPD provides an opportunity to meticulously evaluate patients for comorbid heart disease and initiate treatments that reduce their impending risk of adverse events. However, at present, in line with practice in stable disease, cardiac investigations are performed extemporaneously, based on the clinical suspicions of the physician caring for the patient. This approach is not meeting the needs of our patients, as evidenced by the concerning rates of underdiagnosis and undertreatment – a structured approach to diagnosis applied to all patients is rational and requires evaluation. Investigating the feasibility and effects of a structured intervention to diagnose and prompt treatment of heart disease for patients hospitalised with ECOPD – versus usual practice – is the principal objective of the SCATECOPD study described in subsequent chapters.

This introductory chapter will introduce key COPD concepts, with the subsequent chapter detailing the major cardiovascular diseases associated with COPD, along with the mechanisms by which they occur at excess rates alongside COPD. Subsequently, particular considerations and challenges relating to the diagnosis and treatment of heart disease in patients with COPD are discussed, given their relevance to the methodology of the SCATECOPD study.

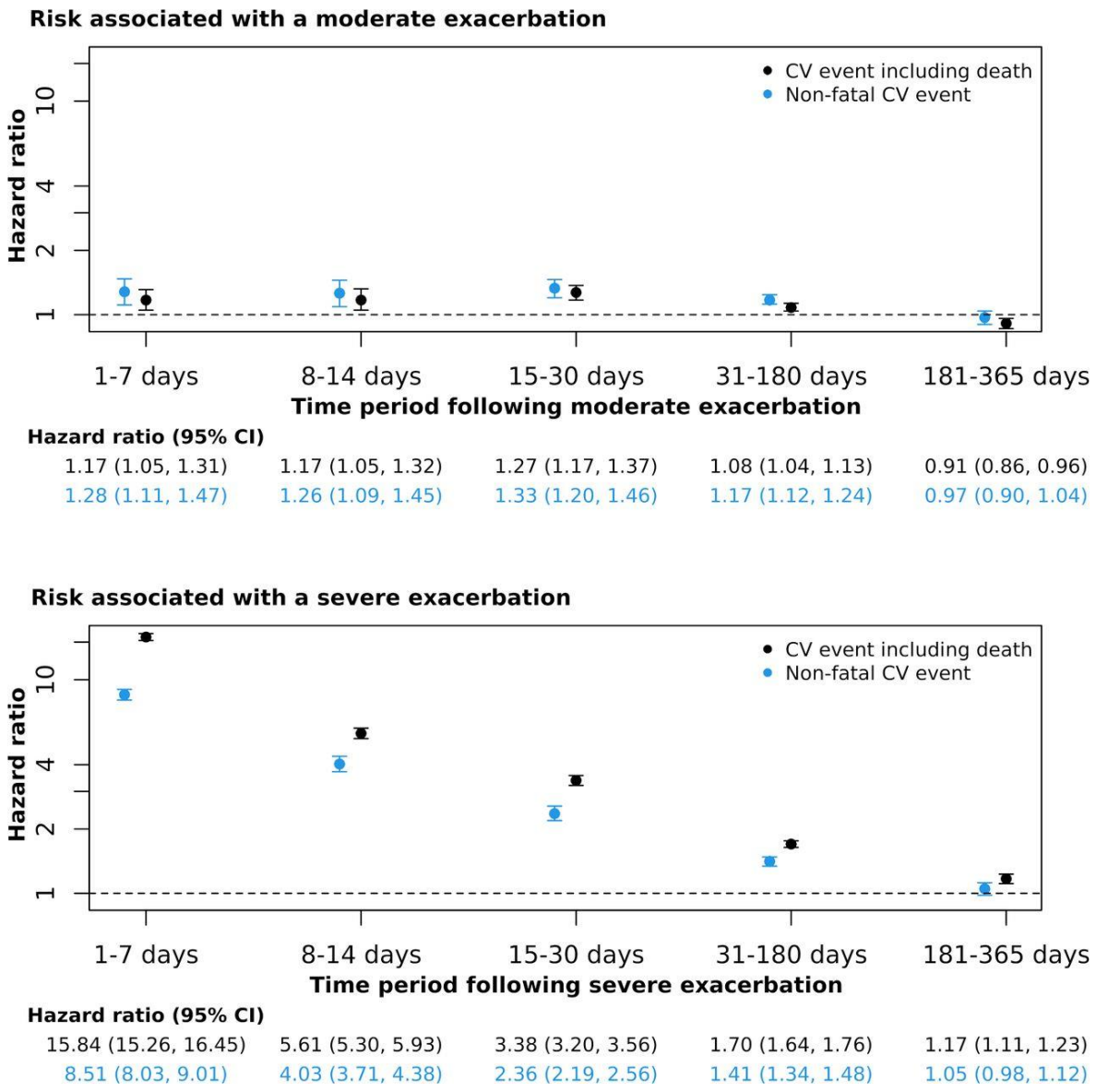


Figure 1: Adjusted hazard ratio for a first cardiovascular event (in combination with death or not) associated with time periods following the onset of moderate (community-treated), or severe (requiring hospitalisation) ECOPD. Non-exposed period for comparison: time prior to the first exacerbation following COPD diagnosis, and all time after the 365 days following any exacerbation. Reproduced from [Elucidating the risk of cardiopulmonary consequences of an exacerbation of COPD: results of the EXACOS-CV study in Germany, Vogelmeier, et al., 11:e002153, 2024] with permission from BMJ Publishing Group Ltd.

1.2 Definition

The definition of COPD has evolved substantially in recent decades. After the pathological entity of emphysema was described in the 17th and 18th centuries, and the clinical syndrome of chronic bronchitis in the 19th century,[16] cigarette smoking was firmly established as a risk factor in the mid-20th century. At this point, the first formal definitions of COPD were devised, focussing entirely on the anatomical and clinical features of the pulmonary disease.[17] Once aetiologies were included in

definitions, they were centred on post-maturity lung damage caused by inhaled noxious particles only.[18,19]

More recently, two important modifications have been made to the definitions of COPD. Firstly, its aetiology has been recognised to include factors beyond inhaled toxins such as cigarette smoke and air pollution, such as abnormalities of lung development, and to be closely tied to lower socioeconomic status.[20] Secondly, the importance of effects beyond the lungs have been recognised, both in terms of extra-pulmonary effects of COPD itself and of the influence of comorbidities on outcomes.[21]

The latest (2023) Global initiative for chronic Obstructive Lung Disease (GOLD) definition of COPD focusses on its unique, defining characteristics to provide a succinct summary of several key features of the disease:

> *COPD is heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction*.[22]

From the definition of the disease, diagnostic criteria follow: COPD is diagnosed in patients with the above cardinal symptoms, exposure to known risk factors and post-bronchodilator (i.e., fixed) airflow obstruction, defined almost universally as FEV1/FVC < 0.7.[23]

The definition above purposefully excludes the aetiology and extra-pulmonary consequences of COPD from this description of lung manifestations, with the reasoning that only characteristics unique to a disease should be included in its definition.[24] However, this is not a universally held position – for example, pulmonary hypertension is defined with explicit reference to the conditions that typically coexist with specific manifestations of the disease.[25] Additionally, a definition that refers to key breakthroughs in understanding would highlight these to non-specialists and may work to undo entrenched perceptions. Therefore, there is a justification to add these elements to form an expanded, novel definition as follows:

> *COPD is a heterogeneous lung condition:*
>
> - *linked to inhalation of noxious substances, incomplete lung maturation and poverty;*
> - *characterized by chronic respiratory symptoms (dyspnoea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema);*
> - *resulting in persistent, often progressive, airflow obstruction, with important multi-system consequences.*

The remainder of this section will focus on the important risk factors for the development of COPD, the scale of its impact both to patients and at the level of healthcare service organisation, the definition and clinical importance of exacerbations of COPD, and the vital importance of considering extra-pulmonary disease when managing COPD.

1.3 Risk factors

Tobacco smoking has long been considered to be the strongest risk factor for COPD, with its link to the disease first established via observational evidence[26] and later by demonstration of the mechanisms by which tobacco smoke induces innate and adaptive immune responses that lead to inflammation and lung tissue destruction.[27]

Although active smoking is undoubtedly the major risk factor for the development of COPD, most studies estimating the population attributable fraction (PAF) for smoking have quoted values of between 40 and 80%.[28] The PAF is the proportion of disease that would disappear from the population if the risk factor in question were eliminated. Therefore, other risk factors must play an important role in COPD development. An obvious candidate is passive exposure to tobacco smoke, the constituents of which differ to that which is directly inhaled[29] but are toxic to the lungs in similar ways to the mainstream smoke inhaled by active smokers.[30,31] Likewise, age is a clearly defined risk factor for COPD, due to both the linked increase in cumulative exposure to toxins such as tobacco smoke and the physiological decline in lung function experienced as part of normal ageing.[32]

Beyond smoking and ageing, exposure to other inhaled noxious substances accounts for a significant proportion of COPD cases, particularly when a global perspective is employed. Estimates of the contributors to chronic airflow obstruction across 41 sites in 4 continents show that, while smoking has the highest overall attributable risk,[33] other factors have differential importance depending on the site studied. Exposure to occupational dusts and fumes is one such factor, with a PAF estimated by a large meta-analysis at 14% (95% CI 10-18%).[34] However, the greatest attributable risk, after smoking, was poor education, with significant risk fraction also associated with malnutrition, particularly in rural settings.[33] These factors relate to the close association between COPD and low socioeconomic status, which as well as increasing the risk of disease development is also a risk factor for worse outcomes within the COPD population.[35,36] The importance of factors besides smoking is illustrated by correlating the national prevalence of airflow obstruction with both smoking prevalence and income per capita shown in Figure 2, derived from the international Burden of Lung Disease study encompassing 34 countries across 5 continents. The scatterplots reveal, counter to

what would be expected based on the historical definitions of COPD, that the correlation between airflow obstruction and low income is stronger than that that with mean pack years of smoking.

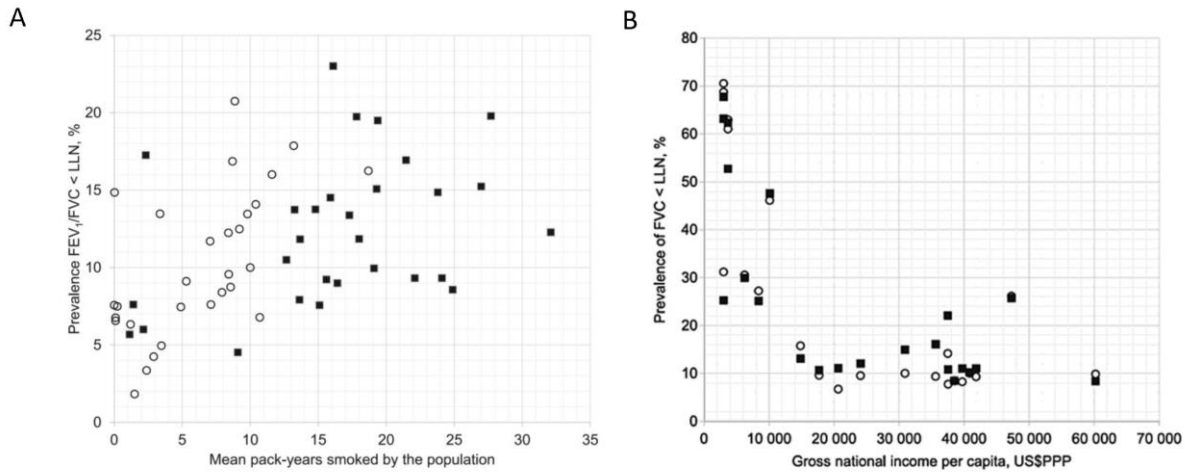


Figure 2: A: Prevalence of airflow obstruction (FEV1/FVC < lower limit of normal) by mean pack-years smoked and gender in the Burden of Lung Disease (BOLD) sites. B: Prevalence of FVC<LLN by gross national income and gender in the BOLD sites; ▪ Male; ○ Female. Reproduced with permission from Lopez-Campos et al.(37)

A final key risk factor for COPD is subnormal lung development. The traditional view of COPD genesis has been that all people experience lung function decline, but smokers experience more rapid decline and therefore reach the points of exercise limitation, respiratory failure and death at an earlier stage than non-smokers (or non-susceptible smokers); this is summarised in the often reproduced survival curve derived from Fletcher and Peto's 1977 stratified sample of 792 British male manual and clerical workers, followed for 8 years (see Figure 3).[37]

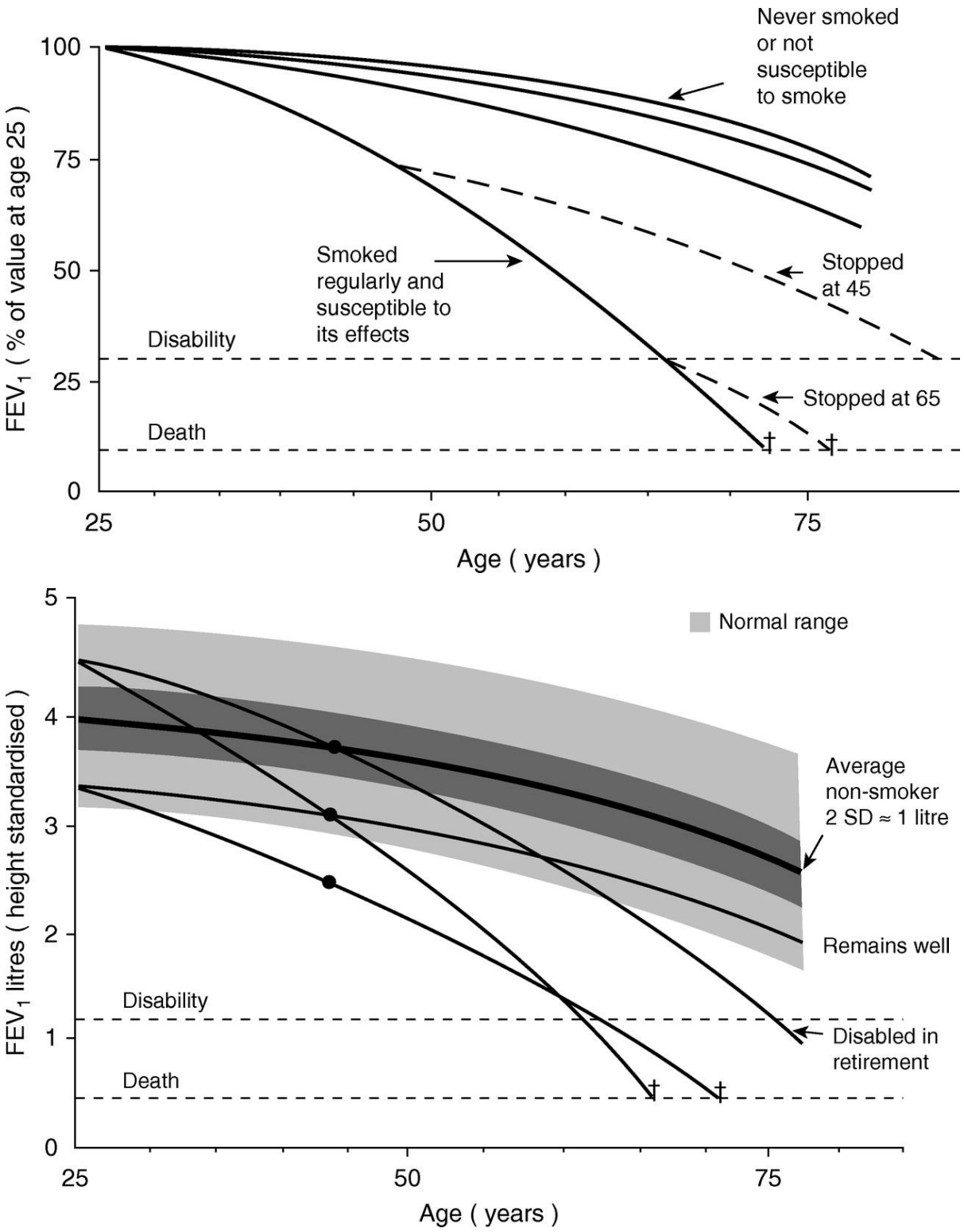


Figure 3: Above, illustration of FEV1 decline according to smoking status, as published by Fletcher and Peto in 1977. Below, demonstration of different rates of FEV1 loss leading to different outcomes despite similar exposures. Reproduced from The BMJ, C. Fletcher and R. Peto, 1:1645, 1977, with permission from BMJ Publishing Group Ltd.

While instrumental in highlighting the importance of accelerated lung function due to tobacco smoking, the less-discussed second figure from the same paper has proven to be highly prescient of

later longitudinal research (see Figure 4). From cohort studies that followed subjects from lung maturity, attained in early adulthood, to age 65, Lange et al demonstrated that, of people who eventually develop COPD, around half do so after attaining abnormally low lung function at maturity and then experiencing average rates (around 20-30ml/year) of FEV1 decline, with the other half having the longer-recognised accelerated FEV1 decline (around 60ml/year) (see Figure 4).[38] This work represents a pivotal breakthrough in the understanding of the origins of COPD, and highlights the contribution of disadvantages during early life to later-life disease risk. It may also explain why, although "poverty cannot be inhaled and it is not a genetic condition,"[39] it still persists as a risk factor for COPD despite controlling for linked confounding factors that accelerate lung function decline such as occupational and domestic air pollution[36]: the pernicious and multitudinous effects of poverty also serve to limit lung maturation, likely from the earliest phases of in-utero lung development.[40]

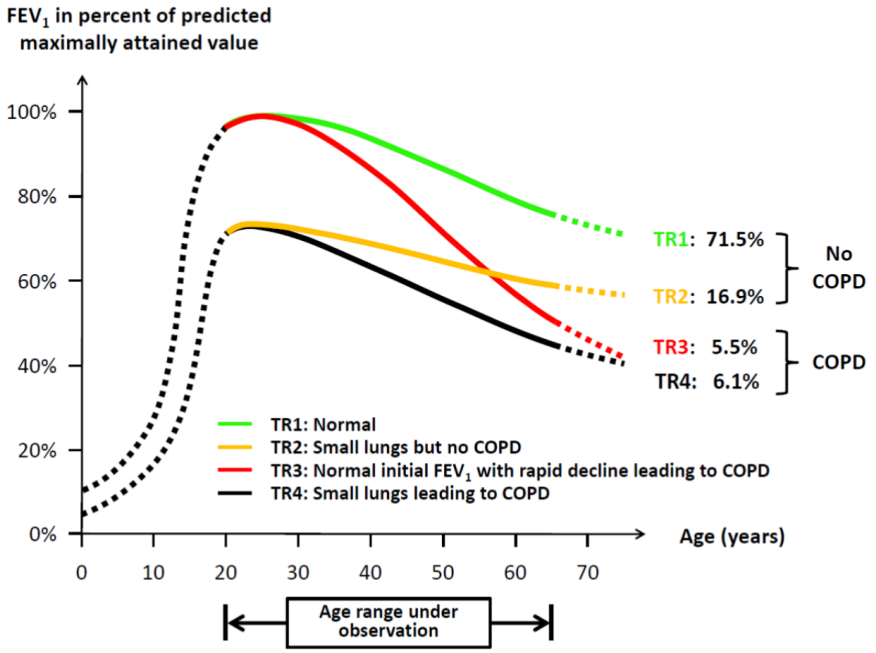


Figure 4: Distribution of 2864 observed participants into the four trajectories T1 to T4 defined according to baseline level of FEV1 (below or above 80% of predicted value) and presence or absence of GOLD grade >2 COPD at final examination. Solid lines represent observed progression of FEV1, broken lines represent hypothetical trajectories. Reproduced with permission from Lange, et al., NEJM, 2015. Copyright Massachusetts Medical Society.

1.4 Impact for patients

A diagnosis of COPD impacts patients' lives substantially. Foremost, it confers a substantially increased risk of death, roughly doubling the age-standardised mortality risk for patients in the UK.[41]

Globally, COPD is the third leading non-communicable cause of early death,[42] accounting annually for tens of millions of years of life lost[43] – a figure that is rising due to advancing population ages and increased exposures to air pollution and tobacco smoke.

Patients who have COPD experience a high burden of symptoms. These are not confined to the cardinal triad of breathlessness, cough and sputum production, but encompass a range of physical and psychological afflictions, with a majority reporting low energy, sleep disturbance, dry mouth, nervousness, irritability and sadness.[44] The median number of different symptoms reported over a week was 13. Evidence of difficulty adjusting to life with COPD is provided by the fact that 44% reported they "Don't look like myself/don't feel like myself"; this proportion rose from 26% in those with mild airflow obstruction to 69% in those where airflow obstruction was severe.[44] Unsurprisingly, this burden of symptoms translates to very poor quality of life scores for patients who have COPD compared with other patients living with chronic diseases.[2] Indeed, for patients with very severe airflow obstruction, physical functioning, mental health, general health perceptions, dyspnoea, activities of daily living and depression scores were all worse than for patients living with stage IIIB and IV lung cancer.[45]

A key contributor to worse quality of life for patients who have COPD is the occurrence of exacerbations: if these are frequent (>2 per year) then patients return significantly worse quality of life scores, across multiple domains including symptom burden, activity limitation and impact on overall wellbeing – between 3 and 4 times the minimal important difference.[46] If patients are hospitalised, their quality of life is impaired even further,[47] with daily impairment in physical function persisting a least one month after discharge.[48] A devastating consequence of hospitalisation with ECOPD is that it begets further hospitalisations, particularly after a second episode, when the rate of hospitalisation with ECOPD is three times higher than it was after the first; by the tenth admission the rate increases 25-fold.[49] The risk is even higher when all-cause admissions is considered: UK audit data indicates that only 3 months after an admission with ECOPD nearly half of patients have been readmitted to hospital for any cause.[50]

The high mortality, dire quality of life and crescendo of readmissions that characterise the experience of patients with deteriorating and advanced COPD underpin the need for palliative care in holistic disease management. However, palliative care provision for patients with COPD has been described as inadequate,[51] with one large-scale UK study noting that comorbid lung cancer increased the likelihood of receiving palliative care, with an odds ratio of 14.7 (95% CI 13.5-16); lung cancer also increased the chances of a patient receiving early palliative care (prior to the last month of life) by 40%.[52] The authors concluded that when palliative care was provided, it appeared to be related to co-diagnosis of lung cancer rather than airways disease. Therefore, these results represent an example of care not meeting the holistic needs of patients with COPD, mirroring the deficiencies in

diagnosis and treatment of cardiovascular disease mentioned in the chapter introduction above and expanded in Chapter 2. More positively, the study did document a significant increase in the proportion of patients with COPD that received palliative care, both overall and in their final year of life, between 2004 and 2015, with a similar increment for those with and without comorbid lung cancer.

Unfortunately, however, themes of inequality and deprivation are recurrently encountered in relation to COPD demographics. COPD burdens the poorest in society excessively, with figures from the UK government demonstrating a nearly 5 times higher mortality from COPD for the most deprived versus the least deprived deciles of society.[53] Worse still, the trend is in the wrong direction, with the mortality risk increasing from 3.2 to 4.6 over the past 20 years. The fact that patients from the most disadvantaged sectors of our society appear to be bearing an ever-increasing degree of the burden from COPD, along with ongoing high rates of mortality and recurrent admissions, and recent evidence for the early life influences on poor lung health, should all serve to motivate research to confront adverse outcomes from COPD.

1.5 Impact for healthcare providers

While the direct impact on patients is of primary importance, COPD also places a huge organisational and financial burden on healthcare systems.

In primary care, patients who have COPD account for a significant proportion of consultations: in the UK the mean number per patient ranges from 2.3 to 15.9 per year, with higher values for patients with greater airflow obstruction and exacerbation frequency.[54] However, it is via hospital admissions that COPD exerts its greatest pressure on healthcare systems: COPD is a leading cause of emergency admission, with rates in England that were stubbornly static in the years preceding the COVID-19 pandemic (when rates fell for multiple reasons including implantation of social distancing, increased home management of exacerbations and COVID-19 as the cause of death in people living with COPD).[53] As highlighted above, readmissions are very common; a particular challenge to reducing readmissions is that around half have non-COPD causes, most commonly acute infections and heart failure,[55] limiting the power of COPD-targeted interventions.

From an economic perspective, the global economic cost of COPD is staggering: projected to be $4.3 trillion between 2020 and 2050 – half of the gross domestic product of India in 2019.[56] Alternatively, and equally strikingly, the cost of COPD could be expressed as a tax of 0.11% (uncertainty interval 0.09–0.14) on global economic output, or the equivalent of US$490 (377- 625) per capita.[56] Evidence collected during recent periods of economic turmoil has suggested that, for both patients and

healthcare systems, when national economic situations worsen, the situation with respect to COPD worsens: with lower uptake of essential preventative healthcare leading to more admissions with ECOPD and further spiralling healthcare costs.[57]

Constructively, research from the Kings Fund suggests that COPD is the most common 'ambulatory care-sensitive' cause of hospital admission in older patients – i.e. the most common cause for which effective management and treatment should prevent admission to hospital.[58] This highlights the huge potential gains at a healthcare system level that would be afforded by wider implementation of effective COPD care.

1.6 Exacerbations

Exacerbations are central to the natural history, morbidity, mortality and socioeconomic burden of COPD. These acute episodes of clinical and physiological deterioration are characterised by increased airway inflammation, most commonly triggered by acute bacterial infection, acute viral infection, or environmental pollution.[59] A widely employed definition for COPD exacerbation is 'an acute worsening of respiratory symptoms that results in additional therapy,'[20] a definition that contains both a symptom-based and event-based component. Pure symptom-based definitions have been employed, such as Anthonisen's well-known characterisation of ECOPD as the onset or increase of breathlessness, sputum volume and/or sputum purulence.[60] While the simplicity and patient-focus of symptom-based definitions is valuable, they are limited by subjectivity and, for formulations such as Anthonisen's, the lack of a threshold difference to trigger the diagnosis of ECOPD in a condition that has variable symptoms even when stable.[61] Additionally, other conditions can cause similar symptoms to ECOPD, leading to misdiagnosis. Observational data suggests that in around 20% of cases the cause of deterioration in a case initially diagnosed as COPD may instead have been cardiac failure[62], or in a similar proportion, pulmonary embolism.[63] In recognition of the propensity to misdiagnosis, authors have suggested that, at least as part of their reasoning process, clinicians adopt the term 'exacerbation of respiratory symptoms in a patient with COPD' so as not to forego investigating for other pathology besides acute airway and lung inflammation (see Figure 5).[64]

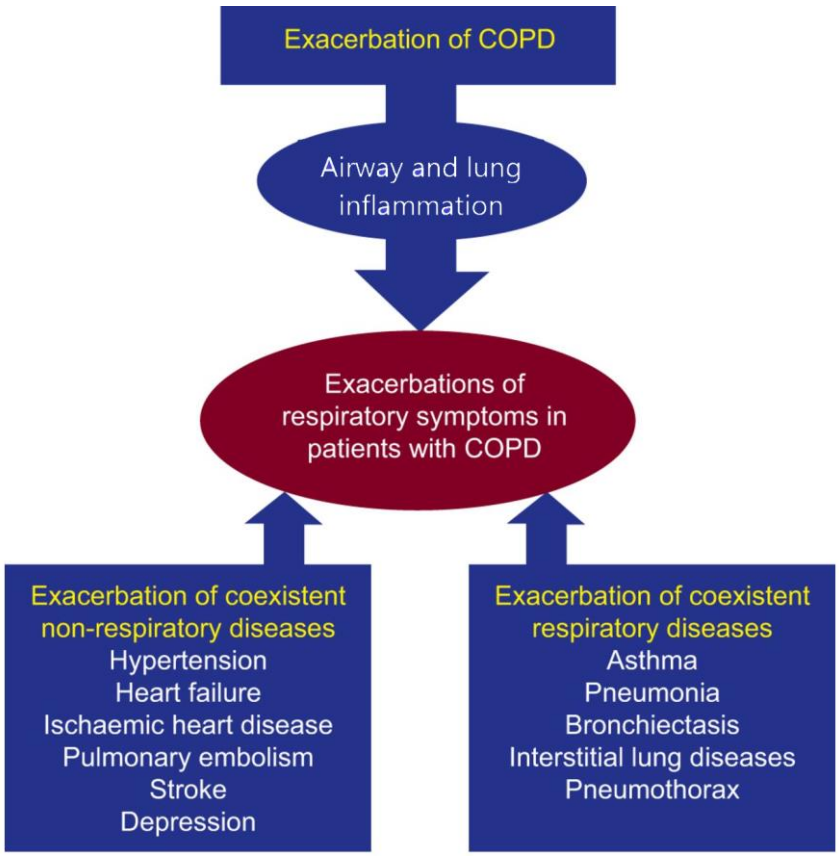


Figure 5: Possible contributors to the exacerbation of respiratory symptoms in patients with COPD. Underlying pathological causes include ECOPD via increased airway and lung inflammation, as well as exacerbation of coexistent respiratory or non-respiratory diseases, as well as a combination of these processes. Reproduced with permission of the © ERS 2025: European Respiratory Journal 41(4): 993-995; Published: Apr 2013; DOI: 10.1183/09031936.00180812

Purely event-based definitions also have limitations, primarily the need for patients and/or clinicians to decide that the event requires additional treatment: this will be influenced by a multitude of factors including individual health beliefs and accessibility of healthcare.[65] This may explain the substantial between-country variability in exacerbation frequency seen in global trials, particularly for moderate severity exacerbations.[66] Accordingly, some groups have integrated objective markers of illness into the definition of COPD.[67] However, this more complex approach sacrifices real-world usability, and is limited by the lack of any single molecular biomarker that can reliably be used for diagnosis of ECOPD.[68]

As well as defining the entity itself, systems have been devised to define the severity of exacerbations. Firstly, event-based definitions can be retrospectively defined by the level of healthcare intervention that was employed in their management: mild if managed with, at most, short-acting bronchodilators; moderate if oral corticosteroids +/- antibiotics used; severe if managed in hospital; very severe if non-invasive ventilation required.[22] For admitted patients, the DECAF (dyspnoea, eosinopenia, consolidation, acidaemia, fibrillation) score combines 5 readily-available

clinical and biological parameters to accurately predict mortality and thus stratify severe exacerbations into low, moderate and high risk.[69]

Regardless of issues with the sensitivity and specificity of different diagnostic systems, exacerbations are of enormous importance to patients and to healthcare systems, and inflict uniquely serious immediate morbidity[70] and mortality[71] as well representing inflection points in the trajectories of lung function [72] and overall quality of life[73] deterioration. They are also moments when cardiac dysfunction is more likely to manifest, by multiple mechanisms including increased stress on the heart that unmasks limited cardiac reserve due to pumping dysfunction, coronary artery stenosis or arrhythmia, or because primary, unrecognised cardiac dysfunction has been masquerading as ECOPD (see section 2.3.6 for further details).

1.7 Comorbidities

As stated in the expanded definition of COPD put forth in section 1.2, the multisystem nature of COPD is central to its morbidity and mortality: for patients with mild to moderate airflow obstruction, extra-pulmonary comorbidities are stronger determinants of impaired quality of life than measures of COPD disease severity,[74] and death is more likely to be from non-respiratory causes than from COPD itself.[75] Multiple mechanisms cause COPD to manifest outside the lungs: firstly, respiratory insufficiency directly impacts other organ systems; secondly, the causes of COPD also cause damage to other systems; thirdly, comorbid conditions accelerate functional decline and impair the response to acute illness.

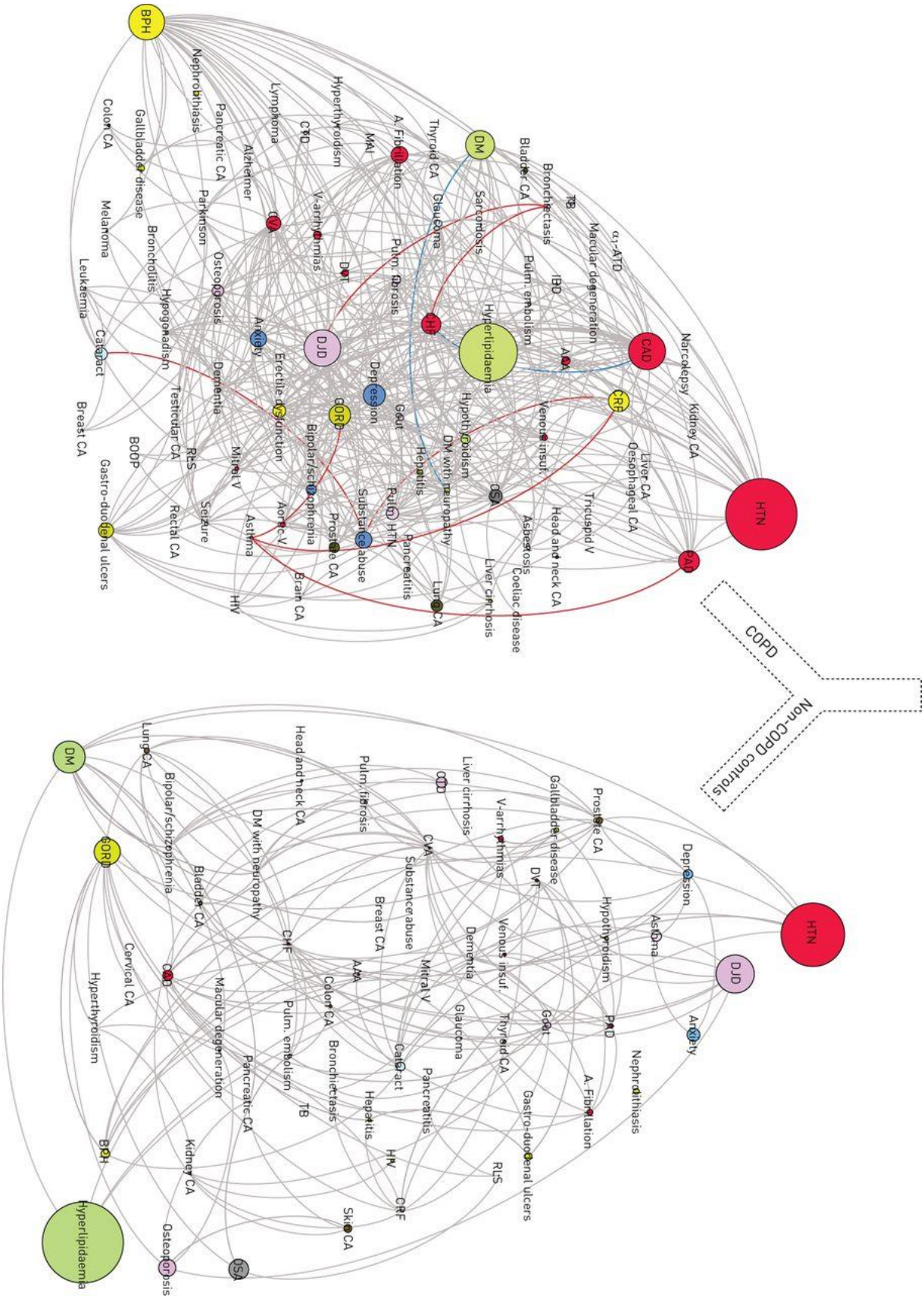
Thus far, reference has been made to comorbidities of COPD, to mean the co-occurrence of additional diseases in the same individual, with reference to an index disease. As illustrated in the previous paragraph, relationships between comorbid diseases are complex and occur through multiple mechanisms,[76] and it is often not logical to preference one condition as primary and others as comorbid. Consequently, the term multimorbidity has become prominent, defined as "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others."[77] From 2018, multimorbidity began to be indexed separately from comorbidity by the National Library of Medicine's MeSH vocabulary, indicative of the term's recent proliferation.[78] When describing COPD as a systemic condition, the language of multimorbidity arguably has greater utility, as it emphasises the need to consider the interrelation of multiple co-occurring conditions on an individual patients' symptoms and risk profile. A multimorbidity approach gives a more accurate conceptualisation of the way COPD manifests for patients; it has been elegantly described as being 'entangled in a network of other chronic conditions'.[79] This network has been appositely illustrated,

and contrasted with that of non-COPD controls, in the lung-shaped diagram published by Divo, et al. (see Figure 6),[80] which depicts the increased number of – and linkages between – conditions diagnosed in the COPD cohort, and highlights the presence of cardiovascular, psychiatric, metabolic and musculoskeletal disease clusters.

In contrast, to speak only of comorbidities confines the model to a 'hub and spoke' configuration, in which interactions independent of the index disease are overlooked. Nevertheless, as this thesis concerns the diagnosis and treatment of heart disease in a group of patients defined by having COPD, the term comorbidity will be used to refer to heart disease in these patients, while recognising that for any individual patient a multimorbidity network may exist that includes both COPD and heart disease. In the remainder of this subsection, comorbidities of COPD that have a particularly significant interaction with heart disease are discussed; a further elucidation of these interactions is found in section 2.3.8.

Figure 6 (following page): Comorbidities networks for 1969 COPD patients and 316 controls. Node size is proportional to disease prevalence; links represent statistically significant correlations (p≤0.01) between two diseases. Abbreviations: A. fibrillation: atrial fibrillation; α1-ATD: α1-antitrypsin disease; AAA: abdominal aortic aneurism; BOOP: bronchiolitis obliterans organising pneumonia; BPH: benign prostatic hypertrophy; CA: cancer; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic renal failure; CTD: connective tissue disease; CVA: cerebrovascular accident; DJD: degenerative joint disease; DM: diabetes mellitus; DVT: deep venous thrombosis; GORD: gastro-oesophageal reflux disease; HTN: hypertension; IBD: inflammatory bowel disease; MAI: Mycobacterium avium–intracellulare; OSA: obstructive sleep apnoea; PAD: peripheral artery disease; Pulm.: pulmonary; RLS: restless legs syndrome; TB: tuberculosis; V: valve; V-

arrhythmias: ventricular arrhymias; Venous insuf.: venous insufficiency. Reproduced with permission of the © ERS 2025: European Respiratory Journal 46(3) 640-650; DOI: https://doi.org/10.1183/09031936.00171614. Published July 9th 2015.



1.7.1 Important non-cardiovascular comorbidity clusters

Firstly, COPD is associated with excess rates of musculoskeletal disorders. Peripheral muscle strength is reduced in patients with COPD,[81] as is endurance,[82] apparently from an accelerated rate of muscle loss.[83] This has been attributed to deconditioning as a result of the activity limitation imposed by breathlessness – although COPD severity measured by airflow obstruction is only weakly correlated with muscle weakness.[84] A combination of systemic factors, including inflammation, blood gas concentrations, malnutrition, direct tobacco toxicity and steroid-induced myopathy, must therefore be contributory.[85] Exacerbations appear once again to play a pivotal role in the development and progression of muscle dysfunction, perhaps because they are associated with worsening of most of the contributory factors listed above.[86] Regardless of initial causation, muscle dysfunction begets a vicious cycle of worsening inactivity, increased sedentary time, a metabolic switch to trigger anaerobic respiration at lower work rates and consequently fatigue and breathlessness with progressively diminishing limitations.[87]

Psychiatric and psychological disorders are also extremely common in patients who have COPD, with the prevalence of depression 2-3 times higher than in controls[88] and likely to be increased to even greater degree in the case of anxiety.[89] Furthermore, cognitive dysfunction appears to be more common in COPD, with a pattern of impairment likened to that seen in multi-infarct dementia.[90] The breadth of definitions available means results of studies of cognitive dysfunction are more heterogenous; nevertheless, prevalence levels up to 50% are reported,[91,92] with significant correlation between cognitive performance scores and both airflow obstruction and resting oxygenation.[93] Co-occurring anxiety and depression are both linked to higher mortality and exacerbation rates for patients with COPD,[94,95] for multiple reasons, including a reduction in health-promoting behaviours such as smoking cessation,[96] physical activity,[97] healthy diet[98] and engagement with rehabilitation.[99] Once again, powerful feedback loops can be discerned, where the development of worsening symptoms worsens the symptoms of depression or anxiety, further hindering health-promoting behaviours. Cognitive impairment is itself a risk factor for depression and anxiety[100] and is associated with sedentary behaviour,[101] lower rates of smoking cessation[102] and higher rates of hospital admission and death.[103] Indeed, the complexity of the relationship between mood disorders, cognitive disorders, health behaviours physical activity and therefore musculoskeletal health is readily apparent, as is the sense in which it is inadequate to consider each of these issues in bidirectional association with COPD.

Moreover, besides these daytime problems with activity, mood and cognition, patients with COPD often suffer from poor sleep health. Alongside a high prevalence of OSA[104] , sleep quality is commonly poor, both according to objective measurements of sleep efficiency[105] and self-report, with 40% stating that COPD negatively affects their sleep.[106] Poor sleep is associated with higher

COPD exacerbation frequency[107] along with other factors that interact with poorer outcomes and life quality, such as mood disorders,[108] physical inactivity[109] and cognitive dysfunction.[110] Patients with COPD reporting poor sleep also report a higher burden of symptoms including cough and breathlessness; in the same cohort study of 98 patients, reported sleep disturbance was also associated with a significantly increased adjusted hazard ratio for death of 5.0 (95% CI 1.4-18).[111]

1.7.2 Accelerated cellular ageing and COPD

One way of understanding the multimorbidity in which COPD commonly exists is to view the condition through the lens of cellular ageing. Ageing is a process by which homeostasis becomes progressively more dysfunctional, leading to increased risk of death and disease. This has its basis in the finite number of times cells can divide before losing this capacity, after which they are termed senescent cells. These cells, while no longer dividing, nevertheless actively undertake specific cellular processes, including the secretion of a pattern of proteins including pro-inflammatory cytokines, growth factors and proteases, termed the senescence-associated secretory phenotype (SASP).[112] The profile of the SASP has a strong similarity to the factors seen in excess in patients who have COPD, who also display many other features of accelerated ageing are also found at a cellular level, including telomere shortening, defective DNA repair, mitochondrial dysfunction and an altered microRNA profile.[113] Accordingly, the argument that COPD is a disease of accelerated lung ageing is persuasive. Accelerated ageing processes can also be discerned at extra-pulmonary locations, for example within the immune system: the circulating leukocytes of patients who have COPD display greater adherence and lower proliferative, phagocytotic and cytotoxic capabilities[114], changes mirrored in aged individuals.[115] Evidence of senescence is also seen in the satellite cells within leg muscles of patients who have severe COPD, with the investigators hypothesising that recurrent damage and repair could have exhausted their proliferative capacity.[116] These findings support the hypothesis that accelerated ageing throughout the body is responsible not just for the pulmonary manifestations of COPD but also its associated pathologies, including heart disease (see Figure 7).

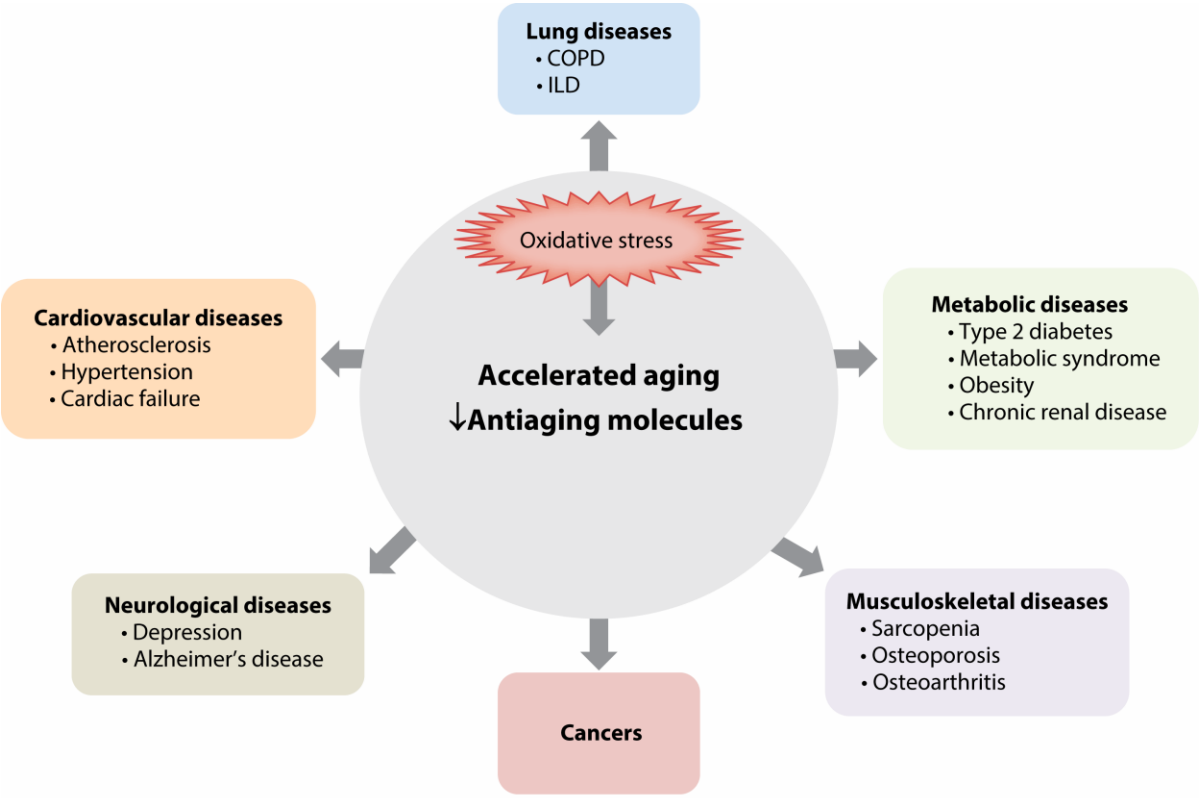


Figure 7: Chronic diseases that share common mechanisms of accelerated ageing, including COPD and many of its most common comorbidities. Reproduced from Annual Review of Physiology, P. Barnes, 1(79), 2017 with permission from Annual Reviews, Inc.

This provides a rationale for treatment of the underlying ageing process that may prove fruitful, since it circumvents a more downstream approach to tackling individual system pathologies that can lead to adverse events in other systems, for example in the case of cardiac adverse events with bronchodilator treatment of pulmonary disease, which occur more frequency with the presence of other comorbidities.[117] Importantly however, the paradigm does not appear to explain approximately half of COPD cases: those that have not exhibited rapid lung function decline but instead had poor early life lung maturation.[38] That said, never-smoking patients with COPD exhibit different clinical characteristics, including generally milder disease, lower levels of inflammation and, interestingly, no increased risk of cardiovascular comorbidities.[118] Therefore it may be that accelerated ageing provides an explanation for the genesis of COPD as part of an senescence-associated multimorbidity profile in the subgroup of patients with accelerated lung function decline.

In summary, multiple other chronic diseases associate with COPD and have profound effects on patients' quality of life and outcomes. Recent research on multimorbidity networks and the concept of accelerated ageing has drawn attention to the importance of considering the ways in which co-occurring conditions interact in order for clinicians to best understand and mitigate morbidity and risk for patients.

1.8 Chapter conclusion

In conclusion, COPD is a highly impactful condition, with significant improvements in outcome yet to materialise despite many decades of research and investment. Patients with COPD often exhibit dysfunction in multiple organ systems. Non-pulmonary phenomena are instrumental in causing functional deterioration, morbidity, hospital admission and mortality. Rather than solely considering bidirectional relationships between COPD and specific comorbidities, it may be more expedient in some contexts to consider the pulmonary manifestations of COPD as part of a network of multimorbidity, and to recognise the underlying role of accelerated ageing in the development of both these pulmonary manifestations and many of the most common and impactful extra-pulmonary disorders. A crucial COPD comorbidity in terms of its prevalence and impact that has yet to be discussed is heart disease: this will be the focus of the next chapter.

Chapter 2: The relationship between COPD and heart disease

2.1 Chapter introduction

The impact of comorbid conditions on the wellbeing and outcomes of patients who have COPD was highlighted in the previous introductory chapter. Here, attention will be on the relationship between diseases of the heart and circulatory system and COPD. The heart and lungs have a long-recognised intimate anatomical and functional relationship: Paul D White, who later co-published the definitive description of Wolff-Parkinson-White syndrome, wrote in 1929 of the heart and lungs that 'not only will derangement of function of one organ affect the other if of sufficient magnitude, but disease or disturbance of structure of the one is apt to spread by contact to the other, or at least displace it.'[119] A century later, understanding of the mechanism by which chronic disease of the lungs, in the form of COPD, is related to disorders of the various functions of the cardiovascular system has grown beyond this straightforward physical interrelationship to include, amongst others, inflammatory and neurohormonal processes. The details of this interrelationship are the focus of this chapter, along with specific considerations relating to the diagnosis and treatment of heart disease in patients who have COPD.

2.2 Cardiovascular diseases associated with COPD

Cardiovascular disease and heart disease are, of course, extremely broad terms – 479 separate disorders of the circulatory system are recognised in the 11th edition of the International Classification of Diseases.[120] This section contains the definitions and features of the heart diseases that are most prevalent amongst patients who have COPD,[9] and highlights both their importance for patients and the extent to which they are found at excess rates in the COPD population. Treatment is also discussed, with a summary of evidence-based treatments contained in tables 2 and 3.

2.2.1 Heart failure

2.2.1.1 Definition

Heart failure is defined as a clinical syndrome that results from structural or functional impairment of ventricular ejection or filling with blood.[121-123] This leads to reduced cardiac output or increased filling pressures, either solely during exertion or also at rest. As it is a clinical syndrome, certain symptoms are required to be present alongside heart structural and functional abnormalities; typically breathlessness, fatigue and ankle swelling. The presence of clinical signs is not an absolute

requirement for diagnosis, however, as it is recognised that they may not be present in early or well-treated heart failure.[123]

Given the breadth of this definition, heart failure has been subclassified according to the abnormalities observed on functional imaging of the heart, with the primary imaging modality being echocardiography. Distinction has been made between cases where the syndrome results predominantly from dysfunction of the left (LV) or right ventricles (RV), and where functional imaging shows a problem mainly with ejection of blood, termed systolic heart failure, or filling with blood: diastolic heart failure. Some care with these dichotomous definitions is necessary, because left-sided heart failure can lead to right-sided heart failure due to transmission of elevated left ventricular filling pressures to the right ventricular outflow tract[124]; similarly, dysfunction of ventricular filling in diastole is seen in most patients with systolic heart failure.[125]

2.2.1.2 Diagnosis

Notwithstanding the above notes of caution, cardiology societies have produced guidelines for heart failure diagnosis that rely predominantly on the echocardiographic LV ejection fraction to define a certain degree of LV systolic dysfunction. Of these classification system, the most widely implemented are those of the AHA/ACC/HFSA and ESC (see table 1 for expanded abbreviations), which differ only subtly in their definition of heart failure with reduced, mildly-reduced and preserved ejection fraction (see table 1).

Society	HF category	Definition
ESC (2021)[123]	HFrEF	Symptoms ± signs LVEF ≤40%
	HFmrEF	Symptoms ± signs LVEF 41–49%
	HFpEF	Symptoms ± signs LVEF ≥50%, Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides
ACC/AHA/HFSA (2022)[121]	HFrEF	LVEF ≤40%
	HFimpEF	Previous LVEF ≤40% Follow-up measurement of LVEF >40%
	HFmrEF	LVEF 41–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, non-invasive and invasive hemodynamic measurement)
	HFpEF	LVEF ≥50% Evidence of increased LV filling pressures as for HFmrEF
NICE (2018)[126]	HFrEF	HF with LVEF < 40%
	HFpEF	Normal or preserved LVEF Evidence of diastolic dysfunction
BSE (2020)[127]	Normal LVEF	LVEF ≥ 55%
	Borderline low LVEF	LVEF 50-54%
	Impaired LVEF	LVEF 36-49%
	Severely impaired LVEF	LVEF ≤ 35%
ESC – European Society of Cardiology; ACC/AHA/HFSA – American College of Cardiology/American Heart Assocation/Heart Failure Society of America; NICE – National Institute for Health and Care Excellence; BSE – British Society of Echocardiography HFrEF – heart failure with reduced ejection fraction; HFmrEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFimpEF – heart failure with improved ejection fraction		

Table 1: Summary of diagnostic systems for heart failure applied by prominent national and international organisations.

2.2.1.3 Treatment

The importance to patients of classifying heart failure by ejection fraction is that this parameter was used to define inclusion criteria for landmark trials of pharmacotherapy, therefore it suggests which therapies have an evidence basis to improve outcomes. From these trials, evidence based drug treatment for patients with HFrEF now comprises use of beta-blocker, angiotensin receptor-

neprilysin inhibitor (ARNI), mineralocorticoid antagonist (MRA) and sodium-glucose co-transporter 2 inhibitor (SGLT2i) agents.[128] Patients with HFmrEF and HFpEF have been the subjects of fewer positive clinical trials; nevertheless post-hoc analysis of large studies suggest benefits of beta-blockade[129] and angiotensin antagonism[129] in HFmrEF. Beginning in 2021, demonstrations of the efficacy of SGLT2i agents in HFmrEF and HFpEF[130,131] have provided ground-breaking evidence that drug therapies can improve clinical outcomes in these patients as well as those with HFrEF. The key evidence-based therapies are summarised in table 2.

Condition	Treatment	Evidence for efficacy*	Notes
HFrEF	Beta blocker	Mortality HR 0.66 (95% CI 0.54-0.81)[132]	Selected agents: bisoprolol, metoprolol, nebivolol, carvedilol
	ACE-inhibitor/ARB	Mortality reduction of 31%[133]	ARNI now first line (see below); ARB if ACE-inhibitor not tolerated
	MRA	Mortality reduction of 30%[134]	
	ARNI (ARB + neprolysin inhibitor)	Mortality or HHF HR 0.80 (95% CI 0.73 to 0.87) vs enalapril[135]	
	SGLT2-inhibitor	Mortality or HHF HR 0.74 (95% CI 0.65 to 0.85)[136]	
	ICD	Mortality reduction of 28%[137]	Secondary prevention after ventricular arrhythmia; primary if LVEF<35% due to ICM with NYHA II-III. Class II recommendation outside of ICM. Life expectancy >1y in all cases.[123]
	CRT	Mortality HR 0.66 (95% CI 0.57–0.77)[138]	Symptomatic with LVEF <35% despite OMT, in SR with QRSD > 150ms and LBBB. Class II recommendation for shorter QRSD/absent LBBB.[123]
HFmrEF	SGLT2-inhibitor	Worsening HF HR 0.79 (95% CI, 0.69 to 0.91)[131]	
	Beta-blocker	CV death HR 0.48 (95% CI 0.24-0.97)[139]	Class II recommendation based on post-hoc IPD meta-analysis
	ACE-inhibitor/ARB	HR 0.76 (95% CI 0.61–0.96)[140]	Post-hoc analysis; class II recommendation
HFpEF	SGLT2-inhibitor	Worsening HF HR 0.79 (95% CI, 0.69 to 0.91)[131]	

*Table 2: Summary of evidence-based treatments for heart failure. Recommendations are class I from prominent guideline development groups unless specified. *HR vs placebo unless specified; all results presented numerically are statistically significant with p<0.05.. Abbreviations: HHF – hospitalisation for heart failure; ICD – implantable cardioverter defibrillator; CRT – cardiac resynchronisation therapy. ICM – ischaemic cardiomyopathy. Other evidence exists besides that cited; landmark trials have been preferentially selected.*

2.2.1.4 Prevalence and relationship with COPD

In the general population, heart failure is common, with an estimated prevalence in developed countries of 1.3% - 4%.[141] There is a discrepancy between prevalence estimates that used healthcare records or patient reports, and estimates derived from echocardiographic screening of population samples. The latter appear around twice as high, suggesting there is a high rate of undiagnosed heart failure in the general population, particularly in patients age >60.[142] The prevalence of diastolic heart failure, or HFpEF/HFmrEF, is higher than the prevalence of systolic heart failure, or HFrEF, with this difference increasing over recent decades such that HFpEF cases now exceed those of HFrEF by a factor of 1.8.[143]

COPD substantially increases the chance of being diagnosed with heart failure, with an odds ratio estimated from US healthcare records of 8.48 (95% CI 7.65 – 9.4)[144]. The risk of comorbid heart failure is not equal for all patients who have COPD: it is highest in those with more severe symptoms and with higher exacerbation frequency.[145] Further cluster analysis of COPD cohorts has found higher heart failure prevalence in subgroups with elevated body mass index (BMI), relatively lesser evidence of spirometric airflow obstruction and radiological emphysema, and higher rates of ischaemic heart disease and diabetes.[146,147]

As in the general population, patients who have COPD and heart failure are more likely to have the HFpEF subtype than HFrEF, with an observed ratio of approximately 3:1.[148] Importantly, those who have COPD plus HFrEF and COPD plus HFpEF have been observed to have different outcomes: the former have higher mortality and heart failure hospitalisation, the latter higher ECOPD rates and length of stay when hospitalised.[148]

Despite high rates of heart failure being documented in patients with COPD, there are a substantial number of cases that are uncounted due to the problem of underdiagnosis.[149] This is of particular importance to patients because undiagnosed disease has several pernicious consequences, including the omission of important therapies, the inadvertent prescription of contra-indicated medications, and the lack of a complete explanation for patients' symptoms. A systematic exploration of the magnitude of the problem of underdiagnosed heart failure is undertaken in Chapter 3 of this thesis.

2.2.2 Coronary artery disease

2.2.2.1 Definition

Coronary artery disease (CAD) refers to clinical syndrome that arises due to the presence of atheromatous plaque within the epicardial arteries. A spectrum of presentations is possible and relates to the extent and time course of the resultant myocardial oxygen delivery impairment.

Patients may have silent disease, stable angina caused by chronic obstruction of blood flow to the myocardium, and acute coronary syndromes (ACS) caused by acute, critical coronary artery obstruction following plaque rupture and local thrombosis.[150] The coronary arteries are often abnormal in patients with advanced COPD, with case series reporting a prevalence of coronary stenosis of around 25% in lung transplant candidates without known CAD.[151,152] These findings are mirrored by an elevated risk of ACS, which increases further with more severe airflow obstruction: by 28% for fatal events and 20% for non-fatal events for every 10% decrease in FEV1.[153,154] Recently, evidence has emerged that ACS events are not distributed evenly over time in patients with COPD, but rather are most likely in the post-exacerbation period. Events are particularly clustered when patients are hospitalised for ECOPD, after which the risk of MI is increased 8-fold over the first 7 days in comparison with the fortnight prior to exacerbation.[155] Consequently, and crucially, hospitalisation with ECOPD represents a critical and urgent moment at which to ensure CAD is identified and adequately treated. The immediate elevation and subsequent steep decrement in incidence rate ratio for MI post-ECOPD shown in Figure 8 illustrates this.

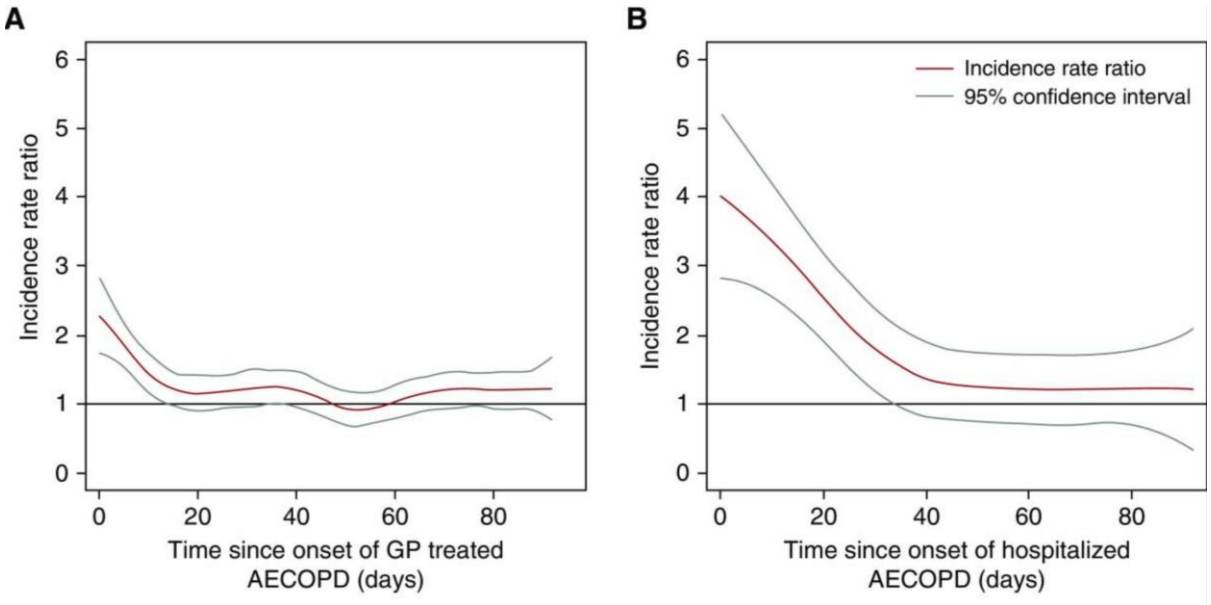


Figure 8: Change in risk of MI over time after (A) moderate GP–treated ECOPD; (B) severe (hospitalised) ECOPD. Extracted from Rothnie, et al(155) (Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved.)

2.2.2.2 Diagnosis

The gold standard diagnostic tool for identifying the presence and extent of CAD has historically been invasive angiography, which can elucidate the location and degree of coronary artery stenosis. More recently, it has been recognised that angiography alone is unable to accurately assess the

functional impact of a lesion on the myocardium.[156] Angiography alone also neglects important information about the characteristics of the vessel wall, such as the extent and composition of atherosclerotic plaques.[157] Consequently, complementing angiography with either non-invasive functional imaging for myocardial ischaemia, or coronary CT angiography, which can also incorporate computational fluid dynamics to calculate fractional flow reserve from the coronary anatomy, is generally recommended for the assessment of coronary artery disease in symptomatic patients.[150,158]

In the asymptomatic population, a screening approach is recommended, using demographic and clinical parameters to provide a risk score for cardiovascular events that guides primary prevention. Imaging is not recommended, although US[159] and European[150] guidelines both state that the CT coronary artery calcium score (CACS) can be used to reclassify intermediate-risk patients as low risk, thereby potentially obviating the need for statin therapy. Other non-invasive tests, such as measurement of arterial stiffness by pulse wave velocity or arterial distensibility, can estimate the likelihood of clinically significant CAD; unlike CAC assessment, these methods are not available outside of research studies.[160]

CT measurement of coronary artery calcium was developed in the 1990s, with increased quantities of calcium being shown to correlate with overall plaque burden,[161] and to a lesser degree (albeit still with a substantial area under receiver-operator curve [AUROC] of 0.8-0.9[162-164]) the extent of significant vessel stenosis. The precision of CAC quantitation as a measurement of significant coronary artery disease is limited by 1) the existence of non-calcified but significant plaque in some patients, particularly those under 40 years old,[165] and 2) non-obstructive arterial calcification, which may occur within the vessel wall rather than the intima; this occurs particularly in association with advanced age, diabetes and renal failure.[166]

The most widely applied scoring system for CAC is the Agatston score, which can be used to classify patients into no, mild, moderate, severe/heavy or very severe/heavy CAC strata, or provide a CAC percentile score according to age and sex. Patients who have COPD have been shown to have markedly higher Agatston scores than matched smokers without airflow obstruction – in an international cohort the median score was 128 (interquartile range [IQR] 2 – 494) vs 0 (0-75). Those with increased CAC also had a significantly increased mortality even above a modest Agatston score threshold of 100[167]. (see Figure 9).

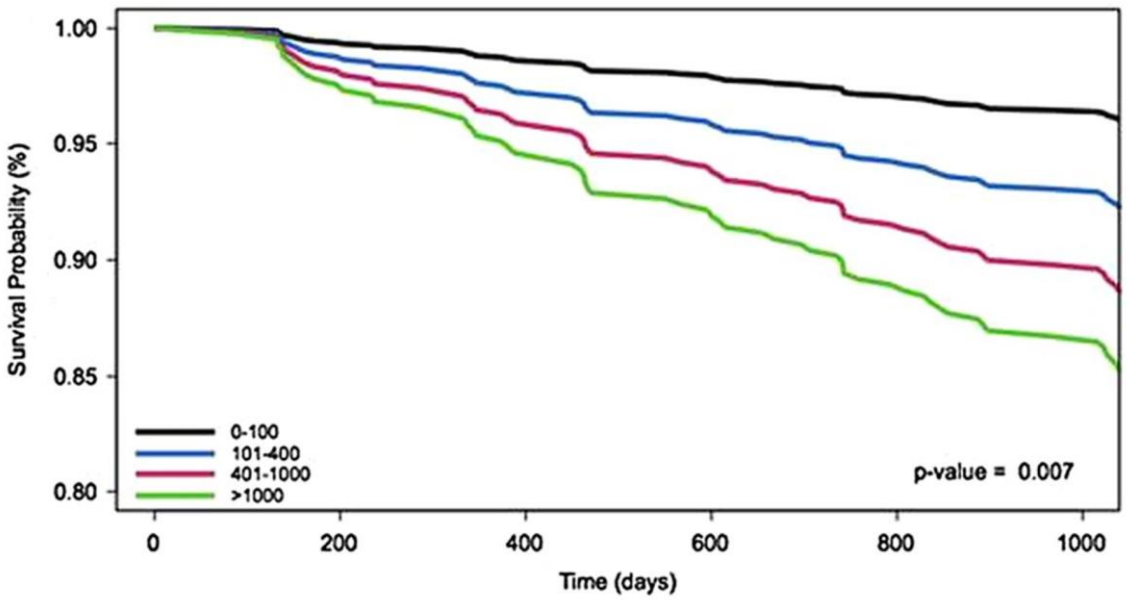


Figure 9: Cox proportional hazards model for mortality in patients with COPD and coronary artery calcium Agatston score, adjusted for age, gender, pack-years, severity of COPD and self-reported cardiovascular disease. Reproduced with permission from Williams et al.(168)

2.2.2.3 Treatment

Treatment of coronary artery disease depends on its clinical manifestations (see table 3). For patients who are asymptomatic but at increased risk, lifestyle and lipid modifications are the cornerstone. For patients who have symptoms of angina, additional management includes symptomatic anti-anginal drug therapy using agents such as nitrates, calcium-channel blockers and beta-blockers that improve the balance of myocardial oxygen delivery and consumption. Antiplatelet therapy is recommended for those who have had a prior MI or revascularisation procedure and is to be considered in others.[150,168] Further management involves consideration of revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Patients who have experienced ACS require more intensive secondary prevention with dual antiplatelet therapy, an ACE-inhibitor (or similar agent), plus a beta-blocker for at least the initial post-MI period, alongside statin therapy and lifestyle modifications, as for other patients with CAD. Coronary intervention is often performed at the time of ACS, either for emergency restoration of perfusion in the case of ST-segment elevation MI (STEMI) or to reduce the risk of death, readmission or further ACS in the case of unstable angina or non-ST-segment elevation MI (NSTEMI).[169]

	Coronary artery disease manifestation		
Recommended intervention	**Asymptomatic**	**Angina without ACS**	**ACS**
Lifestyle modifications*	✓	✓	✓
Blood pressure control	✓	✓	✓
Statin treatment	✓	✓	✓
ACE-inhibitor/ARB	–	–	✓
Beta-blocker	–	✓	✓
CCB/nitrates/other second-line anti-anginals	–	✓	–
Single antiplatelet therapy	(✓)	(✓)	✓
Dual antiplatelet therapy	–	–	✓†
Revascularisation	–	(✓)	✓

✓= generally recommended; (✓) = recommended in certain cases; – = generally not recommended
ARB: angiotensin-receptor blocker; CCB: calcium channel blocker
* Diet, activity, weight, smoking, alcohol; † for 12 months, longer in high-risk cases[150]

Table 3: summary of recommended management of coronary artery disease

2.2.2.4 Prevalence and relationship with COPD

As signified by the markedly increased presence of significant CAC, coronary artery disease occurs at excess rates in patients who have COPD. A large meta-analysis including over 5 million patients reported an odds ratio for all manifestations of coronary artery disease of 2.28[170] (95% CI 1.76 – 2.96) compared with match controls. Odds ratio estimates for myocardial infarction specifically range from 2.71 (95% CI 1.69 – 4.35] in the same analysis to 4.42 (95% CI 3.77 – 5.17), with the highest relative odds in patients with severe COPD.[171] Of the various manifestations of coronary artery disease listed in the meta-analysis by Chen *et al*, it is notable that the odds ratio for a diagnosis of angina is both the highest, at 8.16, and the least precise (95% CI 3.08 – 21.59). This imprecision might reflect the diagnostic difficulty resulting from the closely shared symptoms of COPD and stable angina: breathlessness, chest tightness and largely fixed exercise limitation. What is clear from the above evidence is that coronary artery disease is a potentially high-yield target for intervention in patients who have COPD: it is highly prevalent and amenable to simple evidence-based treatment, with the longitudinal data suggesting that would be a particular benefit to maximising protection from acute coronary events during the peri-exacerbation period.

2.2.3 Atrial fibrillation

2.2.3.1 Definition

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia involving uncoordinated atrial electrical activation and consequently ineffective atrial contraction.[172] It is of high importance to patients with COPD: those with both conditions have worse symptoms and quality of life in comparison with those with isolated AF.[173] Furthermore, the additional presence of AF is related to adverse outcomes: in hospitalised patients a doubling of mortality has been reported, as have increased length of hospital stay and healthcare costs. [174] Atrial fibrillation was the sole cardiac comorbidity that was an independent predictor of mortality in the DECAF) score which is the most robust prognostic tool in ECOPD resulting in hospitalisation, and is widely implemented for risk-stratification of patients hospitalised with ECOPD.[175]

The importance of AF is two-fold: firstly, it increases the risk of embolic occlusion in the systemic arterial circulation, due to stagnation of blood within the inefficiently-emptying left atrium, which thromboses and embolises to the systemic circulation, with the most serious consequence of this being ischaemic stroke. Secondly, it decreases cardiac output due the shortened diastolic filling time associated with tachycardia and the loss of the 'atrial kick' from organised atrial contraction that completes diastolic ventricular filling.[176]

This latter effect is particularly relevant for patients with impaired gas exchange due to COPD, since the additive effect of reduced cardiac output limits oxygen delivery and further reduces exercise capacity.

2.2.3.2 Diagnosis

A distinction is made between clinical and subclinical AF, where the former is apparent on 12-lead ECG and may be associated with symptoms, such as palpitations or exertional dyspnoea. By contrast, subclinical AF occurs in asymptomatic patients with no previous ECG evidence of AF and is detected by a monitoring device such as a wearable ECG monitor. As heart monitoring technology has proliferated, subclinical AF has become increasingly recognised, and researchers have sought to establish the minimum duration of detected AF that significantly increases patients' risk of stroke. While very short events last only seconds do not appear to be associated with stroke, or other adverse outcomes,[177] episodes of ≥5 minutes have been shown to be associated with a statistically significant increased rate of ischaemic stroke (HR 1.76 [95% CI 1.22 – 3.64]).[178]

2.2.3.3 Treatment

Of paramount importance in the treatment of AF is the reduction of the risk of systemic embolism, most importantly ischaemic stroke, through the use of anticoagulation where the risk of stroke is felt to outweigh the risk of bleeding. Scoring tools are available to guide clinicians in making this decision, with the most used being the CHA_2DS_2VASc score to estimate annual stroke risk, and the HASBLED score for bleeding risk.[179,180] For AF not caused by mitral valve disease – which accounts for the overwhelming majority of cases, including those with comorbid COPD[181] – treatment with direct oral anticoagulants has become standard, due to their ease of dosing and lack of requirement for blood test monitoring; otherwise, warfarin is used. A second aspect of management, for patients with permanent atrial fibrillation, centres on control of the ventricular rate to a level that preserves adequate diastolic ventricular filling, without causing excessive bradycardia or inability of the heart rate to increase with exercise. This is accomplished by titrating drugs that block atrio-ventricular conduction or reduce the sino-atrial node depolarisation rate, most commonly beta-blockers (see section 2.5.1), non-dihydropyridine calcium channel blockers and digoxin. The recommended target heart rate varies between guideline development groups, with current NICE guidelines containing no numerical target; the ESC guidelines advise aiming for a rate of below 110 bpm.[172]

2.2.3.4 Prevalence and relationship with COPD

AF is common and occurs at excess rates in patients who have COPD, with an adjusted hazard ratio for incidence of 1.28 (95% CI 1.04 – 1.57). [182] Patients with frequent exacerbations and severe airflow obstruction are at further increased risk.[183] It bears highlighting that COPD also predisposes to other forms of cardiac arrhythmia: for example, it is an independent risk factor for non-sustained ventricular tachycardia (NSVT), with an adjusted odds ratio ranging between 1.34 (95% CI 1.10 – 1.63) to 2.24 (95% CI 1.49 – 3.30).[183] This predisposition to ventricular arrhythmia may contribute to the striking increased risk for sudden cardiac death – 30%, rising to 3.7-fold in frequent exacerbators with evidence of increased baseline systemic inflammation – identified in patients with COPD.[184] However, NSVT itself has minimal specific treatment[185]; by contrast for AF treatment includes restoration of sinus rhythm where this is felt to be appropriate, control of the ventricular rate where rhythm control is not chosen, and, crucially, anticoagulation to reduce the risk of stroke if the bleeding risk is not excessive.[172] Notably, meta-analysis data shows that the coexistence of COPD and atrial fibrillation increases the risk of stroke vs. atrial fibrillation without comorbid COPD (odds ratio [OR] 1.36 [95% CI 1.00 – 1.85]) and also the risk of major bleeding (OR 45 [95% CI 1.17 – 1.80]).[186] This succinctly illustrates the multiplicative detriment of multimorbidity for patients: the combination of conditions is more risky even when treated (see Figure 10).

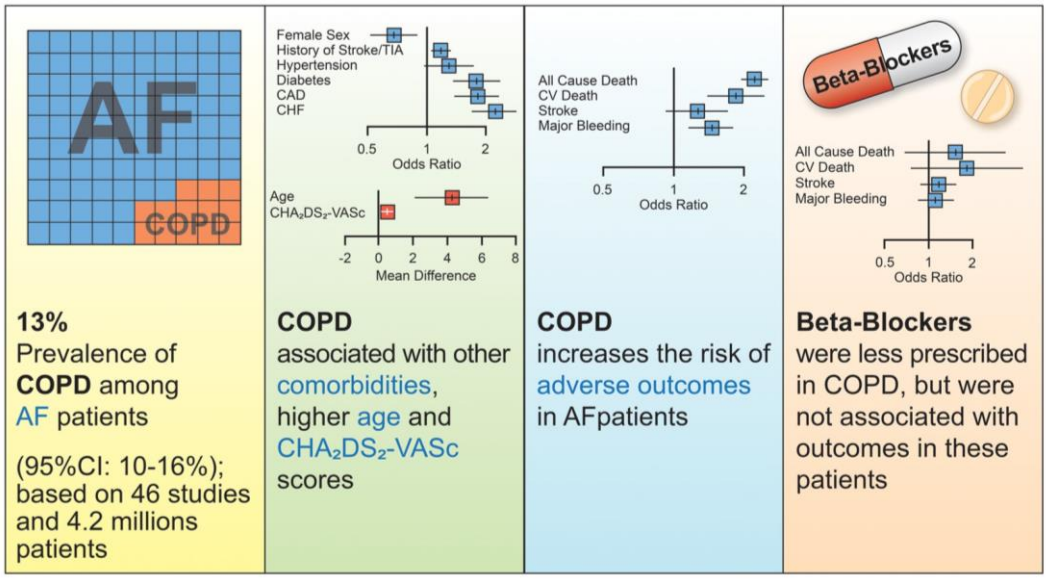


Figure 10: Graphical illustration of the adverse impact of coexistent chronic obstructive pulmonary disease and atrial fibrillation on patient outcomes, multimorbidity profile and healthcare provision. Reproduced with permission from Romiti et al.[186] CHF, chronic heart failure; TIA, transient ischaemic attack.

2.2.4 Other cardiovascular diseases

Besides the three major conditions discussed, COPD is associated with multiple other cardiovascular diseases. Some, such as hypertension and diabetes mellitus, can be characterised as risk factors for the development of the conditions already mentioned, while others, such as stroke and peripheral arterial disease, represent manifestations of similar arterial disease processes to those that cause coronary artery disease.

2.2.4.1 Hypertension

When the systemic arterial blood pressure is persistently raised, atherosclerosis is accelerated atherosclerosis due to endothelial dysfunction, both through direct pressure effects and via increased oxidative stress in the vessel wall.[187] Systemic arterial hypertension also leads to left ventricular remodelling, hypertrophy and dysfunction and consequently also to left atrial dilatation and electrical dysfunction. Thus hypertension, the most common cardiovascular disease in both the general and COPD populations, is an independent risk factor for coronary artery disease, heart failure and atrial fibrillation. COPD is an independent risk factor for hypertension, with more severe airflow limitation increasing risk further.[188] Given the elevated risk for cardiovascular events such as myocardial infarction and stroke in patients who have COPD, control of hypertension is important and can usually be safely achieved using one or a combination of ACE-inhibitor, calcium channel blocker or thiazide-like diuretic agents as first-line agents.[189]

2.2.4.2 Diabetes Mellitus

Diabetes mellitus (DM), characterised by chronic elevation of blood glucose levels, increases cardiovascular risk by structural and inflammatory effects on the arterial wall, with risk increasingly synergistically when hypertension is also present.[190] The subtype of DM most relevant in relation to COPD is type 2 diabetes mellitus (T2DM), characterised by insulin resistance and relative insulin insufficiency, and associated with obesity. Management focusses on education and lifestyle measures to achieve weight loss with the addition of drug therapy if required to achieve adequate reduction of blood glucose levels. First line drug therapy is with metformin, with the choice of second-line agent dependent on individual patient factors.[191] Recently, sodium-glucose transporter 2 inhibitor (SGLT2i) agents have entered guidelines as important treatment for diabetes patients with comorbid heart failure, cardiovascular disease or high cardiovascular risk, due to evidence that they reduce major adverse cardiovascular events (ACE) - including death - and heart failure hospitalisation.[192] As with hypertension, DM often coexists with COPD, in part due to its high, and rising, prevalence but also through an association independent of BMI, smoking, race and education.[188] Patients with the two conditions have been found to have worse COPD outcomes, such as higher mortality and length of stay during hospitalisation with exacerbation, although apparently conflicting results have found diabetes (and hypertension) to be associated with *lower* rehospitalisation rates after admission with ECOPD,[193] even when accompanied by end-organ damage. The authors speculated that increased healthcare contact provoked by these comorbidities may have increased the quality of COPD care, although the unmeasured effect of medications that reduce CV risk may provide an alternative explanation.

2.2.4.3 Cerebrovascular disease

As an end-organ manifestation of both atherosclerotic cardiovascular disease and a common complication of atrial fibrillation, ischaemic stroke predictably occurs at high rates in patients who have COPD. Data on the extent to which the association is independent of shared risk factors is conflicting, however,[194] with estimates of the increased odds of stroke losing statistical significance after adjustment for smoking in some studies,[195] but not others.[196] The contribution of COPD to stroke risk may differ according to stroke subtype: a review of stroke cases at a single centre found that COPD was the strongest measured predictor of stroke being of atherothrombotic aetiology, but COPD was not associated with cardioembolic stroke.[197] The period after hospitalisation with ECOPD is the most hazardous, with stroke incidence rate increased by 1.7 times compared with the stable period.[155] COPD is an independent predictor of mortality after stroke, with a modest adjusted in-hospital odds ratio of 1.06 in a large US cohort,[198] but a very low one-year post-stroke survival of 46% for patients with COPD reported by a single centre in Poland[199] (post-stroke survival was 72% in

controls without COPD). The key aspects of stroke management mirror those of coronary artery disease, with secondary prevention including antiplatelet and statin therapy, plus risk factor management and lifestyle advice as for coronary artery disease. Rehabilitation targeted at recovering lost function is also critical. The parallels with coronary artery disease management extend to the targeting of stenotic carotid arteries with endarterectomy and angioplasty, as well as acute restoration of cerebral blood flow by thrombectomy.[200]

2.2.4.4 Peripheral arterial disease

Given the excess rates of coronary artery disease and stroke seen in patients who have COPD, it follows that peripheral arterial disease (PAD), which has a similar, but not identical, pathophysiology,[201] is also found at increased rates in this population. The large, population-based Rotterdam Study reported that individuals who have COPD have an almost doubled risk of being diagnosed with PAD.[202] When undiagnosed peripheral arterial disease is accounted for, rates are undoubtedly higher; authors have emphasised the under-researched and underappreciated nature of PAD, despite its association with outcomes that are comparably as poor as those seen in CAD and stroke.[203,204] The magnitude of underdiagnosis may be substantial: in patients hospitalised due to COPD, abnormal ankle-brachial pulse indices (ABPI) were seen in 37% of patients,[205] most of whom were not diagnosed with PAD. Smoking appears to be a stronger risk factor for PAD than both CAD and stroke, with the risk for PAD persisting longest after smoking cessation.[206] However, smoking does not explain the entirety of the risk, as demonstrated by stepwise increase in abnormal ABPI prevalence from non-smoking controls to COPD-free smokers to patients with COPD and equal smoking exposure.[207] The management of PAD recapitulates that of CAD and stroke, involving lifestyle modification, lipid lowering with statin therapy first-line, blood pressure control and – for symptomatic disease – exercise therapy, antiplatelets and targeted endovascular and surgical interventions.[208]

2.3 Mechanisms of association between heart disease and COPD

In this section, evidence for mechanisms by which cardiovascular disease occurs with increased frequency in COPD is reviewed. Understanding these mechanisms helps to inform strategies to improve targeted diagnosis of cardiac comorbidities, as well as therapeutic approaches to address the excess morbidity and mortality they cause.

2.3.1 Shared risk factors

The most straightforward means by which two conditions can be linked is if they share common risk factors. Key major risk factors for both COPD and heart disease are discussed in this subsection.

2.3.1.1 Age

COPD and the major heart diseases occur at increasing frequency with increasing age. In developed nations, the majority of people aged over 65 live with multimorbidity,[9] therefore a certain degree of coexistence of COPD and heart disease can be anticipated on this basis.

2.3.1.2 Tobacco smoking

Personal tobacco smoking is the major environmental risk factor for COPD and an important risk factor for heart disease. As well as damaging the airway epithelium via increased oxidative stress and disrupted immune homeostasis,[209] cigarette smoke leads to atherosclerosis through impaired nitric oxide-mediated vasodilatation, increased endothelial inflammation and atherogenic lipid profile modification.[210] Coronary artery disease is the most common cause of HFrEF,[211] therefore smoking is associated with an increased risk of incident HFrEF in both current and former smokers.[212] The same study showed a similar increased risk is seen for HFpEF ; the authors posited pathophysiological mechanisms for HFpEF development that included inflammation-driven ventricular stiffening and impaired mitochondrial oxidative phosphorylation due to direct effects of tobacco smoke. Finally, there is meta-analysis-level evidence that the risk of developing atrial fibrillation is increased by smoking in a dose dependent manner, although the overall relative risk is lower that for coronary artery disease and heart failure.[213] The basis for the increased risk may be a combination of increased rates of atrial fibrillation-predisposing conditions such as coronary artery disease and hypertension, as well as direct effects of nicotine on atrial vulnerability to fibrillation.[214]

As stated in section 1.3, only 40-80% of COPD would be expected to disappear from the population if smoking was eliminated as a risk factor, so other risk factors must play an important role in COPD development. These may in turn be potential shared risk factors to explain the association between COPD and heart disease. An obvious candidate is passive exposure to tobacco smoke, the constituents of which differ to that which is directly inhaled[29] but are toxic to lungs in similar ways to the mainstream smoke inhaled by active smokers.[30,31] Passive smoking is also a risk factor for heart disease, conferring a significantly increased relative risk of CAD, estimated at 1.26 from studies that controlled for other important risk factors for CAD.[215]

2.3.1.3 Impaired lung development

In recent years, researchers have explored risk factors for COPD beyond personal smoking exposure, and an increased understanding of trajectories of lung development from foetal development to adulthood has revealed the importance of early life factors in the later development of COPD.

Longitudinal studies, including prominent work by Lange et al introduced in section 1.3, show that while some patients develop COPD after attaining normal lung function but then experiencing accelerated lung function decline, an approximately equal number fail to attain normal lung function during lung early life and develop COPD as a result of the normal rate of lung decline that occurs with ageing. These trajectories are shown as TR3 and TR4 in Figure 4. Those that have a baseline FEV1 <80% predicted before 40 years old have a strikingly elevated risk of later COPD (overall prevalence 26%, vs 7% of those with normal FEV1 at baseline[38]). The factors that lead to low FEV1 at early adulthood then become salient: these include genetics (see below), poor nutrition, lung infections and episodes of wheezing in childhood.[216,217]

The link between subnormal lung function in early adulthood and subsequent COPD is relevant because an analogous association has been demonstrated for cardiovascular events, with abnormally low spirometric measures conferring increased risks of heart failure and stroke specifically, independent of traditional cardiovascular risk factors.[218] Later in life, low FEV1 is a strong independent risk factor for heart disease and mortality from cardiovascular causes, with a dose-response relationship seen for increasing levels of impairment, even when this was subclinical, i.e. within 1-2 standard deviations of the population mean (see Figure 11).[219] Furthermore, studies of the population-attributable risks of various cardiovascular risk factors have consistently found reduced FEV1 to confer a similar cardiovascular mortality risk as traditional cardiovascular risk factors such as hypertension and hypercholesterolaemia.[219,220] This evidence points to poor lung development being a powerful shared risk factor for the development of both COPD and heart disease.

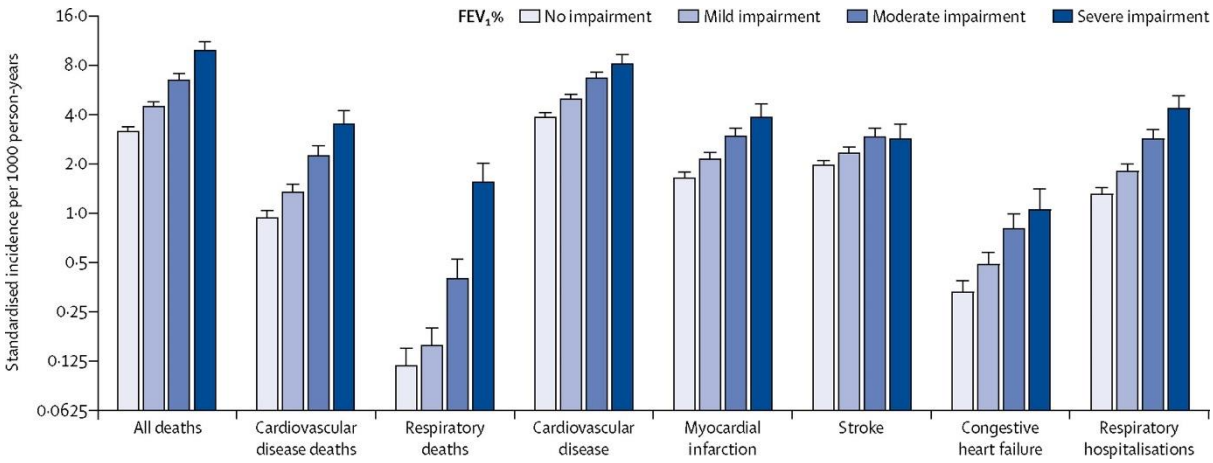


Figure 11: Incidence of all-cause, cardiovascular and respiratory deaths as well as disease incidence, adjusted for age and sex, by country-standardised FEV1% impairment category (mild impairment: FEV1% 0-1 SD below population mean; moderate impairment: FEV1% 1–2 SD below population mean; severe impairment: FEV1% >2 SD below population mean). Reproduced with permission from Duong et al,[219] Copyright © 2019 Elsevier Ltd

2.3.1.4 Low socioeconomic status

Discussions of the factors that lead to development of COPD are incomplete without the acknowledgement of the influence of socioeconomic status on the prevalence of the disease.

Variously defined, but generally stratified according to measures of income, occupation and wealth,[221] socioeconomic status shows a noticeably stronger correlation with the prevalence of spirometrically-defined lung disease than smoking (see Figure 2).

Furthermore, the prevalence of clinically diagnosed COPD, COPD hospitalisation rates and mortality from COPD are all consistently associated with low socioeconomic status.[35,36] However, since "poverty cannot be inhaled and it is not a genetic condition"[39] it is likely that low socioeconomic status functions largely as a surrogate measure of exposure to the causes of poor lung development and accelerated decline already described. Nevertheless, its persistence despite controlling for multiple candidate confounders, including both occupational and domestic air pollution,[36] testifies to the pernicious and complex nature of poverty as a risk factor for disease. It is also a risk factor that is shared between COPD and heart disease[222] and is therefore a prominent candidate for explaining why these two conditions coexist.

Ultimately, the shared risk factors of ageing, inhaled toxin exposure and adverse early life circumstances explain a substantial degree of the association between COPD and heart disease. They provide important pointers towards the pathophysiology of each condition, as well as implying individual and population-based management strategies. However, controlling for these factors does not remove COPD as a powerful independent risk factor for heart disease,[223] therefore there must

be aspects of the disease state that cause or accelerate specific pathophysiological processes leading to the development of heart disease. These aspects are the focus of the following sections.

2.3.2 Genetics

All chronic diseases have a genetic component, with COPD and heart disease being no exceptions.[224] As such, a shared genetic basis for both conditions might explain why they are observed to coexist so frequently.

There is substantial evidence that the risk of developing COPD is heritable. This originated from the observation of an autosomal recessive inheritance pattern for early-onset emphysema, later found to be caused by homozygosity for a deficient allele of the SERPINA1 gene that codes for alpha-1 antitrypsin (AAT). Outside of AAT deficiency, familial clustering of COPD cases has also been observed and has subsequently been demonstrated to be independent of shared socioeconomic status and active and passive smoking exposure.[225] Since the inception of genome-wide association studies (GWAS) at the turn of the millennium the number of genetic loci associated with COPD has rapidly increased into the dozens[226] and includes - in an interesting congruence with the epidemiological evidence for the importance of early life circumstances - a high proportion of genes implicated in developmental pathways.[227]

Heart disease also has a well-established genetic basis, with at least 50 genetic variants linked to CAD. These variants are generally common (mean prevalence 50%), with a small individual effect size (odds ratio 1.02-1.90) – it is the combination of variants inherited that confers meaningful increased individual risk.[228]

As for evidence that a predisposition to both conditions can be inherited through the same genetic variants, a network-based study has highlighted that the proportion of molecules implicated in both COPD and ischaemic heart disease appears high in comparison to that seen with other comorbidities.[229] In particular, polymorphisms affecting proteolytic enzymes and those involved in reducing oxidative stress have been implicated in both atherosclerosis and emphysema.[230] However, while a GWAS found genetic correlations between COPD and *traits* associated with heart disease, such as high resting heart rate and blood pressure, a significant genetic correlation with overt CAD was not seen.[231] Thus, concrete evidence for a shared genetic basis to explain the high prevalence of heart disease in COPD remains elusive.

2.3.3 Inflammation

Airway inflammation is an omnipresent feature of COPD, regardless of aetiology or eventual clinical phenotype.[232] The essential hallmarks of inflammation include aggregation of white cells, secretion of cytokines that augment and differentiate the inflammatory process, activation of protein cascades including those involved in coagulation, complement activation and kinin generation, increased vascular permeability and evidence of oxidative stress.[233] Acutely, these processes provide an essential local defence against pathogenic damage, but, if not appropriately downregulated, may lead to chronic, pathological inflammation which has adverse local and systemic effects.

The airway inflammation observed in patients who have COPD is heterogenous, with a distinction drawn between neutrophil-associated and eosinophil-associated airway inflammation, although patients commonly display features of mixed granulocytic inflammation.[234] Neutrophilic inflammation is most common, and is readily induced by noxious stimuli such as cigarette smoke and infection. The cytokines associated with neutrophilic airway inflammation in COPD are similar to those secreted by senescent cells[235] (termed the senescence-associated secretory phenotype [SASP]), hence the possibility that COPD represents a disease of premature ageing has been persuasively argued – this is summarised in section 1.7.2 in the previous chapter.[236] Eosinophilic airway inflammation is associated with a different cytokine milieu and correlates with blood eosinophil count (BEC).[237] An increased BEC identifies patients at higher risk of higher exacerbation[238] and hospitalisation[239], and who are more likely to benefit from inhaled[240] and oral[241] corticosteroid therapy.

Inflammation in COPD is not confined to the airways: there is abundant evidence for chronic, systemic inflammation in COPD based on serum biomarkers including C-reactive protein (CRP), tumour necrosis factor (TNF) and fibrinogen.[242] Systemic inflammation is an established risk factor for heart disease, as is well recognised in the rheumatological diseases,[243] where cytokine-accelerated atherosclerosis elevates the risk of CAD. A proposed model of the mechanism by which lung inflammation causes vascular disease is shown in Figure 12. Heart failure, particularly the HFpEF subtype, is also associated with systemic inflammation, with elevated CRP, TNF, interleukin (IL)-1 and IL-6 levels seen in these patients.[244] Finally, the elevated risk of AF in patients who have COPD seems to be driven by its occurrence in those with elevated levels of CRP and IL-6.[182] Therefore, a substantial degree of the excess risk for heart disease in COPD may be explained by the increased inflammation seen in these patients.

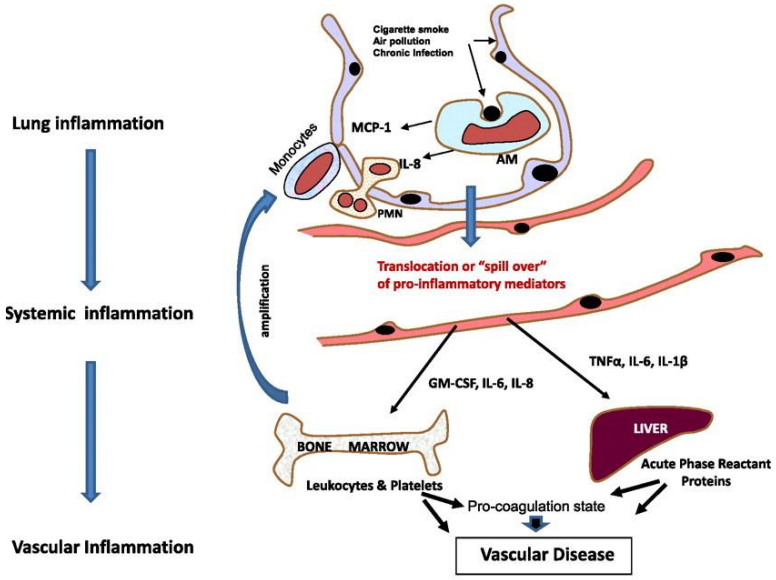


Figure 12: A theoretical model of how lung inflammation contributes to atheroma and thrombosis. AM = alveolar macrophages; MCP-1 = monocyte chemoattractant protein-1; PMN = polymorphonuclear cells; GM-CSF = granulocyte-macrophage colony-stimulating factor. Reproduced with permission from Van Eeden et al.[245]

During ECOPD there is a spike in both lung and systemic inflammation.[246] The magnitude of the inflammatory response has been shown to correlate strongly with the degree of increase in arterial stiffness – a marker of atherosclerosis introduced in section 2.2.2.2 – measured during exacerbation.[247] Exacerbations are instrumental to the harms associated with COPD, and are at the centre of the numerous COPD-relates risk factors that increase the risk of heart disease (see section 2.3.6). Increased systemic inflammation is a prime candidate to explain the increased risk of adverse cardiovascular events observed during ECOPD, via numerous linked processes including endothelial dysfunction, plaque destabilisation and activation of the coagulation cascade (see Figure 13).

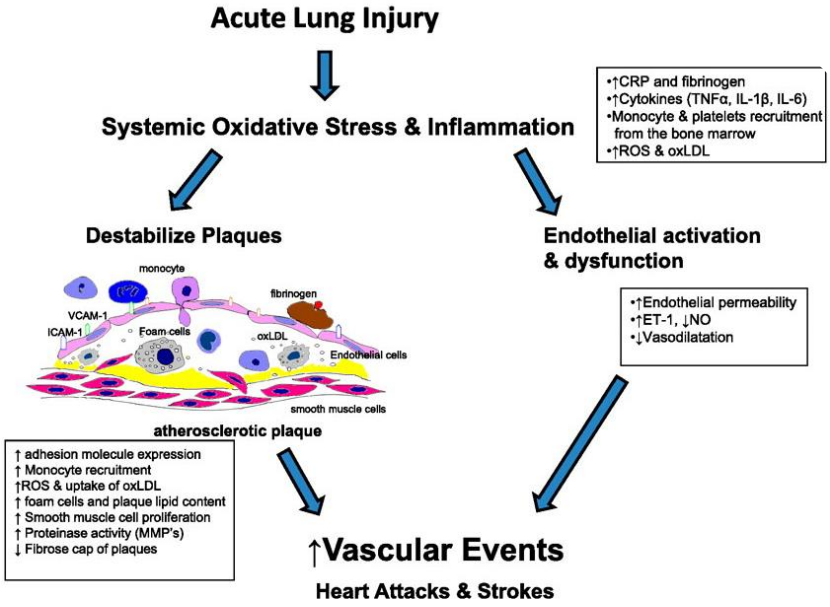


Figure 13: A theoretical model of how acute lung inflammation leads to acute ischemic events. ROS = reactive oxidative species; oxLDL = oxidizing low-density lipoproteins; ET-1 = endothelin-1; NO = nitric oxide; ICAM-1 = intercellular adhesion molecule-1; MMPs = matrix metalloproteinases; VCAM-1 = vascular cell adhesion molecule-1. Reproduced with permission from Van Eeden et al.[245]

2.3.4 Hypoxaemia

Multiple mechanisms predispose patients with COPD to hypoxaemia. Emphysema destroys the pulmonary capillaries, leading to ventilation of non-perfused areas, i.e. increased physiological dead space. Simultaneously, airway inflammation and airflow limitation lead to alveolar hypoventilation and therefore blood is shunted from the pulmonary to systemic circulations without being adequately oxygenated.[248] At night, patients with COPD display accentuated physiological nocturnal hypoventilation, further potentiating the effect of the enlarged dead space on hypoxaemia.[249]

Hypoxaemia in COPD is a spectrum that ranges from mildly subnormal blood oxygen levels, which have minimal physiological effects due to the oxygen-dissociation characteristics of haemoglobin, to levels that cause meaningfully reduced oxygen availability at the tissues, a state that defines *hypoxia*. An important, albeit artificial, cut-off to define severe chronic hypoxaemia is an arterial oxygen partial pressure of 7.3kPa during stable disease, based on the results of randomised controlled trials that demonstrated a survival benefit for long-term oxygen therapy for patients below this cut-off. [250,251]

Hypoxaemia has numerous effects which are relevant in the pathophysiology of heart disease. In hypoxaemic patients with COPD, sympathetic nervous activation increases, as evidenced by significantly elevated circulating catecholamine levels and peripheral sympathetic nerve firing.[252,253] This physiological response to maintain oxygen delivery in the face of hypoxia is associated with

accelerated atherosclerosis, via direct simulation of the haematopoesis of atherogenic monocytes,[254] increased rates of atrial and ventricular arrhythmias[255] and an increase in the symptomatic progression[256] and lethality[257] of heart failure. Sympathetic activity is, of course, potentiated further by the use of beta-adrenoceptor agonists by most patients who have COPD. The major drivers and diverse impacts of sympathetic overactivity on the cardiovascular system are schematised in Figure 14.

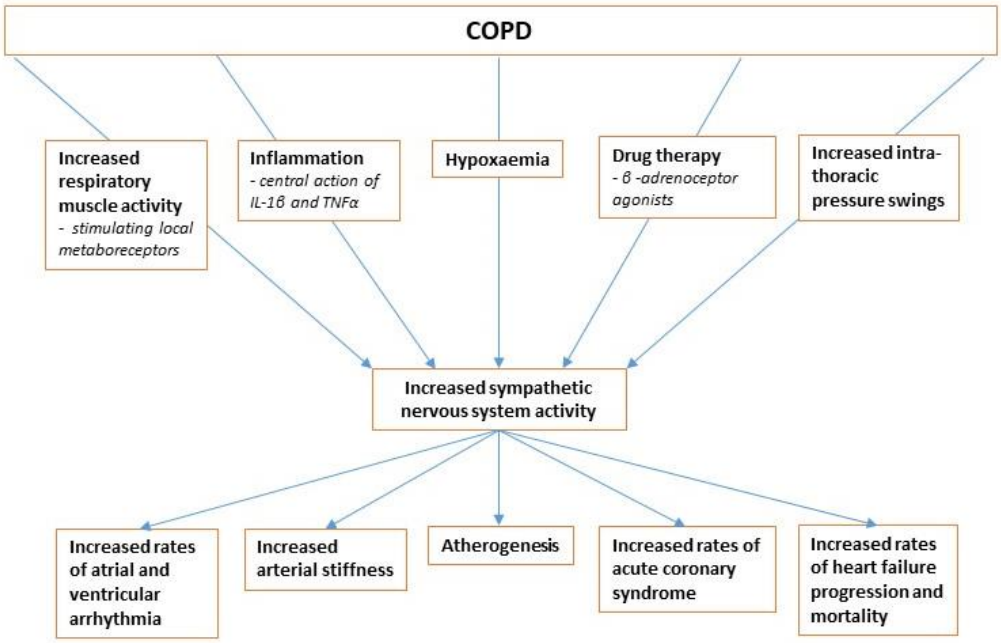


Figure 14: Postulated mechanisms by which COPD contributes to increased sympathetic nervous system activity, and cardiovascular consequences.

Sympathetic stimulation of the renal juxtaglomerular apparatus in response to hypoxaemia leads to activation of the renin-angiotensin system, increasing blood pressure and sodium retention, as well as contributing to hypoxia-induced secondary erythrocytosis.[258] Hypoxaemia promotes platelet aggregation[259] and is correlated with increased arterial stiffness,[260] a reliable predictor of cardiovascular risk. Furthermore, low oxygen levels lead to changes in gene expression that have wide-ranging effects including the upregulation of pro-inflammatory cytokines[261] and, in animal studies, alteration of lipid metabolism towards a more atherogenic profile.[262] Finally, hypoxia within atherosclerotic plaques leads to upregulation of genes that promote evolution of the plaque towards instability, via increased inflammation and angiogenesis.[263]

Hypoxaemia is directly linked to pulmonary hypertension (PH), which results primarily from the unique vasoconstrictory response of the pulmonary arteries to hypoxia, leading to increased

pulmonary artery pressures and vessel remodelling, with additional contributions from inflammatory and thrombotic processes.[264] PH prevalence is correlated with degree of hypoxaemia in patients with COPD, and the resultant pressure-overload of the right ventricle predisposes to right ventricular failure (i.e. cor pulmonale) and death.[265]

Although hypoxaemia is convincingly associated with increased all-cause mortality,[266] there is not compelling evidence linking it to increased prevalence of non-PH-related heart diseases or adverse cardiac outcomes. It remains possible that specific patterns of hypoxaemia relate differently to heart disease, with those who are hypoxaemic at rest having a higher incidence of CAD risk factors such as diabetes, hypertension and obesity than those with exertion-only hypoxaemia.[267]

To conclude, a wealth of evidence links hypoxaemia to pathophysiological processes that increase the risk of heart disease. However, convincing evidence to suggest that hypoxaemia is causative of the increased risk of heart disease amongst patients who have COPD is yet to be produced. Nevertheless, in one of the few longitudinal studies of incident hypoxaemia in COPD, development of severe hypoxaemia (defined as oxygen saturation ≤ 88% breathing ambient air) was independently associated with comorbid heart failure, suggesting that the milder hypoxaemia that precedes clinically significant hypoxaemia may have a significant effect.[268] Additionally, in the same study, the occurrence of at least one severe exacerbation in the preceding year was associated with an adjusted odds ratio of 3.31 (95% CI 1.38–7.90) for incident severe hypoxaemia. The acute hypoxaemia experienced by patients with COPD during exacerbation appears to have unique physiological effects (see section 2.3.6.1) and occurs in the context of other important pathophysiological changes. Therefore acute, exacerbation-related hypoxaemia may be more relevant in explaining the increased risk of heart disease in COPD than chronic, stable hypoxaemia.

2.3.5 Lung hyperinflation

Increased airflow limitation and reduced elastic recoil combine to predispose the lungs of patients with COPD to air trapping, leading to hyperinflation of the lungs and an increased ratio of the residual volume to the total lung capacity (RV/TLC). The reduction in inspiratory capacity that this causes is illustrated in Figure 15.

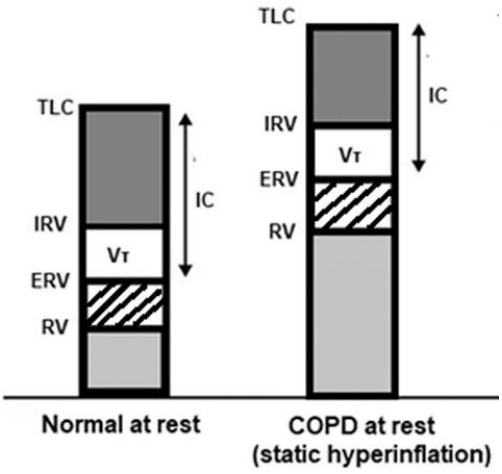


Figure 15: Lung volumes at rest in healthy subjects and those with COPD. Abbreviations: TLC – total lung capacity; IRV – inspiratory reserve volume; ERV – expiratory reserve volume; RV – residual volume; V_T – tidal volume; IC – inspiratory capacity. Reproduced with permission from Kakavis et al.[269]

With more severe airflow obstruction, clinically significant hyperinflation becomes more common, with numerous physiological ramifications, including an increased demand on the respiratory muscles to overcome larger chest wall recoil forces to achieve inspiration, contributing to the sensation of breathlessness. Additionally, hyperinflation increases intrathoracic pressure, which is transferred to the cardiac chambers. The morphological effect of this has long been noted on the plain chest radiograph, which is classically stated to reveal a narrowed cardiac silhouette in patients who have COPD.[270] Echocardiographic studies have subsequently confirmed that patients with COPD who have static lung hyperinflation have smaller cardiac chamber sizes, and have significantly impaired markers of left ventricular diastolic filling.[271] Therapeutic studies show that use of bronchodilators to 'deflate' the lungs leads to an increased left ventricular end diastolic volume,[272] and a clinical trial of endobronchial valve insertion, which aims to reduce hyperinflation, significantly improved several measures of right and left ventricular function.[273]

As such, an association between lung hyperinflation and heart failure with preserved ejection fraction (a condition characterised by impaired cardiac filling) is to be expected. Indeed, COPD appears to be more prevalent in patients with HFpEF than HFrEF.[274] However, magnetic resonance imaging (MRI) and echocardiographic studies have suggested that lung hyperinflation is an aggravating factor when HFpEF occurs in patients who have COPD, rather than an instigating process.[275] [276]

As for coronary artery disease, hyperinflation is a particularly strong predictor of increased coronary artery calcium – more so than FEV1.[277] Although an association rather than a causal link, the hypothesised mechanisms include coronary artery inflammation and atherosclerosis precipitated by a mismatch between increased oxygen demand from a hypertrophied left ventricle and compressed

subendocardial vessels due to increased LV end-diastolic pressure. A further connection is provided by the observation that lung hyperinflation in COPD is associated with increased LV mass[278]; LV hypertrophy is a powerful predictor of cardiac and all-cause mortality in patients with COPD, with a 38% increased mortality risk reported in those with LV mass index above the normal range.[279]

Regarding atrial fibrillation, increased left atrial pressure caused by the compressive effects of hyperinflation has been suggested to contribute to the genesis of AF in COPD,[280] although a direct link between measured hyperinflation and AF risk has not been demonstrated.

An important attribute of lung hyperinflation in COPD is that it is not static. The degree of hyperinflation increases during exertion, when the inspiratory rate increases and the expiratory portion of the respiratory cycle shortens, meaning the individual cannot expire fully before inspiration commences. This shifts the end expiratory lung volume up to a higher point still, compounding the already-present problems of increased respiratory muscle load and increased dead space ventilation (see Figure 16).[281]

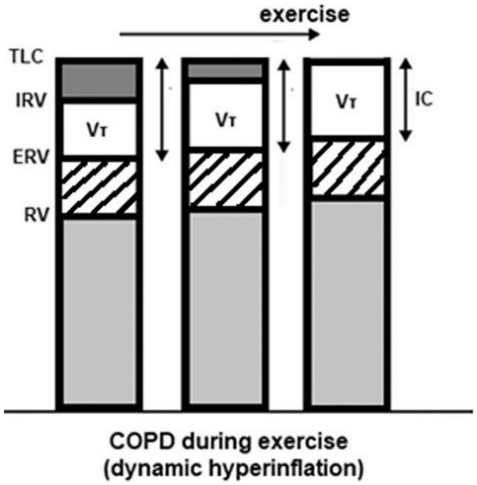


Figure 16: Effect of dynamic hyperinflation on lung volumes in COPD during exercise and exacerbation. Abbreviations as in Figure 15. Kakavis et al; reproduced with permission.[269]

The increased mechanical compression of the cardiac chambers during dynamic inflation impairs diastolic ventricular function even in healthy subjects,[282] In those with COPD, dynamic hyperinflation significantly attenuates the increases in stroke volume, cardiac output and oxygen delivery necessitated during exercise.[283] Indeed, dynamic hyperinflation has been proposed as the major cause of exercise limitation in COPD both during controlled testing and in daily life.[284] Therefore, dynamic hyperinflation may have a causative link to heart disease by consigning patients to an increasingly sedentary lifestyle – this being an independent risk factor for cardiovascular disease and a powerful predictor of all-cause mortality in patients with COPD.[285,286]

Of key importance is that dynamic hyperinflation is also observed during exacerbations of COPD.[287] Its occurrence has specific impacts that predispose to cardiac dysfunction and acute cardiovascular events, as will be detailed in the next subsection.

2.3.6 Exacerbations

Throughout this discussion, a theme has emerged that exacerbations accentuate the inter-related processes of inflammation, hypoxaemia and hyperinflation that contribute to the increased risk from heart disease in COPD. The acute cardiac insult provoked by ECOPD is illustrated by the acute rise in cardiac biomarkers consistently demonstrated in hospital inpatients. Estimates vary but approximately 1 in 2 patients demonstrate elevations of troponin and/or NT-proBNP during ECOPD,[288,289] markedly higher proportions than are seen during stable disease.[290] Raised cardiac biomarkers during ECOPD are important: elevated levels of both biomarkers are independently associated with increased mortality.[291] Furthermore, the prevalence with which they are found to be elevated during ECOPD exceeds that of the conditions they are used, outside of this context, to screen for, namely CAD and heart failure. This points to dynamic processes occurring during exacerbation to cause the release of troponin and NT-proBNP from cardiac myocytes and predispose to adverse cardiovascular events.

2.3.6.1 Hypoxaemia during ECOPD

Firstly, worsening hypoxaemia reduces myocardial oxygen supply, at the same time as demand is increased by hypermetabolic state induced during exacerbation[292]. Tachycardia in this situation may precipitate heart failure, particularly when ventricular filling during diastole is the limiting factor to cardiac output,[293] and may tip the balance in areas of localised myocardial ischaemia into frank infarction.[294] Hypoxia also activates the coagulation cascade in patients with COPD,[295] further heightening the risk of acute cardiovascular events and, in a murine model, induces inflammatory gene expression via the transcription factor NF-κB.[296,297] This connection between hypoxia and inflammation is linked further to acute cardiovascular risk by in vitro experiments that demonstrate that neutrophils exposed to hypoxia secrete more histotoxic proteins and have a greater capacity to damage the vascular endothelium,[298] as well as the increased levels of circulating platelet-monocyte aggregates, key mediators of arterial plaque inflammation and thrombosis, during hospitalisation for ECOPD.[299]

2.3.6.2 Inflammation during ECOPD

The heighted systemic inflammation that affects the heart at the time of exacerbation is caused predominantly other factors besides hypoxia: elevated troponin demonstrated during ECOPD has been attributed to infection (measured by CRP and leukocyte count) rather than hypoxaemia, which was unrelated to troponin level.[300] A wealth of evidence demonstrates that infection can be a precipitant of acute cardiovascular events, primarily through plaque inflammation and disruption.[301] Particularly high risks of early myocardial infarction are found for severe infections of the respiratory tract: hospitalised bacteraemic patients with respiratory infection have a substantially higher risk of 30-day myocardial infarction compared to matched population controls (relative risk (RR) 32, 95% CI 9 – 117).[302] Very large scale UK Biobank data confirms this, and additionally shows that, compared with hospitalisation for infections other than pneumonia, risks for MI are highest with respiratory infection (see Figure 17).[303]

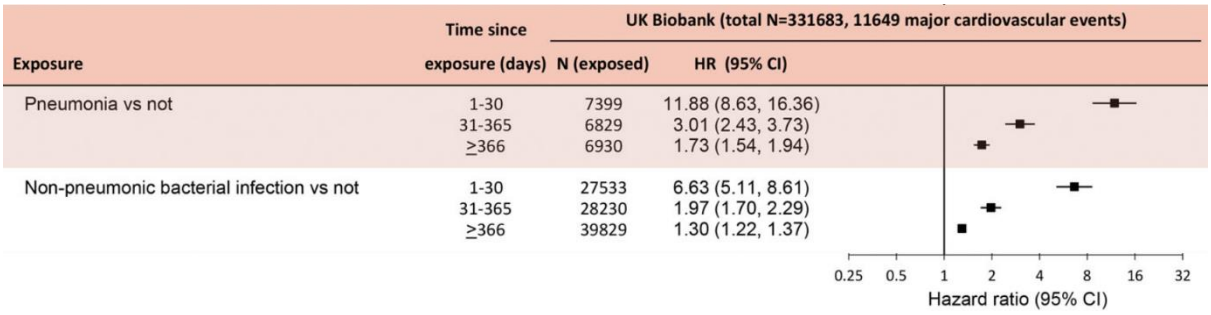


Figure 17: Risk of major cardiovascular event associated with hospital-treated bacterial infections by time since infection in the UK Biobank cohort. Hazard ratios (HRs) adjusted for age, sex, socioeconomic status, smoking, alcohol consumption, hypertension, diabetes, low-density lipoprotein cholesterol, BMI, physical activity, chronic liver disease, chronic kidney disease, COPD, and asthma. Adapted from Sipila et al[303], © 2023 The Authors.

This suggests an especially cardiotoxic aspect to respiratory infection, with hypoxia being a potential candidate for this risk. An interesting aspect to post-infection MI is that it appears to have unique characteristics when compared with MI occurring outside the context of recent infection, with patients more commonly tachycardic and manifesting simultaneous acute heart failure, and having classical chest pain and very marked troponin elevation less often.[304] This atypical mode of presentation increases the likelihood of underdiagnosis unless a high index of suspicion for cardiac damage is maintained by clinicians caring for patients with respiratory infection.

2.3.6.3 Dynamic hyperinflation during ECOPD

Cardiac risk during ECOPD is compounded further by the occurrence of dynamic hyperinflation, described in section 2.3.5. Bronchoconstriction and airway luminal narrowing by sputum and inflammatory exudate increase expiratory flow limitation at the same time as increased respiratory drive – induced by hypoxia, hypercapnoea, ventilation-perfusion mismatch and anxiety – reduces the time permitted for expiration to return lung volume to its previous end-expiratory level.[287] This process creates a positive feedback loop, with significant hyperinflation demonstrated even in moderate-severity exacerbations.[305] Given the above-described negative effects of hyperinflation on heart function, an acute worsening of this effect during ECOPD emerges as a candidate to explain the increased risk of acute cardiac events, such as MI, during this period. Indeed, longitudinal measurement of lung volumes suggests that exacerbation-driven dynamic hyperinflation takes around 2 weeks to resolve,[305] corresponding closely to the period of significantly increased risk for MI (see Figure 18).[155] Data correlating echocardiographic markers of heart failure and hyperinflation during and outside the exacerbation period in the same patient have not been published, but would help to clarify the strength of this link.

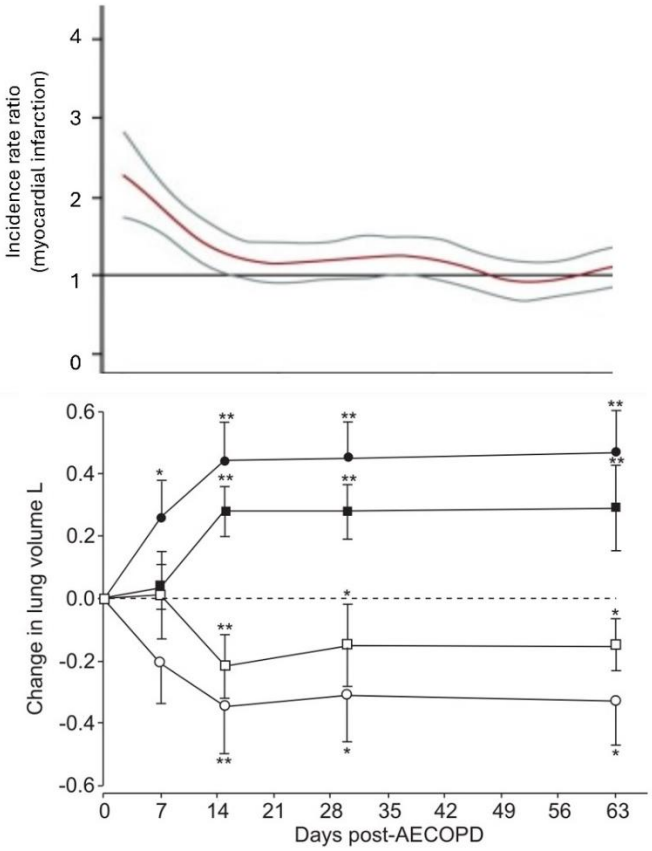


Figure 18: Co-occurrence of return to baseline for incidence rate ratio of myocardial infarction and lung volumes following onset of moderate COPD exacerbation. •: slow vital capacity; ▪: inspiratory capacity; □: functional residual capacity; ○: residual volume. Adapted from: Rothnie, et al[155] (Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved.) and Parker, et al. (Reproduced with permission)[305]

2.3.6.4 Sympathetic overactivity

A final important characteristic of the exacerbation period is derangement of the autonomic nervous system, specifically sympathetic overactivity. This phenomenon has been observed in patients with *stable* COPD, in studies assessing skeletal muscle innervation,[306] heart rate variability,[307] circulating catecholamine levels[308] and the direct effect of COPD on catecholamine handling at the left ventricular myocardium.[309] Sympathetic overactivity is an important element in almost all cardiovascular system disorders, from predisposing conditions such as hypertension and diabetes[310] to outcome following MI.[311] The development, progression and treatment of heart failure are all rooted in neurohormonal processes, with the sympathetic nervous system at the epicentre.[312] During exacerbation, sympathetic activity increases, both in order to compensate for reduced tissue oxygen supply and as a direct result of bronchodilating medications administered as treatment. Observational data suggests that the need for hospital admission for ECOPD is correlated with increased autonomic derangement,[313] which is congruent with the heightened increased risk for adverse cardiac events in patients with severe rather than moderate ECOPD.

In conclusion, critical factors that link the presence of COPD to the presence of heart disease – hypoxaemia, inflammation, lung hyperinflation and autonomic derangement – have been demonstrated to be intensified during the exacerbation period, with a corresponding increased risk for cardiac events, particularly coronary artery thrombosis and decompensated heart failure. This establishes the exacerbation period as an opportune moment for intervention to reduce the excessive morbidity and mortality caused by heart disease in this population.

In the remainder of this section, further additional factors that may increase the burden of heart disease are discussed, including long-term COPD treatment and the effect of other comorbidities.

2.3.7 Treatment of COPD

As well as being used in high doses during exacerbations, with potentially cardiotoxic side effects (see section 2.3.6.4), inhaled bronchodilators are a cornerstone of long-term COPD management. The mechanisms of action of the major classes – beta-adrenoceptor agonism and muscarinic acetylcholine receptor antagonism – imply potentially significant cardiac side effects. Accordingly, the detection of these has been an important outcome of randomised controlled trials of such drugs,[314,315] with large long-term studies concluding that an increased risk for cardiac side effects is not present with these drug classes.[316,317] Indeed, subsequent randomised controlled trial evidence has suggested that, due to favourable effects on exacerbation rates, inhaled bronchodilators may in fact reduce cardiac morbidity.[318,319]

This positive framing of the cardiac effects of inhaled bronchodilator therapy has been countered, however, by the observation that these studies generally excluded participants with significant comorbidities and with recent history of cardiac events, produced very low event rates that could not be distinguished statistically, and additionally involved a large proportion of patients to whom these drug classes were not novel, potentially masking the presence of adverse cardiac effects occurring on initiation of such drugs.[320] Observational studies on more representative populations have reported increased cardiovascular risk,[321,322] but such studies acknowledge the potential for biased effect estimates due to unmeasured confounding. The effect of new prescription of bronchodilators has been examined specifically and returned results suggesting there is a heightened risk of myocardial infarction, stroke and arrhythmia in the first weeks after starting these drugs.[320,323] However, two possible sources of bias remain in these studies. The first is that, although cases and controls were matched for COPD severity, unmeasured increased COPD severity may have been present in the group newly-prescribed bronchodilators (and indeed may have prompted these prescriptions). There may then have been a lag period of increased risk, correlating with COPD severity rather than caused by bronchodilator use, until this risk was reduced by the relatively reduced exacerbation frequency in this more intensely treated group. Secondly, protopathic bias may have been present: this phenomenon involves the prescription of medication for a condition that is as-yet diagnosed, causing it to be apparently causative of the disease (see Figure 19).[324] It is highly plausible here, as worsening respiratory symptoms, prompting bronchodilator escalation, may well have been caused by undiagnosed (and hence unmatched) angina or heart failure, which became manifest afterwards.

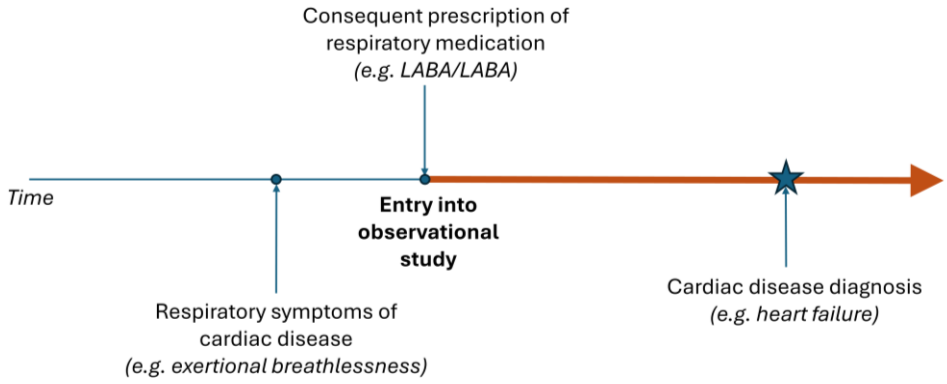


Figure 19: illustration of the mechanism of protopathic bias. In this individual case, unrecognised heart failure results in worsening breathlessness in a patient with COPD, leading to the prescription of a LABA/LAMA inhaler; the recognition of the co-existing heart failure occurs subsequently. If this occurs systematically throughout a cohort, protopathic bias may result. Based on the schema published by Suissa and Dell'Aniello.[325]

In summary, while undoubtedly influential to some degree on cardiac function, and plausibly causative of some adverse cardiac events within the COPD population, the consensus is that

appropriately-used bronchodilator therapy has a net beneficial effect on cardiovascular event rates,[20] and that this aspect of treatment does not provide a major contribution to the excessive rates of heart disease for patients with COPD. However, not all patients will be at equal risk, and if the signal for increased side effects at initiation of treatment is indeed real, enhanced vigilance during this period for higher-risk patients is prudent.

Alongside bronchodilators, inhaled corticosteroids are the most commonly prescribed long-term medications for COPD, with audit data finding they are prescribed in a higher proportion of patients than expected from guideline recommendations.[326,327] Inhaled corticosteroids are absorbed systemically, with their pharmacokinetic profiles and effects on endogenously cortisol secretion varying significantly for different molecules[328] and delivery devices.[329] Corticosteroids have side effects directly linked to cardiovascular disease, such as hyperglycaemia, hypertension and fluid retention, however these do not appear to occur at the levels of exposure produced by inhalation.[330] Corticosteroids also exert effects that, while not traditional cardiovascular risk factors, predispose to sedentary behaviour and physical inactivity, such as osteoporosis and muscle weakness. This may explain the increased risk of events such as myocardial infarction and stroke,[331] as well as atrial fibrillation,[332] reported with low dose oral corticosteroid use. However, randomised controlled evidence of the effect of inhaled corticosteroids in COPD specifically have not shown evidence of an effect on cardiovascular endpoints, with some observational studies in fact concluding that their use *reduces* cardiovascular mortality.[333]

It is likely, therefore, that appropriate use of inhaled corticosteroids does not contribute to the excess risk of heart disease for patients with COPD. Indeed, optimal matching of agent to patient may be unequivocally beneficial for cardiovascular outcomes.[334] Use in non-exacerbating patients, and those with a less steroid-responsive inflammatory endotype,[335] may however be indirectly causative of some cardiac events, given the excess risk of pneumonia demonstrated with these agents – in particular, one systematic review concludes, fluticasone[336] – and the association of respiratory infections with contemporaneous myocardial infarction.

Other therapies used in COPD have recognised cardiovascular effects that may contribute further to overall risk. These include theophylline, a xanthine with effects that include adenosine antagonism and, consequently, an increased risk of tachycardia and arrhythmia.[337] Accompanying evidence of adverse cardiac events was not found, however, in a systematic review of randomised controlled trials[338]. It seems probable that, although undoubtedly cardiotoxic in overdose, theophylline is not a meaningful contributor to population-level cardiac risk in COPD, particularly given it is currently prescribed comparatively rarely.[339] Patients with recurrent infective exacerbations may be prescribed prophylactic macrolide antibiotics, most commonly azithromycin, which is associated with QT-interval prolongation and sudden cardiovascular death.[340] Nevertheless, modelling suggests

azithromycin need only confer a small benefit in terms of exacerbation reduction, of the order of 5%, to be of overall benefit to patients.[341]

In conclusion, it does not seem plausible that the excess risks of heart disease and cardiac mortality in patients who have COPD can be substantively explained by their use of COPD medications. Nevertheless, the totality of evidence suggests two key points: firstly, none of the major therapies are free from cardiac risk; secondly, exacerbation reduction may be the major route by which COPD therapy can exert a benefit on cardiac outcomes. Therefore, minimising risk involves ensuring that overtreatment is avoided and that careful risk-benefit assessments are carried out in those at excess risk of adverse effects. The corollary to this final point is, of course, that the true risk to individuals is often obscured by underdiagnosis of cardiac comorbidity; this is a focus of Chapter 3.

2.3.8 Effects via other comorbidities

As discussed in section 1.7, multiple chronic conditions coexist at elevated rates with COPD, and have been recognised to interact in multimorbidity networks.[342] Many of these conditions act synergistically with COPD and each other to increase heart disease risk. For example, the presence of musculoskeletal dysfunction contributes to reduced activity levels and an increased sedentary time, which has a significant dose-response relationship with cardiovascular disease and mortality.[343] Additionally, psychiatric and cognitive conditions are also highly impactful on cardiovascular health; for example, depression has been associated with a doubled risk of coronary artery disease[344] and a higher mortality after MI – the latter holds even for subclinical depressive symptomatology.[345] Anxiety has been associated with an increased incidence of CAD,[346] with an estimated hazard ratio of 1.26 (1.15 – 1.38). Lastly, where obstructive sleep apnoea (OSA) coexists with COPD, there is an additive effect on the development of heart disease: particularly heart failure and coronary artery disease[347,348]. Outside of OSA, a wealth of evidence links poor sleep quality to heart disease and cardiovascular mortality, with suggested mechanisms including increased inflammation and sympathetic overactivity.[349]

It is clear to see how the existence of any of the above conditions alongside COPD can lead to the development or worsening of dysfunction in another system. For instance, reduced activity levels due to muscle dysfunction may lead to increased social isolation and worsening of depression, while sleep dysfunction has a bidirectional relationship with both anxiety and depression.[350] More broadly, the importance of low socioeconomic status was discussed is section 2.3.1 as a shared risk factor for both COPD and heart disease, and, although it is not a comorbidity in a strict sense, it interacts with many of the above mentioned comorbidities. For example, the socioeconomic status of patients with COPD has been found to be inversely related to participation in exercise

rehabilitation programs,[351] which have been robustly shown to have a positive impact on anxiety and depression as well as markers of physical activity.[352] Importantly, social determinants of outcomes in COPD, and health generally, run deeper than those measured by conventional indices of socioeconomic status such as the index of multiple deprivation, with social support networks positively impacting mental wellbeing and self-care behaviour.[353]

In summary, patients who have COPD commonly exhibit dysfunction in multiple organ systems. The interacting effects of musculoskeletal, psychiatric and sleep dysfunction are particularly important in contributing to the increased risk for heart disease in the population, although co-occuring dysfunction in virtually every organ system may potentiate cardiac risk through direct effects on cardiac function, treatment side effects and negatively impacts on activity levels and psychiatric wellbeing. Importantly, the impact of diagnosis and treatment of heart disease for patients in the SCATECOPD study discussed in this thesis is likely to be affected by individual multimorbidity profiles – as has been recognised in cardiovascular care more generally[354] – as well as their individual social factors and support networks.

2.3.9 Section conclusion

In this section, the evidence for the causes of the association between COPD and heart disease has been explored. Key reasons why patients who have COPD suffer from an excess of heart disease morbidity and mortality include shared risk factors, increased systemic inflammation, the diverse effects of hypoxaemia and the direct impact of lung hyperinflation on the heart. During a COPD exacerbation, inflammation, hypoxaemia and hyperinflation are all magnified, making this period especially hazardous to the heart. Inappropriate use of COPD medications may directly and indirectly increase cardiac risk. The framework of multimorbidity provides an important perspective on the relationship between COPD and heart disease, since many other commonly co-occurring conditions are themselves associated with adverse cardiovascular outcomes. It is essential for clinicians to understand the disease profiles of their patients with as much accuracy as possible in order to provide effective integrated care. In the next section, the manner in which this is challenging with regard to heart disease and COPD specifically is explored.

2.4 Diagnostic challenges

This section details the major challenges to accurate diagnosis of heart disease for patients who have COPD, along with the ways that the design of the structured cardiac assessment trialled in the SCATECOPD study accommodates and may overcome these.

2.4.1 Overlapping clinical manifestations

The most basic challenge in recognising heart disease in a patient with COPD is that they cause similar symptoms, eliminating the motivation to seek further diagnostic explanation.

Cardinal symptoms of both COPD and heart disease are breathlessness, chest tightness and progressive limitation of exercise capacity. It is taught that the nature of these symptoms, and the existence or absence of certain other symptoms and signs, helps to establish whether these cardinal symptoms are caused by COPD, heart failure, their combination, or alternative pathology. For example, the presence of orthopnoea or paroxysmal nocturnal dyspnoea in a patient with an established diagnosis of COPD suggests concurrent heart failure. However, respectively, only one third and one fifth of older patients with heart failure report these symptoms,[(355)] rendering their absence insufficient as a reason to forego further investigation for heart failure. Clinical guidelines additionally advocate establishing the presence of physical signs such as oedema in order to decide which patients might need an echocardiogram.[(191)] Once again, though, only 45% of those with a left ventricular ejection fraction below 40% have the signs and symptoms necessary to establish a clinical diagnosis of heart failure,[(356)] despite this sub-clinical group having an estimated hazard ratio for death that substantially overlaps with that for symptomatic systolic heart failure.[(357)] Overall, only a third of heart failure diagnoses based on symptoms, signs and chest radiography were shown to be correct in a cohort of patients subsequently subjected to more detailed investigation, including echocardiography.[(358)] These findings serve to highlight the difficulty in separating the causes of common symptoms without the use of objective diagnostic information, which translates into substantial rates of under-diagnosis of heart failure in the COPD population.[(149)]

Comparable diagnostic difficulties have been documented when coronary artery disease and COPD coexist. Chest pain is highlighted as a useful indicator that myocardial ischaemia may be coexisting with airflow limitation,[(359)] however 18-38% of patients who have COPD report this symptom[(360)] and, in a small study, the presence of COPD significantly reduced the positive predictive value of stable angina symptoms for significant coronary artery disease.[(361)] Conversely, COPD appears to increase the likelihood that patients will present atypically with acute coronary syndromes[(362)] and, in the stable state, the presence of airflow obstruction doubles the chances of asymptomatic coronary artery obstruction, which is significantly more severe when present in such patients.[(363)] As such, conventional reliance on symptoms cannot be expected to accurately identify those patients that may need further investigation or treatment for coronary artery disease;

The major diagnostic challenge relating to the diagnosis of atrial fibrillation in patient who have COPD is the natural history of the disease, which tends to begin with shorter paroxysms of AF that may be asymptomatic. In many patients there is progress to longer, more clinically detectable, and

potentially permanent AF, although in a 7-year pacemaker study the majority of patients remained in a paroxysmal state.[364] Paroxysmal AF, while commonly causative of palpitations, appears to be much less likely to be associated with dyspnoea than permanent AF,[365] therefore it is unlikely that AF is underdiagnosed due to symptom overlap with COPD.

A rigorous demonstration of the shortcomings of clinical history and examination to detect heart disease in patients with COPD was provided by the comparison of the yield of clinical diagnosis with rigorous evaluation by dynamic cardiac CT in patients admitted with ECOPD conducted by Leong, et al.[366] As displayed in Figure 20, the yield of clinical assessment was 61% for severe CAD, 33% for HFrEF and 33% for significantly imparied RV systolic function. It can inferred that for milder forms of these conditions clinical assessment will be even less sensitive.

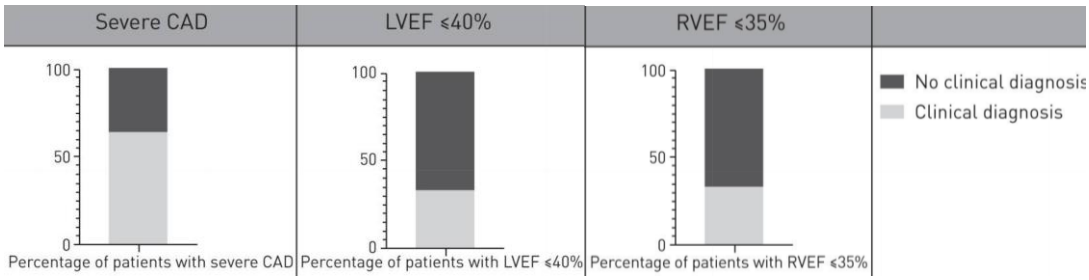


Figure 20: Dark grey portion of the bars represent the additional yield of dynamic CT investigation over clinical assessment, based on history and examination and shown in light grey. Reproduced with permission © ERS 2025: ERJ Open Research, 8;7(1):00756-2020. Published: Feb 2021.DOI: 10.1183/23120541.00756-2020

2.4.2 Technical challenges to diagnosis

2.4.2.1 Tests for heart failure

A major barrier to accurate diagnosis of heart failure in patients who have COPD is the technical difficulty of performing echocardiography. Reasons include poor conduction of acoustic waves through emphysematous lung, as well as changes in cardiac alignment with hyperinflation.[367] In inpatients, tachycardia and tachypnoea complicate measurement further, as can the effect of positive-pressure non-invasive ventilation on assessment of chamber volumes and functional parameters.[368] Patients are commonly frail, with limited mobility and discomfort lying flat, limiting the scope of views further. Despite these recognised limitations, it is unclear to what extent this quantitatively reduces the yield of echocardiography in the COPD population. In one retrospective study of lung transplant candidates with a mean FEV1 of 23% predicted, fewer than half of patients with COPD had a 'satisfactory' examination, compared with 90% of those with idiopathic pulmonary fibrosis.[369] However, in another study of stable patients in primary care, 10.4% studies were of 'poor' quality, with only one of 405 studies being too poor for LVEF to be estimated. This discrepancy

could be taken to demonstrate that greater disease severity and acute exacerbation make echocardiographic assessment more difficult. Alternatively, since the former study was a retrospective record review and the latter a prospective study, it could indicate that a degree of pessimism about the ability to obtain measurements in this cohort has been prevalent. Although controversial, the existence of such an attitude has been suggested by clinicians' disproportionately negative prognostic assessments of the sickest patients admitted with acute exacerbations.[370]

A second important diagnostic tool in the assessment for heart failure, serum natriuretic peptide measurement, is also affected by the presence of COPD. Although not reliably and significantly increased by the presence of COPD in stable patients, levels of NT-proBNP are consistently raised during COPD exacerbation.[288] Reported positive and negative predictive values of NT-proBNP for the presence of heart failure in COPD vary significantly, due to the use of different thresholds and different study populations. The thresholds reported to yield high negative predictive values are often far above those used in the general population – for example, a negative predictive value for LVSD of 0.98 with NT-proBNP >935 pg/ml during exacerbation.[371] This cut-off provides a positive predictive value of only 0.47 and an overall accuracy far lower than that seen in the acute setting in the general population.[372]

2.4.2.2 Tests for coronary artery disease and atrial fibrillation

There are fewer technical issues present with the use of diagnostic tests relating to coronary artery disease and atrial fibrillation. Nevertheless, the use of the ECG as a screening tool for the presence of concomitant cardiac ischaemia, as recommended by NICE,[12] appears flawed, because despite the higher risk of disease, patients with stable COPD are not more likely than controls to have detectable ECG changes consistent with myocardial ischaemia.[373] On the other hand, examination of ECG recordings from the day of admission with ECOPD revealed a high rate of ischaemia-associated abnormalities, with the majority of these patients having no diagnosed myocardial infarction.[374] This may reflect cases of myocardial infarction with non-obstructive coronary arteries (MINOCA), with which co-existent COPD is associated with excess future adverse events.[375] Similarly, troponin testing as a screening test for CAD is also inaccurate: the mean proportion of patients with elevated levels at admission for ECOPD in a 2013 review was 46%,[289] indicating insufficient specificity for underlying CAD, due to troponin release due to processes other than atheromatous coronary artery occlusion (see section 2.3.6).

If patients do progress to further investigations for CAD, stress echocardiography poses the same potential challenges as discussed for the diagnosis of heart failure, and invasive coronary angiography appears to carry a slightly higher risk of serious complications, as might be expected in

this frailer cohort.[376] CT investigation of the coronary arteries, by contrast, appears to present no specific issues; a small study has even suggested that assessment of coronary artery calcium by a standard un-gated chest protocol may be accurate.[377]

In summary, just as clinical signs and symptoms may have less accuracy to diagnose heart disease in patients who have COPD, certain diagnostic tests appear to be less precise in the population. Therefore, there is limited rationale for relying upon signs, symptoms and basic investigations to identify a subgroup of patients who should have more detailed investigations, particularly in those patients hospitalised for ECOPD, who are likely to have an especially high burden of undiagnosed heart disease, and to be at especially high risk for adverse events if this is under-treated.

Instead, in these patients, widespread application of the most accurate diagnostic tests appears justified; the SCATECOPD study presented in subsequent chapters of this thesis was designed to test this hypothesis.

2.4.3 Healthcare engagement

A pre-requisite for the adequate diagnosis of heart disease is that the patient who has heart disease receives a suitable assessment. However, within this simple statement resides one of the major barriers to successful management of heart disease in patients who have COPD: suboptimal engagement with healthcare services.

COPD is not obviously a condition associated with poor healthcare engagement: it is known to be extremely burdensome in terms of healthcare utilisation and costs, and reduced healthcare use is seen as a positive outcome from interventional studies. However, the critical factor is the quality and efficacy of this healthcare use, which is related to the concept of 'health literacy'. This extends beyond reading ability to encompass the capacity to understand and act on health information, and to know which health services to use and when.[378] A consistently high prevalence of low health literacy is found among patients who have COPD[379,380]; multimorbidity appears to increase this prevalence further.[381] Low health literacy is linked to an increased use of emergency healthcare services such as emergency departments[382] over preventative services.[383] The association of low health literacy with COPD is likely to substantially increase the chances of heart disease going underdiagnosed, since the primary role of emergency services is to address life-threatening problems based on known information, rather than seek to make new diagnoses, which is a key role of screening and chronic disease management services. The link between COPD and low health literacy may be that low health literacy leads to increased smoking rates, due to poor understanding of its risks and poor access to cessation services, although this association is found inconsistently in cross-sectional studies[384,385]. Likely to be a more important is that COPD and health literacy have the

shared risk factor of poverty – those with the lowest income had twice the frequency of inadequate healthcare literacy in a Turkish cross-sectional study.

Associated psychiatric and psychological problems further impede effective healthcare engagement for patients who have COPD. Depression and anxiety reduce patients' desire to seek explanations for worsening symptoms due to feelings of hopelessness and avoidance of difficult conversations,[386] or even the outside world generally.[387] Practical difficulties with access are also cited as a barrier to healthcare engagement, as are perceptions of stigma due to the prevalent view that COPD is a 'self-inflicted' condition.[388]

A final compounding factor may be the attitude of healthcare professionals. Primary care physicians and nurse practitioners have been found to be excessively pessimistic about the benefits of COPD treatment, with the majority disclosing that they believe that COPD medications do nothing to improve symptoms or reduce exacerbation frequency, despite extensive evidence to the contrary.[389] As such, clinicians may not see the value in trying to further explain patients' symptoms by performing further assessments such as objective tests for heart disease.

The discussed factors highlight the many obstacles that exist to the appropriate assessment of the patient who has COPD and co-existent heart disease. A structured assessment for heart disease at time of exacerbation for all patients, irrespective of presenting symptoms and signs, is a method to overcome many of these, including reduced engagement with preventative services for access, health literacy, psychological reasons, and physician pessimism – since the assessment is offered to all patients during admission.

2.5 Treating heart disease in patients who have COPD

Diagnosis of heart disease is not sufficient to improve outcome - effective treatment needs to be started. This section is concerned with special considerations for the use of key therapies for heart disease in patients who have COPD. A summary of the observational and interventional evidence relating to the most important medications, along with evidence for their underuse in patients with COPD, is contained in Table 4. Importantly, the evidence presented here is from studies which included COPD patients with and without known CVD (and hence specific indications for treatment)

Medication	Observational evidence of benefit/safety in COPD*	Results of interventional trials in COPD*	Evidence of under-prescription in COPD+CVD

Beta-blockers	Decreased FEV1 with non-selective agents (mean change -140ml with propranolol)[390] HR for ECOPD 0.78 (95% CI 0.74 – 0.82)[390]	No effect on exacerbation frequency, severe ECOPD HR 1.91 (95% CI 1.29 - 2.83) with metoprolol[391] No effect on exacerbation frequency, no increased adverse events with bisoprolol[392]	OR for use in COPD+HF vs HF 0.54 (95% CI 0.51-0.58)[393] COPD patients 65% more likely to be discharged without beta-blocker post-MI[394]
Antiplatelets	OR for mortality 0.81 (95% CI 0.75-0.88)[395] IRR for ECOPD 0.78 (95% CI, 0.65-0.94) with aspirin [396]	No effect on lung function or symptoms[397]	OR for non-use in COPD+MI vs MI 1.24 (95% CI 1.16-1.32)
Statins	HR for mortality 0.69 (95% CI 0.58 – 0.84)[398] OR for exacerbation 0.67 (95% CI 0.48 – 0.92)[399]	No effect on ECOPD rate or time to first ECOPD[400]	OR for non-use in COPD+MI vs MI 1.50 (95% CI 1.41-1.59)
ACE-inhibitors/ ARB	OR for 90-day post-exacerbation mortality 0.55 (95% CI 0.46 – 0.66)	No effect on muscle strength or exercise performance with fosinipril[401] No effect on progression of emphysema[402]	OR for use in COPD+MI vs MI 0.83 (95% CI 0.73 – 0.93)
SGLT2-inhibitors	HR for severe exacerbation 0.62 (95% CI 0.48 – 0.81)[403]	None conducted	None available

*Table 4: Summary of evidence relating to use of cardiovascular medications in patients with COPD. *Outcome ratios are for adjusted comparison of use of the agent with non-use. All results presented numerically are statistically significant with p<0.05.*

2.5.1 Beta-blockers

Of all the medications used in the treatment of heart disease, there has historically been the most apprehension in patients with COPD about the use of beta-blockers. These drugs are more precisely described as inverse agonists at the beta-adrenoceptors, reducing their constitutive adenylyl cyclase activity. At the myocardial beta-1-adrenoceptor, this results in reduced heart rate, contractility and oxygen consumption, which is useful for the treatment of ischaemic heart disease and heart failure. Activity at the beta-2-adrenoceptor, however, results in bronchial smooth muscle contraction which leads to concerns that these drugs may compound airflow obstruction. Evidence to support these concerns came mostly from case reports, although some experimental evidence has been published. [404] [405] Consequently, attention has been given to the degree to which certain agents act preferentially at the beta-1 receptors and not at the beta-2 receptors; this is referred to as *cardioselectivity*. Beta-blockers traditionally classified as cardioselective include bisoprolol, metoprolol and atenolol. However, some of these agents are not as selective for the beta-1-

adrenoceptor as commonly believed: metoprolol for example had a beta-1:beta-2 selectivity ratio of only 2.3 in a whole cell study.[406] This may explain why, along with propranolol, a known non-selective agent, it has been shown to increase airway hyperresponsiveness.[407] Notwithstanding these isolated findings, subsequent meta-analysis has demonstrated conclusively that there is no significant effect of agents considered to be cardioselective on respiratory function or the incidence of COPD exacerbation.[408,409]

Moreover, observational evidence has suggested that beta-blocker use in patients with COPD is more than simply safe: it confers a significant benefit in terms of mortality, admissions and exacerbations[410] This effect appeared to be independent of a history of cardiovascular disease,[411] which catalysed prospective studies of the use of beta-blockers as an intervention to improve outcomes for the general COPD population. However, the BLOCK-COPD randomised controlled trial (RCT), investigating the effect of metoprolol on exacerbation frequency in patients with moderate to severe airflow obstruction and no cardiac indication for beta-blocker therapy, was terminated early due to a *higher* frequency of severe exacerbations in treated patients.[412] A subsequent RCT, BICS, anticipated more favourable results through the utilisation of bisoprolol, a more cardioselective agent, again in patients with COPD who did not otherwise have an indication for beta-blocker use. While there was indeed no difference in adverse event rates between the bisoprolol and placebo arms, there was also no difference in the primary outcome of COPD exacerbation rates between the arms.[392] Notably, however, only a third of the planned recruitment target was achieved due to the impact of the COVID-19 pandemic.

Despite trial exploration of the use of beta-blockers as an active therapy for COPD, real-world data suggests that the historical concerns over their use continue to limit their prescription for recognised cardiovascular indications in this population. For example, in a Swedish registry study, comorbid COPD increased the chances of being discharged without a beta-blocker after MI by 65%.[413] In a UK study of patients with heart failure, the prescribing of beta blockers was roughly 50% lower when patients also had COPD[414].

Overall, beta-blockers have been found to be safe and effective for use in patients who have COPD and a cardiac indication. However, when they are needed, they are underused, exposing patients to an unnecessary increased risk for heart disease-related morbidity, hospitalisation and mortality. There is not yet evidence to suggest that beta-blocker use should be expanded to patients with COPD but no diagnosis of ischaemic heart disease or heart failure. Given the known rates of both known and undiagnosed heart disease in COPD, it is likely that benefits seen in retrospective studies relate to effects seen in this subgroup of patients. The design of the SCATECOPD study is informed by this rationale, as it focuses on addressing the underdiagnosis of indications for beta-blocker use in

patients admitted with a COPD exacerbation, and maximising the use of these agents where their benefits are known to exist.

2.5.2 Antiplatelets

The primary role of platelets is to mediate thrombosis, although their involvement in the action of the innate and adaptive immune systems is increasingly recognised.[415] Although their biogenesis begins in the bone marrow, it has been shown that the lung is a - perhaps *the* - major site of platelet release from megakaryocytes[416]; remarkable video evidence for this now exists[417]. COPD predisposes to thrombocytosis, and those with evidence of thrombocytosis have been found to have higher mortality rates.[418,419] The use of aspirin by patients with COPD is reliably associated with reduced all-cause mortality, independent of the presence of ischaemic heart disease,[420] as well as reduced exacerbations, less dyspnoea[396] and half the rate of radiological emphysema progression.[421]

Given these observational findings, and mirroring developments in the study of beta-blockers, aspirin has been suggested as an intervention to improve outcomes in COPD.[422] Only a single randomised trial of antiplatelet therapy primarily investigating COPD outcomes has been published; this study examined the effect of a supranormal dose of aspirin on FEV1 and terminated early due to a lack thereof.[397] Intriguing results were obtained from a study of aspirin, ticagrelor, their combination and placebo in patients who had COPD but no indication for antiplatelet therapy.[423] Although not highlighted by the authors, due to the study not being powered to detect differences in outcomes such as COPD exacerbation and mortality, a signal of higher severe exacerbation rates (16%) in the placebo arm versus the treated arms (3% for all) was noteworthy.

As is the case for beta-blockers, the side effect profile of antiplatelet treatment in the COPD population requires careful consideration, in particular the increased risk of bleeding. In a large observational study of post-ACS patients including approximately 130 patients with COPD, the presence of COPD was associated with lower adherence to aspirin therapy, but not with an increased risk of bleeding.[424] COPD itself is a risk factor for peptic ulcer bleeding, with a hazard ratio comparable to that conferred by non-steroidal anti-inflammatory drug (NSAID) use,[425] yet studies using the same Taiwanese database found no significant association between COPD and bleeding during use of either aspirin[426] or clopidogrel.[427]

Despite the evidence to suggest that COPD does not increase the risk of adverse events cause by antiplatelets, the presence of COPD has been found to be an independent risk factor for non-use of aspirin immediately after a first myocardial infarction.[11] The odds ratio (OR) for non-use was 1.24 (95% CI 1.16 – 132; $p < 0.001$) over a period of study comprising 2006 to 2015; concerningly, the

treatment gap between patients with and without COPD widened over the total period studied (see Figure 21).

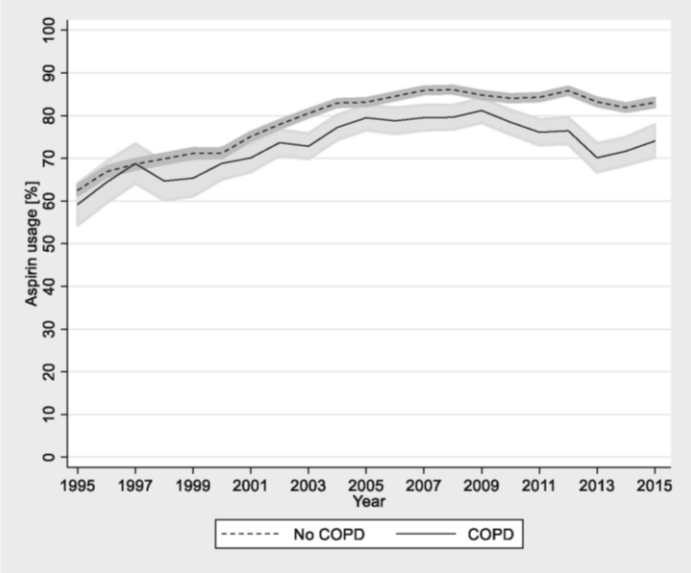


Figure 21: Temporal trends of aspirin usage after first-time myocardial infarction in Danish patients with and without COPD, from 1995 to 2015. Rasmussen et al; reproduced with permission.[11]

In summary, antiplatelet drugs are vital for treating known cardiovascular disease in this population, but they are under-utilised. They have been suggested to have a role in treatment of COPD itself, perhaps owing to the significance of the lungs in the platelet lifecycle, but no positive interventional studies have been published. Antiplatelet drugs have side effects that caution against their indiscriminate use in the COPD population, given the association of COPD with advanced age and multimorbidity. Based on these findings, in the intervention arm of the SCATECOPD study, patients are assessed for objective evidence of the presence of coronary artery disease prior to the recommendation for antiplatelet treatment.

2.5.3 Statins

Besides lowering serum cholesterol levels, statins have been recognised to have diverse additional benefits, including improved endothelial function, decreased Th1-mediated inflammation and reduced vascular smooth muscle proliferation.[428] Given the prominent roles of inflammation and atherosclerotic cardiovascular disease in the morbidity and mortality of COPD (see section 2.3.3), statins have therefore attracted attention as an intervention to improve outcomes in COPD .

As for beta-blockers and antiplatelets, supporting evidence for this hypothesis initially emerged in the form of observational studies. For example, a cohort study using New Zealand hospital discharge diagnoses of COPD exacerbation reported an adjusted hazard ratio for death with statin use of 0.69 (95% CI 0.58 to 0.84) over a 3-4 year follow up period.[429] This was irrespective of prior history of cardiovascular disease. Examining the effect of statins on exacerbations, a Danish case-control study concluded, differently, that statin use was beneficial only in patients with established cardiovascular disease[399]; nevertheless, this was an encouraging demonstration of the potential pleiotropic benefits of these drugs.

A meta-analysis of several subsequent randomised controlled trials demonstrated that statins have a statistically and clinically significant effect on quality of life, and a small and probably clinically insignificant effect on walk distance and lung function. There was no measurable effect on mortality - however this was over very short study periods of 1-12 months, with 94% of the estimate weight contributed by a study that excluded patients with CVD (i.e. those that had an indication for statin therapy).[430] A prominent multi-centre trial of simvastatin in patients with COPD but no known need for statins, STATCOPE, was negative for an effect on exacerbation rates.[400] It has been suggested that a potential cause of this was that the exclusionary strategy meant that only the lowest-risk, most 'statin-unresponsive' patients were studied .[431]

Regarding the side effect profile of statins in patients with COPD, it notable that side effects including myalgia and myopathy have been reported at indistinguishable rates in both arms of placebo-controlled trials,[430] implying no increase in adverse events with these agents in patients who have COPD. Despite this, discontinuation rates remain high with real-world usage,[432] implying a powerful 'nocebo' effect that has a meaningful effect on efficacy at a population level. Perception of muscle side effects has been suggest to negatively impact physical activity in statin users,[433] which could have adverse consequences for both cardiovascular and COPD outcomes; data are conflicting on the overall effect of statin therapy on physical activity, however.[434]

It has been a theme of this section that observational studies that have suggested a beneficial effect of specific cardiovascular drugs on COPD outcomes have not been accompanied by positive outcomes from randomised controlled trials of the same agents. This suggests the existence of bias in the observational studies, and indeed specific examples of the presence of several common biases have been identified in the studies that show a benefit of aspirin in patients with COPD, including immortal time bias and unmeasured confounding.[435]

In the intervention assessed in the SCATECOPD study, as for beta-blockers and aspirin, statin therapy is recommended only where evidence for coronary artery disease or elevated cardiovascular event risk has been objectively established by thorough contemporaneous assessment. This should confine

the use of statins to those most 'statin-responsive' patients, in contrast to the design of the negative STATCOPE trial.

2.5.4 Other drug therapies

A COPD-specific review of the efficacy, safety and potential pleiotropic effects of all classes of medications to treat heart disease is not feasible or desirable here. However, given the evidence that exists relating to beta-blockers, antiplatelets and statins, and the multifactorial, multi-system nature of COPD, there are likely to be similar important considerations pertinent to several other drug classes; those that are particularly significant are mentioned.

Considering the importance of the renin-angiotensin system in the pathogenesis of heart failure and ischaemic heart disease, as well as its links to pathology in lung and skeletal muscle,[436] it is unsurprising that drugs inhibiting this axis have been linked to improved outcomes for patients who have COPD, with observational results including lower post-exacerbation mortality[437] and protection from rapid lung function decline for patients prescribed ACE-inhibitors.[438] Randomised controlled trials of drugs targeting this pathway in the COPD population and reporting clinical outcomes have not been published, however.

The evidence relating to SGLT2 inhibitors must also be highlighted. These agents have emerged in the past decade as antidiabetic medications with additional benefits in terms of cardiovascular outcomes. Their mechanism of action has been discovered to extend beyond increased glycosuria and diuresis, to encompass a rebalancing of nutrient status and restoration of autophagy, along with anti-fibrotic, antioxidant and anti-inflammatory effects.[439] Subsequent randomised controlled trials on non-diabetic patients with heart failure have demonstrated beneficial effects on hospitalisation rates and quality of life,[439] even in patients with a preserved ejection fraction.[131] Tests of interaction between presence or absence of COPD have been negative for interaction with these outcomes in both type 2 diabetes[440] and heart failure populations.[441] Furthermore, there is observational evidence of an association between the use of SGLT2 inhibitors and improved COPD outcomes: reduced severe exacerbation rates have been found in comparison with patients who used sulfonylureas,[403] as has a reduction in the incidence of obstructive airways for SGLT2 inhibitors versus dipeptidyl peptidase IV (DPP4) inhibitors.[442] These observational findings suggest that these agents may have a role as COPD-specific therapy; although no prospective trials appear to be registered as yet. The evidence to support SGLT2 inhibitor use in HFpEF arrived after the SCATECOPD study had commenced, so these medications are not included in the study management summaries as they are for patients with HFrEF.

2.6 Chapter conclusion

The evidence reviewed in this chapter highlights the excess morbidity and mortality caused by heart disease for patients who have COPD. The mechanisms by which heart disease occurs to excess in this population have been shown to be numerous, inter-related and potentiated during acute exacerbation. Diagnosing heart disease appears to be more challenging in this population for technical and behavioural reasons and, although treatments exist that readily lower morbidity and mortality, they are under-used in patients who have COPD. A structured cardiac assessment, provided at the time of COPD exacerbation, warrants assessment as a strategy to overcome these challenges. This will be described and evaluated in the remaining chapters.

Chapter 3: Systematic review and meta-analysis of prevalence of undiagnosed cardiac comorbidities in COPD

3.1 Chapter introduction

In the preceding chapters, the close relationship between COPD and heart disease was outlined, along with the extent to which heart disease is known to exist at excess rates within the COPD population. It was emphasised that diagnosing heart disease is challenging in patients with COPD, for reasons that include overlapping clinical manifestations, reduced test accuracy and socioeconomic factors. The existence of these difficulties was put forth as a justification for evaluating an intervention to improve the diagnosis and treatment of heart disease in COPD through structured, objective testing. For such a strategy to be impactful, a significant degree of under-diagnosis of heart disease would need to exist in the population studied. This chapter contains the methodology and results of a systematic review and meta-analysis which sought to establish estimates of the prevalence of underdiagnosis of heart disease in patients with COPD, and has been published.[443]

3.2 Systematic review and meta-analysis abstract

It is often stated that heart disease is underdiagnosed in COPD. Evidence for this statement comes from primary studies but these have not been synthesised to provide a robust estimate of the burden of undiagnosed heart disease. We aimed to understand underdiagnosis rates in more detail and conducted a systematic review of studies using active diagnostic techniques to establish prevalence of major cardiac comorbidities in patients with COPD.

The MEDLINE, Embase, Scopus and Web of Science databases were searched for terms relating to heart failure (specifically, left ventricular systolic dysfunction), coronary artery disease and atrial fibrillation, relevant diagnostic techniques and COPD. Studies published since 1980, reporting diagnosis rates using recognised diagnostic criteria in representative COPD populations not known to have heart disease, were included. Studies were classified by condition diagnosed, diagnostic threshold used, and whether participants had stable or exacerbated COPD. Random effects meta-analysis of prevalence was conducted.

Prevalence estimates for undiagnosed cardiac comorbidities in COPD had broad confidence intervals, with significant study heterogeneity. Nevertheless, a prevalence of undiagnosed LVSD of 14.6% (9.2 – 21.0) was obtained when defined as LVEF <50%. Further studies using recent diagnostic advances, and investigating therapeutic interventions for patients with COPD and heart disease, are needed.

(PROSPERO ID CRD42021242972).

3.3 Systematic review and meta-analysis introduction

A common assertion of published research concerning heart disease and COPD [9,444-446] is that cardiac comorbidities are substantially underdiagnosed in patients with COPD. However, high-level evidence to support this statement is lacking: meta-analysis-level evidence for rates of cardiac comorbidity in COPD derives from use of clinical coding or medical records.[170] This only captures heart disease that has attracted clinical attention through overt signs and symptoms, or conspicuous adverse events such as acute myocardial infarction or decompensated heart failure (HF). By these methods, significant underestimation is inevitable, not least because the symptoms of heart disease and COPD overlap (see section 2.4.1): breathlessness caused by HF has no unique characteristics[447] and patients with COPD are more likely to present with atypical chest pain during acute coronary syndromes.[362] Furthermore, diagnostic confirmation requires specific testing, resources for which are limited – amongst diagnostic tests on the NHS, echocardiography waiting times are amongst the longest[448] – with hospital-based tests often practically less accessible to patients with COPD.[388]

For a more accurate understanding of the scale of underdiagnosis of heart disease for patients with COPD, active diagnostic processes must be applied to populations of patients with COPD that are selected to exclude those with existing cardiac diagnoses. Positive cases in these studies represent undiagnosed disease. A literature review including studies using these methods to diagnose unknown HF specifically exists,[449] however many subsequent primary studies have been published across the spectrum of heart disease. A systematic literature review and meta-analysis was therefore devised to examine the rate of underdiagnosis of major cardiac comorbidities in patients with COPD, when active diagnostic processes were employed.

3.3.1 The challenge of measuring underdiagnosis

In considering the problem of underdiagnosis of cardiac comorbidities in COPD it must be recognised that diagnosis of all conditions is subject to errors of both over- and under-estimation, and also that the process of diagnosis is complex and evolves over time, both in the meeting of diagnostic criteria by an individual and the very parameters of these criteria. This latter factor can also vary by location, as local influential groups may set different diagnostic thresholds, for example an LV ejection fraction below which LVSD is defined. For this reason, pre-specified diagnostic criteria were not used; rather the authors' criteria were used provided they broadly aligned with recognised major cardiological society guidelines.

3.3.2 Defining major cardiac comorbidities in COPD

Three major heart diseases were selected for investigation: heart failure with LVSD (more recently termed HFrEF if LVEF <40%, or HFmrEF for LVEF 40-49%), coronary artery disease and atrial fibrillation. This is because there is established evidence for treatments that reduce mortality and adverse events for each condition, in contrast to, for example HFpEF, for which evidence for outcome-improving therapy has only recently emerged and is yet to have widespread adoption by prominent society guidelines. Furthermore, these represent endpoint manifestations of heart disease, rather than what could be considered risk-enhancing disease processes such as hypertension or diabetes.

3.4 Systematic review methods

3.4.1 Search Strategy

A search was made for relevant studies in adults over 18. Studies published prior to 1980 were excluded because echocardiography, the key diagnostic technique for HF, was not fully developed until this point. For consistency, this cut-off was used for the other two conditions.

With these limitations, The MEDLINE, Embase, Scopus and Web of Science databases were searched in April 2021 for studies containing terms related to COPD, one of the three major heart diseases, and appropriate diagnostic techniques. Each database was therefore searched three times. The searches were updated in August 2023 in order to capture all recently published data. For studies relating to LVSD, a broad range of terms relating to HF were searched for, to avoid overlooking studies that used different terminology. The search terms used are detailed in Appendix B.

Search results were exported to Endnote 20. Duplicates were removed and study title and abstracts screened. Studies selected for full text review were reviewed for inclusion by two independent reviewers, with discrepancies settled by a third reviewer.

The review was registered on PROSPERO (ID CRD42021242972) and conducted according to the PRISMA (2009) guidelines.[450]

3.4.2 Study inclusion/exclusion

Studies included satisfied the following criteria: reported the number of positive cases of one or more major heart diseases after active testing of a population of patients with a clinical diagnosis of COPD who did not have known heart disease; used spirometic evidence of airflow obstruction (FEV1/FVC ratio < 0.7) to support the diagnosis of COPD; studied representative COPD populations – i.e. not highly selected populations such as only lung transplant candidates or only those were all comorbidities (not just heart disease) were rigorously excluded. Additionally, studies where diagnostic tests were only performed in subjects with high prior probability of a positive test – for example angiography in patients with positive troponin, were excluded.

3.4.3 Study critical appraisal

The Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross sectional studies was used to assess the trustworthiness and relevance of the included papers.[451]

3.4.4 Data extraction

Data including number of participants, age (mean/median and measure of spread), COPD severity (as indicated by FEV1% and need for long term oxygen therapy), key inclusion and exclusion criteria, COPD status (exacerbation or stability), study setting, diagnostic technique and criteria, and number of patients diagnosed were extracted, where available.

3.4.5 Statistical analysis

The primary outcome of this systematic review is the proportion of patients that had diagnosis of the heart disease in question, i.e. the prevalence of underdiagnosis. Weighted pooled estimations of this prevalence were sought. Included studies were classified according to whether patients were stable or hospitalised and diagnostic cut-offs used. Pooled estimations were only created where this would appreciably increase understanding of the data – the threshold for this was set at where ≥4 studies could be pooled. Sensitivity analysis of the effect of pooling studies across inpatient and outpatient populations on between-study heterogeneity was conducted, due to the possibility of exaggerated diagnostic rates due to the reversible cardiac dysfunction that has been identified during COPD exacerbation.[452]

Prevalence data were pooled using the binomial equation, with the variance estimate transformed because otherwise, for small or large prevalences (< 0.1 or > 0.9), the study variance tends towards zero, giving such studies a disproportionately large weight.[453] An appropriate transformation for the

data obtained here is the arcsine square root transformation, since while there are, inevitably, differences in sample sizes present, they are not of the several orders of magnitude size that can produce misleading results after back-transformation of the variance.[454] A random-effects model was used due to the inevitability of other sources of variance, besides sampling error, in the prevalence of heart disease between the populations sampled in the studies included. Amongst the sources of variance are age, geographical location and COPD phenotype (see discussion below).

Assessment of study heterogeneity was performed by calculation of the I^2 statistic and its confidence interval for each meta-analysis performed.

Assessment of publication bias is recommended in guidelines for conducting observational study meta-analysis and is commonly performed in meta-analyses of prevalence.[455] However, given the low number of studies anticipated to be pooled in this study, tests of publication bias would be under-powered.[456] Nevertheless, funnel plots were produced for the meta-analyses performed.

Analyses were performed in MedCalc for Windows version 20.027 (MedCalc software, Ostend, Belgium). Andrew Bryant (Faculty of Medical Sciences, Newcastle University) reviewed and finalised the statistical analysis plan.

3.5 Systematic review results

3.5.1 Search results and study selection

After removal of duplicates, the searches, performed initially in April 2021 and updated in August 2023, returned 5947 studies relating to HF, 6167 relating to CAD and 1344 relating to AF.

After title and abstract screening, 96 studies relating to HF, 35 studies relating to CAD and 27 studies relating to AF were selected for full text review. After resolution of discrepancies, data were extracted from 16 studies relating to LVSD, 5 studies relating to CAD and 5 studies relating to AF.

Studies from which data were extracted are summarised in Table 5, Table 6 and Table 7. Further data about individual study inclusion and exclusion criteria, particularly exclusion criteria relating to known heart disease, and patient COPD severity, are summarised in Tables A-C in Appendix C.

Study ID	n	Age (mean)	Age (s.d.)	Stability	Setting	Diagnostic tool	Diagnostic threshold	Number diagnosed	Prevalence
Akpinar 2020[457]	86	71.8	9.6	Hospitalised	Acute hospital, Turkey	TTE	LVEF < 50%	15	0.174
Freixa 2013‡[458]	114			Stable	Multi-centre, Spain	TTE	LVEF < 50%	12	0.105
Guo 2018[459]	655	71.5	5.4	Hospitalised	Acute hospital, China	TTE	LVEF < 50%	108	0.165
Hilde 2020[460]	100	63.5	6.6	Stable	Outpatients, Norway	CMR	LVEF < 50%	19	0.190
Lee 2013[461]	18	71.2		Hospitalised	Acute hospital, New Zealand	TTE	LVEF < 50%	3	0.166
Nishimura 2014[462]	54	75.4	7.6	Hospitalised	Acute hospital, Japan	TTE	LVEF < 50%	3	0.056
Noordegraaf 1997[463]	10	67.8	8.4	Stable	Outpatients, Netherlands	CMR	LVEF < 50%	2	0.200
Pothal 2018‡[464]	80			Stable	Outpatients, India	TTE	LVEF < 50%	8	0.100
Rachakonda 2016‡[465]	97			Stable	Outpatients, India	TTE	LVEF < 50%	35	0.361
Rahman 2022[466]	100	68.3	9.9	Hospitalised	Acute hospital, Bangladesh	TTE	LVEF < 50%	23	0.230
Watz 2008[467]	170	64	6.6	Stable	Outpatients, Germany	TTE	LVEF < 50%	5	0.029
Boudestein 2009[468]	244	78.2	5.1	Stable	Primary care, Netherlands	TTE	LVEF < 45%	27	0.111
Lopez-Sanchez 2013[469]	73	65.5	7.5	Stable	Outpatients, Spain	TTE	LVEF < 45%	2	0.027
Vonk-Noordegraaf 2005[470]	25	68	7	Stable	Outpatients, Netherlands	CMR	LVEF < 45%	4	0.160
Leong 2021‡[366]	117			Hospitalised	Acute hospital, Australia	Dynamic CT	LVEF < 40%	8	0.068
Rahman 2022[466]	100	68.3	9.9	Hospitalised	Acute hospital, Bangladesh	TTE	LVEF < 40%	16	0.160

Summary of studies reporting prevalence of undiagnosed LVSD in COPD patients. Abbreviations: CMR – cardiac magnetic resonance imaging, TTE – transthoracic echocardiography, CT – computed tomography ‡ Age data missing for whole cohort or subgroup.

Table 5: summary of key characteristics of studies selected for systematic review and meta-analysis of prevalence of underdiagnosis of LVSD

Study ID	n	Age (mean)	Age (s.d.)	Stability	Setting	Diagnostic tool	Diagnostic threshold	Number diagnosed	Prevalence
Bhatt 2018[471]	928	61.8	8	Stable	Outpatients, US	CACS	Agatston ≥ 400	112	0.121
Gaisl 2015[472]	81	64.3	10.3	Stable	Outpatients, Switzerland	SPECT	EANM/ESC ischaemia	11	0.136
Kahnert 2022[473]	399	66.0	8.2	Stable	Outpatients, Germany	CACS	Agatston ≥ 1500	59	0.149
Leong 2021‡[366]	100			Hospitalised	Acute hospital, Australia	CACS	Agatston ≥ 400	18	0.18
Ozyilmaz 2016[474]	42	49.7	7.6	Stable	Outpatients, Turkey	CACS	Agatston ≥ 400	1	0.023

Summary of studies reporting prevalence of undiagnosed CAD in COPD patients. Prevalence reported to 3 decimal places. ‡ Age data missing for whole cohort or subgroup.
Abbreviations: SPECT – single-photon emission computed tomography; EANM/ESC – European Association of Nuclear Medicine/European Society of Cardiology guideline

Table 6: summary of key characteristics of studies selected for systematic review of prevalence of underdiagnosis of CAD

Study ID	n	Age (mean)	Age (s.d.)	Stability	Setting	Diagnostic tool	Number diagnosed	Prevalence
Carta 2021[475]	80	56.2	9.6	Stable	Outpatients, Kyrgyzstan	Repeated 12 lead ECGs	0	0
Einvik 2017[476]	119	64.7	7	Mixed	Acute hospital, Norway	24h ECG	4	0.033
Hanrahan 2008[477]	1758	63.2	10.1	Stable	Multicentre outpatients, US	24h ECG	13	0.007
Morganroth 2004[478]	226	67		Stable	Outpatients, US	24h ECG	0	0
Shivnitwar 2023[479]	150	54.0	9.4	Hospitalised	Acute hospital, India	12 lead ECG	8	0.053
Terzano 2014[480]	173	79.1	5.1	Hospitalised	Acute hospital, Italy	Repeated 12 lead ECGs	35	0.202

*Table 7: summary of key characteristics of studies selected for systematic review and meta-analysis of prevalence of underdiagnosis of **AF***

Study ID	Criteria for inclusion clearly defined?	Subjects and setting described in detail?	Exposure measured in reliable, valid way?	Objective, standard criteria for measurement?	Confounding factors identified?	Strategies to deal with confounders stated?	Outcomes measured in valid, reliable way?	Appropriate statistical analysis used?	**Overall Appraisal**
Akpinar 2020	Y	Y	Y	Y	N/A	Y	Y	Y	Include
Guo 2018	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Lee 2013	Y	Y	Y	Y	Y	N	Y	Y	Include
Nishimura 2014	Y	Y	Y	Unclear	Y	Y	Y	Y	Include
Hilde 2020	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Noordegraaf 1997	Y	Y	Y	Y	N	N	Y	Y	Include
Paudel 2008	Y	Y	Y	Y	N	N	Y	Y	Include
Pothal 2018	Y	Y	Y	Y	N	N	Y	Y	Include
Rachakonda 2016	Y	Y	Y	Y	N	N	Y	Y	Include
Rahman 2022	Y	Y	Y	Y	Y	N	Y	Y	Include
Watz 2008	Y	Y	Y	Y	Y	N	Y	Y	Include
Freixa 2013	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Boudestein 2009	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Lopez-Sanchez 2013	Unclear	Y	Y	Y	N/A	N/A	Y	Y	Include
Vonk-Noordegraaf 2005	Y	Y	Y	Y	N	N	Y	Y	Include
Bhatt 2018	Y	Y	Y	Y	Y	N/A	Y	Y	Include
Gaisl 2015	Y	Y	Y	Y	N	N	Y	Y	Include
Kahnert 2022	Y	Y	Y	Y	N	N	Y	Y	Include
Leong 2021	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Ozyilmaz 2016	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Carta 2021	Y	Y	Y	Y	N/A	N/A	Y	Y	Include
Einvik 2017	Y	Y	Y	Unclear	Y	Y	Y	Y	Include
Hanrahan 2008	Y	Y	Y	Y	Y	N	Y	Y	Include
Morganroth 2004	Y	Y	Y	Y	Y	N	Y	Y	Include
Shivnitwar 2023	Y	Y	Y	Y	Y	Y	Y	Y	Include
Terzano 2014	Y	Y	Y	Y	N/A	N/A	Y	Y	Include

Table 8: results of risk of bias assessment performed using JBI critical appraisal checklist for studies reporting prevalence data

3.5.2 Risk of bias assessment

For included studies, there was lack of clarity or satisfactory information in at most two of the 9 domains assessed by the JBI critical appraisal checklist for analytical cross sectional studies. The inclusion criteria that studies should include representative populations and to diagnose based on recognised criteria meant there was an element of pre-selection for highly scoring studies. Results are summarised in Table 8.

3.5.3 Results synthesis

3.5.3.1 LVSD

Studies were categorised into i) sampling from populations with stable COPD or ECOPD requiring hospitalisation and ii) using left ventricular ejection fraction (LVEF) threshold used to define LVSD of <50%, <45% and <40%.

Individual study results are presented in Table 5 and grouped as above. Meta-analysis of prevalence was performed when appropriate as pre-specified above; 95% CIs are in brackets.

From 10 studies using an LVEF threshold of 50%, prevalence of undiagnosed LVSD was 14.6% (9.2 – 21.0) – see Figure 22. I^2 was high at 87% (77 – 92).

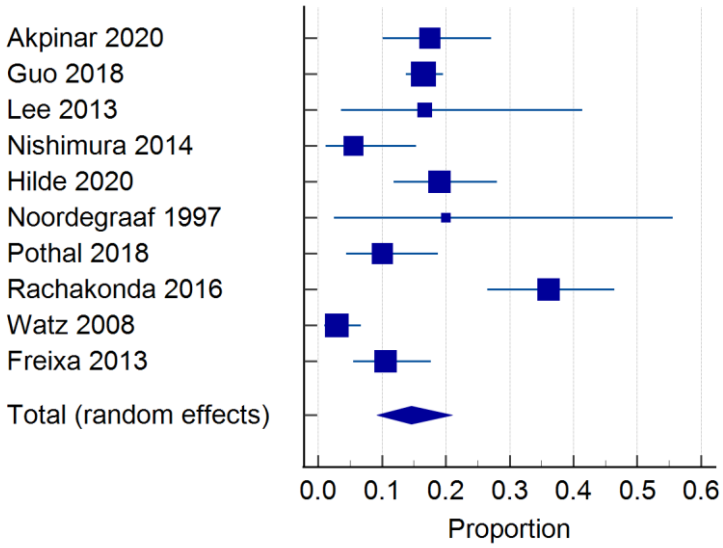


Figure 22: Forest plot and meta-analysis of prevalence of undiagnosed LVSD (LVEF <50%)

A sensitivity analysis separating studies of hospitalised and non-hospitalised patients at this diagnostic threshold did not discernibly change the prevalence of undiagnosed LVSD; heterogeneity as measured by I^2 was higher in the non-hospitalised group. In hospitalised patients, prevalence of LVSD as defined by LVEF < 50% was 14.7% (9.9 – 20.2; I^1 49% [0 – 83]); for non-hospitalised patients it was 15.1% (6.2 – 27.1; I^2 92% [84-95]).

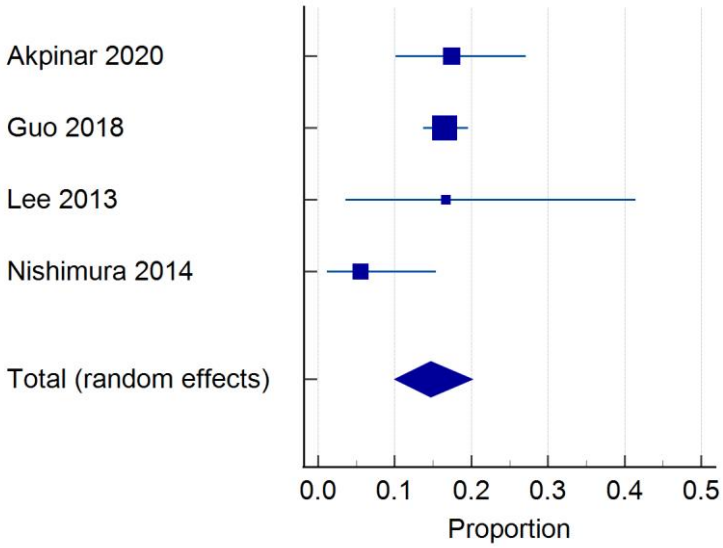


Figure 23: Forest plot and meta-analysis of prevalence of undiagnosed LVSD (LVEF <50%) in hospitalised patients

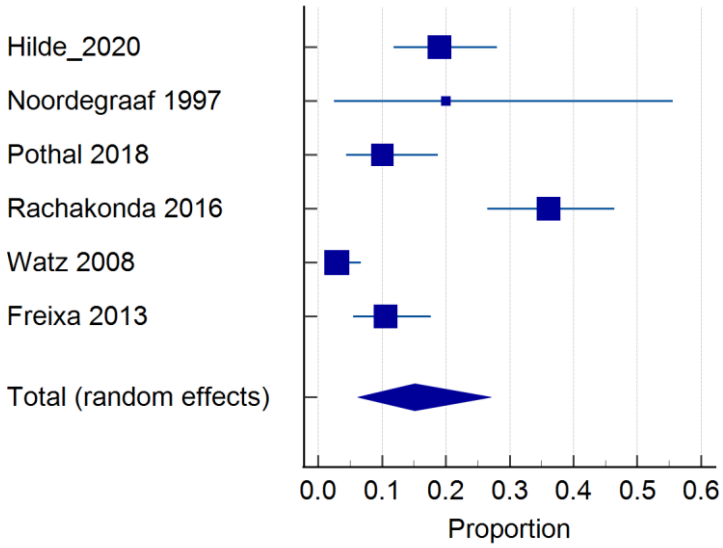


Figure 24: Forest plot and meta-analysis of prevalence of undiagnosed LVSD (LVEF <50%) in non-hospitalised patients

From 4 studies using an LVEF threshold of 45% (all in stable patients), prevalence of undiagnosed LVSD was 13.0% (5.2 – 23.8) with a notably broader CI. I^2 was 84% (59 – 94).

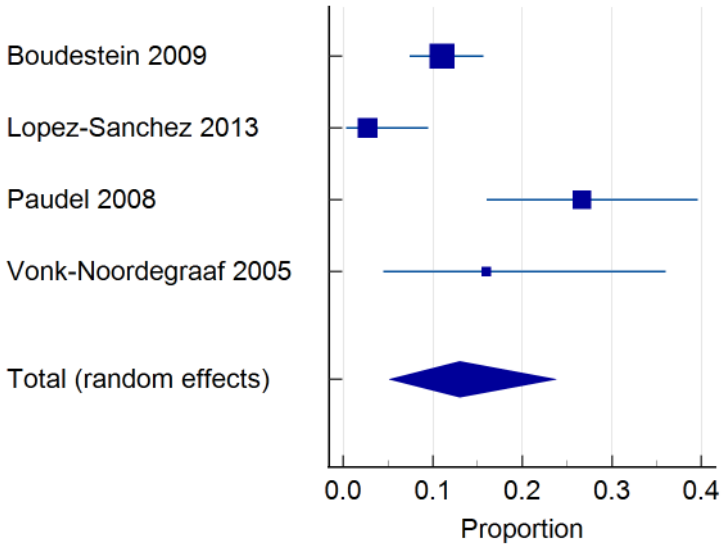


Figure 25: Forest plot and meta-analysis of prevalence of undiagnosed LVSD (LVEF <45%)

A single study used an LVEF threshold of 40%, reporting a lower prevalence of undiagnosed LVSD of 6.8%.

Funnel plots were generated including the studies comprising each meta-analysis performed; in each case Egger's test for asymmetry was negative (see Figure 26and Figure 27).

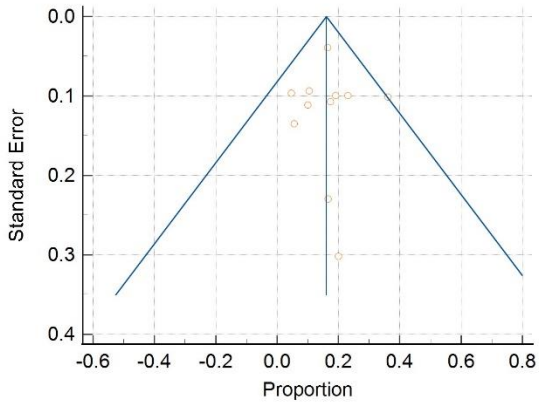


Figure 26: Funnel plot including all studies reporting prevalence of undiagnosed LVSD (defined as LVEF <50%) in COPD. Egger's test: P = 0.913

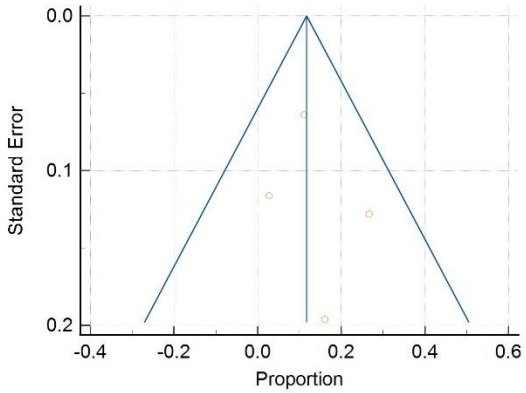


Figure 27: Funnel plot including studies reporting prevalence of undiagnosed LVSD (defined as LVEF <45%) in COPD. Egger's test: P =0.755

3.5.3.2 CAD

Individual study results are presented in Table 6. No meta-analysis of prevalence was performed because studies used a number of different diagnostic strategies. Reported prevalence of undiagnosed CAD ranged from 2.3% in non-hospitalised patients using Agatston score >400, to 18% in a hospitalised cohort using the same criteria.

3.5.3.3 AF

Individual study results are presented in Table 7. Forest plots shown in Figure 28 and Figure 29 demonstrate how inclusion of the single study of admitted patients significantly altered the prevalence estimate and heterogeneity, this study was therefore considered separately. Estimated prevalence of undiagnosed AF in stable patients assessed by 24-hour electrocardiogram was low at at 1.4% (0.3 – 3.5). By contrast, in admitted patients receiving serial electrocardiograms, undiagnosed AF was found in 20.2%.

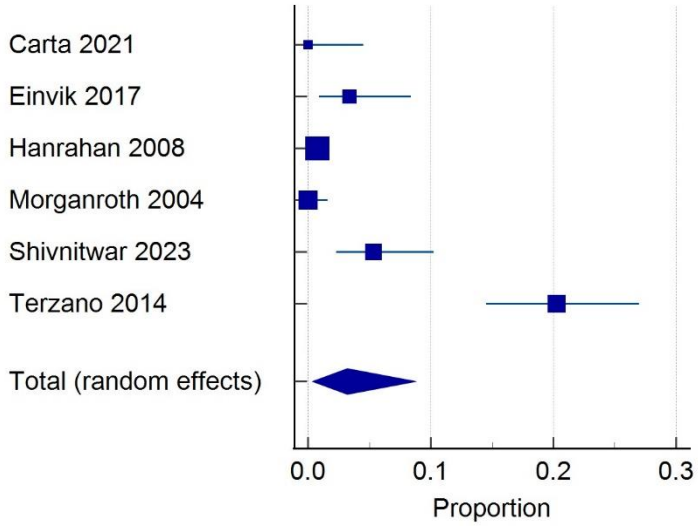


Figure 28: Forest plot of 6 studies reporting prevalence of AF in patients with COPD. Pooled prevalence estimate 3.2% (0.4 – 8.8). Heterogeneity: I2 96% (95% CI 93 – 97)

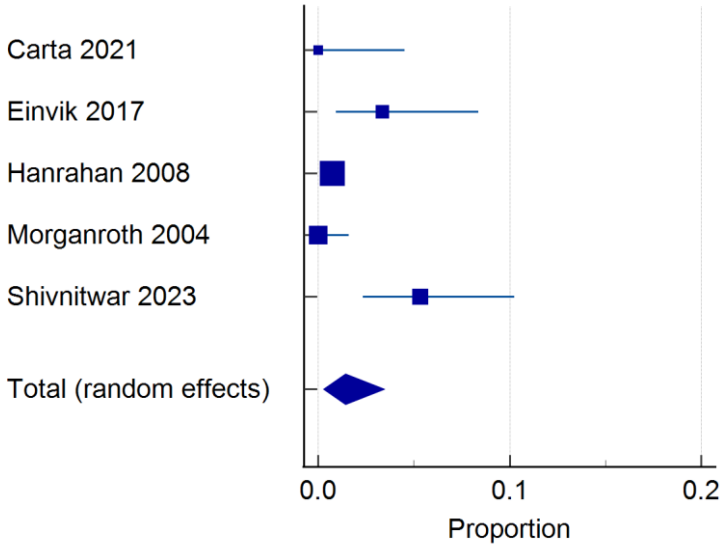


Figure 29: Forest plot of 5 studies reporting prevalence of AF in patients with stable COPD. Pooled prevalence estimate 1.4% (0.3 – 3.5). Heterogeneity: I2 82% (95% CI 57 – 92)

A funnel plot was generated including all studies including in these meta-analyses; Egger's test was negative.

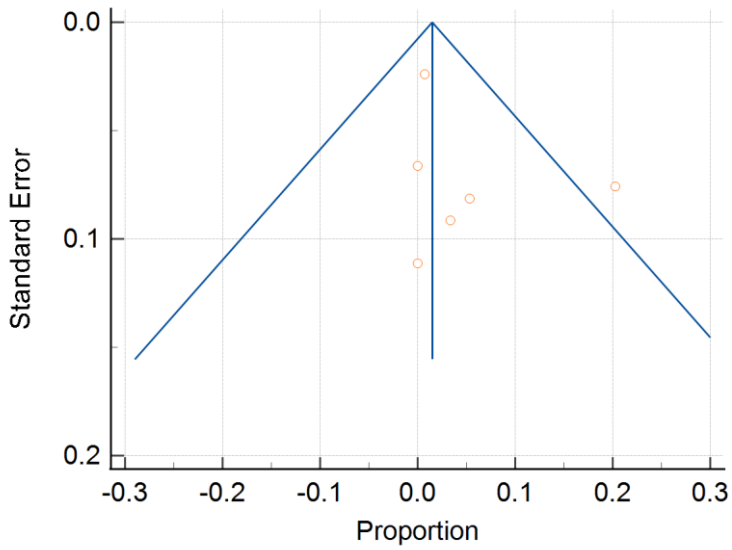


Figure 30: Funnel plot including 6 studies reporting prevalence of AF in patients with COPD. Egger's test: P = 0.338

3.6 Systematic review discussion

3.6.1 Main findings

This systematic review considered 26 published studies employing active diagnostic techniques to quantify undiagnosed heart disease in populations of patients with COPD.

The headline finding is that the prevalence of undiagnosed LVSD in patients with COPD, when a cut-off LVEF of 50% is applied, is between 10 and 20%. This represents at least 120000 people in the UK alone[481] and tens of millions worldwide[481,482]. Due to the study design it may even be an underestimate: patients not tested due to existing CAD have been shown to have the highest undiagnosed rates of HF[483]. Two thirds can be expected to have HFrEF and one third mildly reduced LVEF[148], of which at least three quarters would have other structural abnormalities satisfying a diagnosis of heart failure with mildly reduced ejection fraction (HFmrEF)[484] – all patients who are not being offered indicated, safe, effective therapy to reduce admissions and mortality.

No further synthesis was possible for studies reporting rates of undiagnosed CAD, although the highest reported rate was seen in a study on patients hospitalised with ECOPD. This is congruent with the association between ECOPD and cardiac events[485] and also the hypothesis that unrecognised CAD could contribute to the symptoms and signs leading to hospitalisation with a diagnosis of ECOPD. The somewhat lower rate of underdiagnosis of CAD compared with LVSD may reflect the multiple routes to impaired heart function in COPD beyond ischaemic cardiomyopathy;

these include myocardial inflammation and fibrosis[486] as well as direct impairment of cardiac filling due to the increased intrathoracic pressures that accompany lung hyperinflation.[271]

The discrepancy in rates of undiagnosed AF in stable and hospitalised patients occurs because paroxysms of AF in predisposed patients are much more likely in the conditions of increased sympathetic activity (caused by hypoxia and hypercapnia as well as drug treatment), systemic inflammation and intrathoracic pressure changes associated with ECOPD[280]. These results suggest that screening in patients with stable COPD, without other known heart disease or risk factors, is unlikely to identify much undiagnosed AF.

3.6.2 Limitations and implications for future research

This review has limitations.

The certainty of the evidence synthesised is reduced by the presence of considerable inconsistency as measured by I^2 and indicated by wide confidence intervals for prevalence estimates. Several small meta-analyses had to be carried out due to the variability of study settings (hospital vs. outpatient) and diagnostic definitions employed. The breadth of the estimations may also result from the heterogeneity inherent in the COPD patient population, which can be subdivided into different severity classes and phenotypes. For example, the association of the frequent exacerbator phenotype with higher rates of MI[485] implies that estimations of rates of CAD in COPD as a whole will be less precise if the prevalence of this phenotype within different study populations is variable. An individual patient data meta-analysis to explore the relationship of phenotype to the rates of undiagnosed cardiac comorbidities would be worthwhile and may provide further useful prevalence estimates for underdiagnosis rates of the other major cardiac diseases. Finally, the estimates obtained are vulnerable to sampling bias: patients participating in research studies are likely to be among the more effective accessors of healthcare, and therefore may already have sought and obtained diagnostics excluding heart disease; once again, however, this likely to mean the results obtained are underestimates, therefore the scale of the problem may be even greater than demonstrated.

Regarding LVSD, a reliance on LVEF for diagnosis has disadvantages.[487] As a test for LVSD it may produce false negative results in patients with left ventricular hypertrophy and a small left ventricular cavity.[488] When reduced LVEF is found, it is not regarded as solely sufficient for a diagnosis of the syndromes of HFrEF or HFmrEF,[123] which require the presence of symptoms and/or signs of HF and may be supported by other echocardiographic parameters and biomarker

measurements. In most patients with COPD, this requirement for symptoms is automatically satisfied due to the presence of breathlessness. However, studies generally do not report a syndromic diagnosis, hence the use of LVSD as defined by ejection fraction in this review. A threshold to define LVSD is also difficult to apply, since historical evidence for effective therapy was established in LVEF < 40%, yet retrospective analysis suggests patients with LVEF < 50% benefit from the same treatments. This higher threshold is included in some international guidelines,[123] but not others[489]; it does however define a population of patients with COPD who have worse physical and psychological status[490] and was therefore included here. A final challenge in establishing meaningful LVSD rates was that many studies reported mean LVEF without reporting cases below a threshold, meaning potentially useful data could not be included.

Other studies have explored left-sided cardiac dysfunction in COPD beyond reduced LVEF.[491] and many others have studied the right heart using strain-based indices.[492] Undoubtedly there is value in establishing the true prevalence of non-LVEF-defined cardiac dysfunction in COPD, but it was beyond the scope of this review. Novel, prognosis-informing techniques to evaluate cardiac function, such as global longitudinal strain,[493] plus long-awaited outcome-improving treatment in heart failure with preserved ejection fraction,[130] both have potentially important roles in the care of patients with COPD and should be evaluated further in this population.

Finally, practical and cost-effective approaches to reducing the rates of undiagnosed and untreated heart disease for patients with COPD must be identified. The data presented here suggest current approaches are failing; equally, universal application of tests to diagnose heart disease in the large COPD population could overwhelm healthcare resources. A structured approach to guide clinicians would be valuable, perhaps using simple screening tests such as NT-proBNP to identify patients for further testing; further research is needed to establish the ideal thresholds and regularity of testing that would best balance reducing underdiagnosis and cost-effectiveness.

3.7 Conclusion

This systematic review and meta-analyses sought to establish if high level evidence could be found to support the statement that heart disease is substantially underdiagnosed in COPD. Studies were heterogenous and CIs broad, and the threshold above which a rate of underdiagnosis becomes substantial, or unacceptable, is subjective. Despite this, a striking estimate of the magnitude of undiagnosed HF was obtained, which should be noteworthy to all clinicians treating patients with COPD.

The findings from this systematic review and meta-analysis support the rationale of the SCATECOPD study, which aimed to assess the effect of a structured cardiovascular assessment, with treatment of problems identified, on outcomes for patients admitted to hospital with COPD exacerbation. The design and conduct of this study is the focus of the next chapter.

Chapter 4: SCATECOPD study methods

4.1 Chapter introduction

The preceding three chapters have highlighted the close interrelationship between COPD and heart disease, the particular importance of COPD exacerbations in increasing the risk and impact of heart disease, and the significant burden of undiagnosed heart disease in patients who have COPD. These three fundamental points motivated the design of the SCATECOPD study. This chapter describes the details of the study and the plans made for its conduct and analysis, alongside specific considerations relating to the investigational methods and outcome measures used.

4.2 SCATECOPD study design

The SCATECOPD (Structured Cardiac Assessment and Treatment following Exacerbations of COPD study was a pilot, 1:1 randomised trial of the addition of a structured cardiovascular assessment (SCA) to usual care for patients admitted to hospital with ECOPD. A pilot study can be succinctly defined as 'a small study for helping to design a further confirmatory study'.[494] In line with previously formulated definitions, the study had defined hypotheses, objectives and methodology, and was also conducted with the intention of informing the design of a subsequent, larger and definitive trial.[495] Hence, prominent within the study objectives was the examination of the utility of various outcome measures alongside a selected primary outcome measure, which was the number of days alive outside hospital (DAOH) recorded at one year following discharge. The rationale for assessing this outcome is detailed in section 4.3.1. The protocol was initially developed by Dr John Steer, Professor Stephen Bourke, Dr David Ripley, Dr Keith Gray and Professor Jo Gray.

4.2.1 Hypothesis

A comprehensive, structured cardiovascular assessment, with treatment of problems identified, increases the number of days patients spend alive outside hospital following a hospital admission with ECOPD

4.2.2 Objectives

Primary objective: To assess the effect of SCA on important clinical outcomes to allow powering of a multi-centre randomised controlled trial.

Secondary objectives:

1. Report rates of cardiovascular disease, including undiagnosed and undertreated heart disease in patients admitted with ECOPD.
2. Examine the utility of DAOH as an outcome measure in COPD, and its relationship with other outcome measures including mortality, readmissions and quality of life.
3. In the intervention group, examine the relationship between changes in cardiac function from baseline to 90 days and severity of COPD, ECOPD and comorbid heart disease.
4. Collect healthcare resource use data to report differences in health costs and quality adjusted life years (QALYs) between the study arms .
5. Assess the feasibility of collecting healthcare resource use data to carry out an economic evaluation of the intervention in a future randomised controlled trial.

4.2.3 Patient focus

Addressing the role of comorbidities in COPD exacerbations was identified as a priority by respondents (80% of them patients and caregivers) to the James Lind Alliance priority setting partnership survey in 2021.[496] There was no prompt towards this issue included in the survey document, and it chimes with the need for holistic management, focussing on multimorbidity, highlighted following the 2017 National Asthma and COPD Audit Programme (NACAP).[50] Local patient opinion was also sought during the design of SCATECOPD, with 9/10 patients with COPD surveyed stating they would want to be recruited, and modifications made to financial support for the follow-up process made on the basis of responses. The patient-focussed nature of the study is further underlined by the selection for evaluation of an outcome measure that synthesises mortality with time spent hospitalised. The latter was valued as one of the 'most important' outcomes by patients with COPD, according to a synthesis of 217 quantitative studies assessing the relative importance of outcome measures.[497]

The specific potential patient benefits foreseen at the set-up of the study were stated in the protocol as follows:

1) Highlighting the significance of heart disease for patients hospitalised with ECOPD, with this increased awareness benefitting patients by reducing the diagnostic and treatment gaps.
2) Showing, to commissioners and healthcare organisations, the benefit that can be yielded from ensuring sufficient access to cardiovascular diagnostics

3) Establishing the utility of an emerging outcome measure (DAOH) for ECOPD
4) Improving service delivery: the major driver of improved in-hospital mortality rates for patients with ECOPD in recent years (no new treatments have become available during this time). Better diagnosis and management of heart disease could substantially improve patient outcomes and reduce health resource use

4.2.4 Inclusion and exclusion criteria

The inclusion and exclusion criteria were designed so that almost all patients admitted with ECOPD would be eligible for the study, so that its findings would have broad generalisability (see Table 8).

The inclusion criteria centred around ensuring the background diagnosis of COPD was secure and that the diagnosis of ECOPD as the cause for admission was similarly robust. As discussed in Chapter 1, various definitions of ECOPD have been proposed, depending to variable degrees on changes in symptoms, healthcare utilisation and biomarkers. The definition selected here was that the consultant seeing the patient on the post-take ward round had decided that the reason for admission was a diagnosis of ECOPD. This choice is pragmatic and uncomplex. It bears noting that at the centre in which the study was conducted, Northumbria Specialist Emergency Care Hospital, patients admitted with ECOPD are typically transferred directly to an acute respiratory ward from the emergency department. This means, in the vast majority of cases, that the consultant making the diagnosis of ECOPD is a specialist respiratory physician, heightening the accuracy of this criterion.

The exclusion criteria focussed on ensuring that randomisation to the intervention would be safe (given the use of ionising radiation during cardiac CT) and that survival after discharge was not likely to be strongly affected by a non-COPD condition. Given the significant number of follow-up encounters that recruitment entailed, it was not felt appropriate to seek surrogate consent for recruitment; inability to provide informed consent at the time of identification for inclusion was therefore stipulated as an exclusion criterion, accepting that this would exclude patients with significant acute and chronic cognitive impairment.

Inclusion criteria	Exclusion criteria
• Age > 35 years • > 10 pack year history (PYH) smoking • Clinical diagnosis of COPD • Previous spirometry with FEV1/FVC < 0.7* • Admission to hospital with the primary cause being ECOPD†	• Reason for admission not ECOPD in view of attending clinical team. • Unable to provide informed consent • Any non-COPD condition likely to limit survival to less than 12 months • Contra-indication to cardiac CT‡ • Pregnancy or breastfeeding
* Most recent spirometry performed in lung function department, or, if no departmental lung function available, most recent GP-recorded spirometry. † ECOPD documented as the primary problem at consultant post-take ward round ‡ Including inability to tolerate CT scan due to profound orthopnoea	

Table 9: SCATECOPD study inclusion and exclusion criteria

4.2.5 Randomisation

Eligible, consenting patients were randomised to receive either:

- usual care for ECOPD – during and after hospitalisation (the UC arm)
- usual care plus structure cardiac assessment (the intervention, or SCA, arm)

Because the outcome of days alive outside hospital is derived from readmission and mortality rates, randomisation was stratified by the PEARL score[(498)] at the time of presentation to hospital with ECOPD, with the intention of providing balance in the baseline risk of readmission between arms. PEARL comprises five indices, as shown in Table 10.

PEARL provides a score between 0 and 9 and allows categorisation of patients into low (score 0-1), medium (score 2-4) and high (score 5-9) risk for readmission or death at 90 days. The eMRCD score was assessed according to methodology employed previously, where it has been shown to offer improved prognostic strength in comparison with the tradition MRCD scale (see Table 11).[(499)]

Previous admissions for ECOPD	0-1	0 points
	2+	3 points
eMRCD score	1-3	0 point
	4	1 point
	5a	2 points
	5b	3 points
Age	< 80	0 points
	80 +	1 point
Right ventricular failure	Absent	0 points
	Present*	1 point
Left ventricular failure	Absent	0 points
	Present†	1 point
* RV failure was defined as a clinical diagnosis of cor pulmonale, or echocardiogram showing right ventricular impairment or pulmonary artery systolic pressure (PASP) > 35mmHg † LV failure was defined as a pre-existing diagnosis based on echocardiography		

Table 10: Indices comprising the PEARL score. Adapted from Echevarria et al[498]

eMRCD score: *'In the past 3 months, when you were feeling at your best, which of the following statements best describes your level of breathlessness?'*	
Only breathless on strenuous exertion	**1**
Breathless hurrying on the level or walking up a slight hill	**2**
Walks slower than contemporaries, or stops after walking on the level for 15 min	**3**
Stops for breath after walking 100 m, or for a few minutes, on the level	**4**
Too breathless to leave the house unassisted but independent in washing and/or dressing	**5a**
Too breathless to leave the house unassisted and requires help with washing and dressing	**5b**

Guidance notes:

Remember that you are asking the patient about their level of breathlessness on a good day over the preceding 3 months, not breathlessness during an exacerbation/on admission.
A patient only achieves a higher grade if they are as breathless as defined in that higher grade.

- *eg, if worse than defined in eMRCD 3, but not as bad as eMRCD 4, they remain eMRCD 3.*

A key distinction is between eMRCD 4 and eMRCD 5a/5b:

- *only score 5a or 5b if the patient cannot leave the house without assistance.*
- *If a patient can only walk 30 to 40 metres, but can leave the house unassisted, they are eMRCD 4.*
- *if a patient can walk 5 or 10 metres, perhaps from their front door to a car, but need a wheelchair otherwise, they require assistance: eMRCD 5a or 5b. Simple walking aids do not constitute assistance.*

If a patient requires assistance in personal washing and dressing they are eMRCD 5b. If they only require assistance in washing or dressing they are eMRCD 5a. Remember to ask about putting on socks and shoes. If patients are limited for a reason other than breathlessness, score based on their functional limitation.

Table 11: eMRCD scoring criteria and guidance notes; source: Echevarria, et al; 2016[500]

Randomisation was additionally stratified according to the presence or absence of known significant heart disease prior to admission, defined as a previous diagnosis of any of:

- Left ventricular systolic dysfunction with LVEF < 45%
- Atrial fibrillation
- Myocardial infarction or coronary artery disease requiring need for revascularisation

The three PEARL strata (low, medium, high) and two cardiac disease strata combine to create 6 strata. Blocked randomisation was accomplished by an online platform.[501] With blocked randomisation, imbalance between study arms is possible. At the recruitment target of 120 patients the magnitude of imbalance was calculated to have the following probabilities: no imbalance (41.7%), 2 patients (48.5%), 4 patients (9.3%), 6 patients (0.6%).

4.2.6 The intervention: structured cardiac assessment

Patients undergoing SCA underwent a set of investigations and assessments during admission. In all cases, investigations were done as soon as practicable after randomisation and discharge was not delayed for the purposes of carrying out interventions for the SCA.

4.2.6.1 Transthoracic echocardiography

A transthoracic echocardiogram (TTE) was performed at the bedside by a British Society of Echocardiography accredited echocardiographer.

The use of non-invasive ventilation (NIV) alters haemodynamics, producing artificially improved measures of left and right ventricular function.[502] Patients treated with NIV were therefore required to be weaned to the point of being NIV-free for 4 or more hours before TTE, with the assessment carried out at the end of the NIV-free period.

A standard dataset was requested from echocardiographers; locally used normal ranges for quantitative variables were based on the BSE reference intervals published in 2020 and are shown in Table 12. LV ejection fraction was measured by Simpson's biplane method preferentially, with subjective visual assessment if this was the only method of deriving a quantitative value. Diastolic function was graded according to the BSE (2013) guidelines, requiring pulse-wave doppler and tissue

doppler imaging of the mitral valve.[503] Pulmonary hypertension probability was assessed according to the BSE (2018) guidelines, using tricuspid regurgitation velocity (if measurable) and other structural and functional echocardiographic variables to categorise this as low, medium or high.[504]

- Left heart measurements: LVEF (%), LV end-diastolic diameter and volume, LV wall thickness and architecture, presence of global/regional hypokinesis, diastolic dysfunction grade, left atrial (LA) diameter and mitral E/e'.
- Right heart measurements: RV function assessment (good or impaired) and fractional area change, tricuspid regurgitation (TR) velocity, TAPSE, tricuspid valve S', right atrial size, estimated PASP and right atrial (RA) pressure/probability of pulmonary hypertension (low, medium or high).
- Valve assessment

Echocardiographic variable	**Normal range**	**Comments**
LV ejection fraction (%)	≥ 55	
LA diameter (mm)	30 - 40 (male) 27 - 38 (female)	
LA volume (indexed, ml/m^2)	< 34 34 - 48 – borderline	Used to determine presence of dilatation
LV internal diameter, end diastole (mm)	37 - 56 (male) 35 - 51 (female)	
LV end diastolic volume	30 - 79 (male) 29 - 70 (female)	
Left ventricular posterior wall, end diastole (mm)	6-12	
E/e'	< 8	
RV fractional area change (%)	≥ 30 (male) ≥ 35 (female)	
TR velocity (m/s)	≤ 2.8 m/s	If measureable
TAPSE (mm)	≥ 17	
Tricuspid valve s' (cm/s)	≥ 9	
Right atrial area (cm^2)	≤ 22 (male) ≤ 19 (female)	
RA volume (indexed, ml/ m^2)	≤ 25 (male) ≤ 21 (female)	
Estimated PASP (mmHg)	≤ 35	Derived from TR velocity and estimated RA pressure

Table 12: normal ranges for quantitative measurements recorded from echocardiograms conducted as part of SCA

If endocardial border definition was insufficient to obtain quantitative measurement of LVEF, echocardiographic contrast was administered intravenously in the form of sulphur hexafluoride microbubbles (Sonovue™). If doubt about the presence and/or severity of left ventricular dysfunction persisted, consultant cardiologist advice was sought about the need for further investigation with cardiac MRI. Where measurements were not possible by the echocardiographer, the input of a second practitioner was sought to ensure objectives measurements were obtained wherever possible. If precise LVEF% measurement remained impossible, ranges were accepted, with midpoint values used when required for further analysis.

4.2.6.2 Cardiac CT for coronary artery calcium scoring

Non-contrast, ECG-gated cardiac CT was performed for assessment of coronary artery calcification and Agatston score calculated by an independent consultant cardiologist specialising in cardiac imaging. Where cardiac CT could not be performed prior to discharge it was done on an urgent outpatient basis. Patient who already had existing revascularizing material in the coronary arteries did not have Agatston score calculated as interference from this material confounds accurate assessment.

4.2.6.3 Portable 3-lead ECG

This was applied by the researcher and removed after 24-hours, or as close as practically possible. Patients were discharged with the recorder in place if necessary. Analysis and reporting was performed by an accredited cardiac physiologist with the presence of any supraventricular or ventricular arrhythmias recorded, along with the predominant rhythm and overall quality of recording. Any potentially life-threatening arrhythmias detected were urgently discussed with a consultant cardiologist.

4.2.6.4 Blood tests

Samples from the earliest possible time point following admission were tested for blood glycated haemoglobin (HbA1c) and serum nt-proBNP, troponin T, fibrinogen and non-fasting lipid profile. Where feasible, tests were added to the stored samples taken at admission, otherwise subsequent samples were tested or further blood samples drawn at the earliest opportunity. 10-year cardiovascular risk by QRISK-3 score[505] was calculated, using cholesterol measurements along with demographic details and clinical information including BMI and pre-discharge blood pressure.

4.2.6.5 Blood pressure assessment

Blood pressure measured during routine observations over the final 24 hours of admission was examined for the presence of raised systolic and/or diastolic values. Ambulatory blood pressure assessment was offered for the confirmation of suspected hypertension, unless values were very significantly raised (see section 4.5.1.6, and summary of management for hypertension [Appendix C] for full details of diagnostic criteria and indications for treatment without further confirmatory investigations).

4.2.7 Usual Care

Patients randomised to the usual care arm of the study received management for their admission with ECOPD and follow-up as determined by the consultant responsible for their in-hospital care, and any clinicians reviewing them during the follow-up period, for example for routine scheduled outpatient COPD clinic. Aside from an ECG at admission, no investigations for heart disease are a mandatory part of the standard protocol for ECOPD management at a local or national level. However, the local management guidelines for both inpatient and outpatient COPD care do emphasise a proactive approach to identifying heart disease: both coronary artery disease and heart failure through NT-proBNP and echocardiography, hence a process of responding to clinical signs suggestive of undiagnosed heart disease was anticipated in the usual care arm. In an observational study that included patients from the same site, as well as a neighbouring general hospital, 23.3% had investigations for heart failure within 100 days of admission for ECOPD (although only 6.7% had these within 7 days of presentation).[506] Therefore, patients within usual care were anticipated to receive a degree of investigation for heart disease but for this to be of a significantly reduced degree when compared with those in the structured cardiac assessment arm.

Regarding treatment of heart disease, no specific recommendations were made for patients in the usual care arm of the study, although their management would be expected to follow local and national protocols with respect to identification and management of hypertension, diabetes and existing cardiac comorbidities. Furthermore, local protocols for management of heart failure, coronary artery disease and atrial fibrillation (with which the management summaries for the structured cardiac assessment corresponded) were available to guide clinicians who did diagnose these comorbidities in patients under their care who were within the usual care arm of the study.

4.2.8 Recruitment

Recruitment took place from December 2020 to May 2022. The initial recruitment target was 120 patients, based on a pragmatic assessment of recruitment numbers for similar studies at the same centre. A power calculation was not performed as there was no basis for an estimated effect size due to the novelty of the intervention and the selected primary outcome measure. Patients were identified as suitable for recruitment by the team providing their usual hospital care for ECOPD, and subsequently invited to provide informed consent. As recruitment was carried out by a single researcher, consecutive sampling was not feasible.

4.3 Outcome measures

The following outcome measures, listed in Table 13, were specified at trial registration.[507] Whilst a primary outcome of interest was selected, the overarching objective of the trial was to examine the utility of all important clinical outcomes to enable the design and powering of a future clinical trial. The specific methods for measuring the study outcomes, along with the principles underpinning their inclusion in the study, are discussed in the subsequent subsections. Outcomes have been grouped together according to the objectives underpinning their selection.

Primary outcome:	The number of days spent alive outside of a hospital environment during 12 months following hospital discharge
Secondary outcomes:	1. Time to readmission or death following hospital admission for ECOPD
	2. All-cause readmission rates at 90 days and 12 months post discharge
	3. All-cause mortality rates at 90 days and 12 months post discharge
	4. COPD exacerbation rates, from health records and self-report, at 90 days and 12 months.
	5. Rate of adverse cardiovascular events* at 90 days and 12 months post discharge
	6. Rate of new diagnosis of cardiovascular disease at 90 days and 12 months
	7. Prevalence of undertreated cardiovascular disease at baseline, 90 days and 12 months
	8. Change in 4 metre gait speed at 90 days and 12 months, compared with baseline
	9. Mean change in quality of life measured by St. Georges' Respiratory Questionnaire over 12 months.
	10. Health costs and estimated Quality Adjusted Life Years (QALY), measured by health records and patient resource utilisation proforma, at 12 months
In the intervention arm:	11. Changes in right heart function† between baseline and 90 days
	12. Relationship between changes in right heart function† and ECOPD severity measured using DECAF score
	13. Relationship between changes in right heart function† and comorbid CVD
	14. Relationship between right heart function† and COPD severity at baseline.
	15. The associations between DAOH and right heart function at baseline†.
* non-fatal stroke or myocardial infarction, and cardiovascular death; † Including estimated pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography.	

Table 13: SCATECOPD study outcome measures

4.3.1 Days alive outside hospital

As this was a pilot study, rather than a feasibility study, a primary outcome was selected for assessment for suitability for use in a potential definitive multi-centre RCT.[(494)] When thinking beyond pilot studies to the performance of definitive trials, selecting an optimal primary outcome measure is critical to the effective evaluation of an intervention.[(508)] Such an outcome will have several attractive qualities including simplicity of definition, frequency, and importance to both clinicians and patients. A single endpoint is attractive because of its simplicity, but there may not be enough events within the study period for statistical tests to have adequate power to identify significant differences between arms. As such, composite endpoints are often selected for their ability to allow a reduction in sample size and follow up time by increasing the overall event rate.[(509)]

However, a key problem with the use of a composite endpoint is that any effect demonstrated between arms might be presumed to be accounted for by an equal change in all components of the endpoint. However, this may not be the case, and is particularly problematic when different components of the endpoint are of very different importance to clinicians and patients – as illustrated in the results of the widely-cited PEITHO trial of intermediate-risk pulmonary embolism thrombolysis.[510] Here, the primary outcome of death or haemodynamic compensation occurred more frequently in the placebo arm, but this was accounted for almost entirely by an increase in the latter, less impactful component of the primary outcome (see Table 14).

Outcome	Tenecteplase N=506	Placebo N=499	Odds ratio (95% CI)	P value
Primary outcome – no. (%)	13 (**2.6**)	28 (**5.6**)	0.44 (0.23 – 0.87)	0.02
Death from any cause	6 (**1.2**)	9 (**1.8**)	0.65 (0.23 – 1.85)	0.42
Haemodynamic decompensation	8 (**1.6**)	25 (**5.0**)	0.30 (0.14 – 0.68)	0.002

Table 14: Results of the PEITHO trial, illustrating unequal contributions of differently impactful components of the primary outcome on a statistically significant difference between study arms.[510]

An outcome measure that simultaneously captures composite outcomes while preserving the differential importance of some outcomes over others is desirable. A potential solution is to measure the *days spent alive and outside hospital* (DAOH) over a period of time following the delivery of an experimental or control intervention. At the time of SCATECOPD design, this outcome had only been used in one published COPD study, and only to a time point of 14 days.[511]. However, it is used increasingly in cardiology research,[512] where it has also been referred to as 'home time'.[513]. The essence of the calculation of DAOH for each study participant is to subtract any time spent admitted to hospital and any time following death, if it occurs, from a fixed time period. However, a review of the methods employed (see Table 15) reveals that differences exist in the definitions of the day from which the count is started, and how time in hospital is accumulated for subtraction from the total DAOH value. Studies reviewed in Table 15 often discuss admissions lengths in terms of 'days' without a rigorous definition of what this means. This is important because an admission that lasts 12 hours on one calendar day is counted as zero days outside hospital if dates of discharge and admission are subtracted from each other to yield admission lengths in days. Conversely, a brief admission of 2 hours, that includes midnight, would yield an admission of 1 day length by the same methodology. Despite this discrepancy, this was the method selected for calculation of admission durations in the SCATECOPD

	First author	Year	Journal	Speciality	Measure	Definition of day 1	Definition of admissions	Notes
1	Wasywich[514]	2010	Eur J HF	Cardiology	DAOH 30/365/2y	Day after admission	Not precise; appears to be number of nights	• If died during admission, DAOH 0
2	Ariti[515]	2011	Am Heart J	Cardiology	DAOH	Day after randomisation	Stated as 'days in hospital'	• Often referenced as methodology used by other cardiology studies
3	Myles[516]	2017	BMJ Open	Surgery	DAH30	1st post-operative day (not discharge)	Appears to be number of nights in hospital	• If died during follow up period: 0 • MCID suggested: 0.5 (of 30 days) • Often referenced by papers in surgery/anaesthestics
4	Jerath[517]	2019	Anaesthesiol	Anaesthetics	DAOH 30/90/180	1st post-operative day	Stated as 'days spent in hospital'	• Used '1st [etc] post-operative day'
5	Roth[518]	2021	J Clin Med	Cardio-thoracics	DAOH	Unclear: day of or 1st day after heart transplant	Hospitalisation of at least one day duration	
6	Awada[519]	2022	Acta Oncologica	Surgery	DAOH 30/365	1st post-operative day (not discharge)	Days with an overnight stay	• DAOH365 = 365 days – (DAIH365 + DD365) • Most detailed methodology published
7	Sandau[520]	2022	Eur Clin Respir J	COPD	DAOH 14/30	Admission (not clear if used as day 0 or 1)	Not used	• Unusually, readmission didn't contribute to DAOH
8	Spurling[521]	2022	Br J Anaesth	Anaesthetics	DAOH 30/90	1st post-operative day	Referenced [3], no added definition	
9	Noly[522]	2023	JAMA surgery	Cardio-thoracics	DAOH 365	Day after LVAD implantation	Appears to be number of nights in hospital	• Calculated %DAOH (and considered distribution before/after intervention)
10	Grieve[523]	2023	HSDR	Surgery	DAOH 90	Date index episode started	Used ONS linkage; likely number of nights	• Powered for difference of 1 day (from 90) • Death = 0

Table 15: Summary of methodology employed by studies using DAOH as a primary outcome measure

study, for the following reasons: first, it is straightforward and therefore error-resistant to extract dates of admission and discharge for calculation of admission duration; second, it is a methodology used by NHS organisations to calculate admission lengths; third, no accepted threshold exists to decide when a long day-time admission would be more negatively impactful for patients than a short admission across midnight; fourth, this straightforward method is more amenable to up-scaling in a multi-centre definitive trial.

It was also recognised that patients in study populations often spend time in healthcare facilities that are not their homes in an equally-impactful way, for example in community hospitals and rehabilitation facilities, therefore time spent admitted at such locations was counted in the equivalent manner as for acute hospital admissions.

Some studies did define a calculation for to explain how DAOH values were yielded, and this explicit approach is taken in the SCATECOPD study. The calculations are presented below:

1) *For a patient alive on post-discharge day 365 (PDD365):*

   DAOH = 365 – ([Admission 1 end date] – [Admission 1 start date]) – ([Admission 2 end date] – [Admission 2 start date]) - … etc … – (other total nights spent in healthcare facilities)

   **Last date to be included for admissions: PDD365 (use as final discharge date if patient in hospital on PDD365)*

2) *For a patient who died before PDD365:*

   DAOH = ([Death date] – [Index discharge date]) – ([Admission 1 end date] – Admission 1 start date]) – … etc… – (other total nights spent in healthcare facilities)

   **Last date to be included for admissions: Death date (use as final discharge date if patient in hospital on Death date)*

As a result, the definition of DAOH in the SCATECOPD study is: “the number of days the patient was alive and not in a hospital (or other healthcare facility that was not their residence) at the start of each of the first 365 days after discharge following their index admission for ECOPD”.

To illustrate the difference from a binary composite outcome measure, the maximum DAOH value that could be achieved is 365: a patient who survives from discharge to end of follow-up without

readmission to hospital. A patient who has a single 7-day readmission after 30 days and survives to end of follow-up would have a DAOH value of 358; a patient who is readmitted after 30 days but dies in hospital would have a DAOH value of 30. By contrast, a binary or time-to-event outcome measure would have the same value for these two patients.

The distribution of DAOH in prior published studies has been highly negatively skewed,[517] with the majority of patients having a DAOH value close to the maximum. It is probable that the distribution of DAOH in the two arms in SCATECOPD will show the same skew, albeit potentially to a lesser degree due to the high rate of mortality and (repeated) readmission seen following admission with ECOPD. Importantly, all-cause hospitalisation, rather than hospitalisation for COPD and/or cardiac reasons only, was selected as the substrate for DAOH because the major impact on patients is the hospitalisation itself, rather than its underlying cause, and to make the outcome measure simple to calculate without the need for adjudication.

Limitations of DAOH have been described. Authors have cautioned against assessing DAOH over a time period greater than 30 days due to the excessive influence of early mortality on the distribution.[524] However, this was in a population suffering a single significant physiological insult (emergency laparotomy), which would be expected to have experienced the majority of mortality in the early phase of study, rather than one subject to a progressive, regularly-exacerbating (and hence repeatedly life-threatening) chronic condition such as COPD. The best method of classifying DAOH values as favourable or unfavourable is not yet established, with one study using a 10th centile cut off to define 'shorter' DAOH[517] and another using the 33rd centile[524]. It is likely that the underlying mortality rate of the population in question is the key determinant of an optimal cut-off, if such a distinction is considered useful.

4.3.2 Adverse event rates

Outcomes 1-5: evaluate the effect of the intervention on time to, and/or total burden of, adverse events such as death, readmission, COPD exacerbation and adverse cardiac events

These secondary outcomes represent events that are important to patients with COPD [497] and are standard outcomes in trials of similar populations and interventions.[317,525] As discussed, this study was not powered to detect a difference in the rate of any of the listed events. However, observed differences would be noteworthy and suggest avenues for further research.

4.3.3 Diagnosis and undertreatment

Outcomes 6 and 7: report rates of new cardiovascular disease diagnoses during study follow up, and prevalence of undertreated cardiovascular disease

As discussed in Chapter 2, systematic testing of patients with COPD reveals abundant undiagnosed heart disease. This challenges the position of major COPD guidelines, which advocate for the same approach to the diagnosis of cardiac disease in patients with COPD as without COPD, namely undertaking investigations based on the presence of signs and/or symptoms of disease, such as heart failure or angina.[12,20] This is the approach undertaken in usual care SCATECOPD. A proportion of patients in usual care are expected to receive cardiac investigations, particularly echocardiography, during or shortly after admission, as a results of clinicians' suspicion of undiagnosed or incompletely-assessed heart disease. A difference in the rates of new cardiovascular disease diagnosis between the study arms will therefore be an estimate of the differential yield between the two diagnostic approaches – structured and traditional - in this patient cohort. A further difference in cardiovascular disease diagnosis may occur during follow up, due to different levels of primary prevention between the study arms. A higher proportion of patients in the intervention arm are anticipated to be treated with antiplatelet and statin medications in order to reduce the rate of adverse events such as myocardial infarction and stroke. Alternatively, it may be that the patients in the usual care arm of the study 'catch up' with those who received the intervention because their undiagnosed heart disease becomes sufficiently overt to attract diagnostic tests during the year of follow-up.

As already discussed, when patients with COPD have received a cardiac disease diagnosis, they are less likely to receive optimal treatment. The difference in application of key aspects of cardiac disease management – such as beta-blocker and ACE-inhibitor use in heart failure, and antiplatelet and statin use in coronary artery disease – between study arms will be an additional measure of the effect of the structured cardiac assessment.

4.3.3.1 Definitions of heart disease and CVD

As highlighted in section 2.2, these terms are extremely broad. They are also used variably in the literature. Therefore, they must be defined specifically for the purposes of this research study. The presence of heart disease was the major outcome considered, and was defined according to conditions for which outcome-influencing medications were in wide use at the time of study design.

In reporting outcomes, the following definitions were used, with the intention that be both sufficiently comprehensive and straightforward to apply:

Heart disease: Defined as present if patients had any of:

- Heart failure with LVEF < 45%
- CAD, defined as MI, CACS > 100/CT or invasive angiographic evidence of CAD
- AF

Cardiovascular disease: Defined as present if patients had a diagnosis of any of the following conditions:

- Heart failure (any type)
- CAD (any type, including angina)
- Arrhythmia
- Stroke/TIA
- Peripheral vascular
- Diabetes
- Hypertension

In assessing prescription of statins and antiplatelet drugs (see section 7.2.1 and section 7.4.3), **atherosclerotic heart disease** (ASCVD) was also defined as comprising CAD, ischaemic stroke/TIA and PVD.

4.3.4 Quality of life and physical performance

Outcomes 7 and 8: evaluate the effect of the intervention on quality of life and physical performance

COPD is associated with a multitude of physical, psychological and social effects, as described in the introductory chapters (see section 1.4). Taken together, these comprise each patient's objective and subjective experience of living with COPD.[526] The nature of this experience has been termed 'quality of life' in a body of medical literature originating in the 1960s,[527] resulting in a plethora of efforts to define and measure patients' quality of life in objective, subjective, general and disease-specific terms.

In COPD, there is some correlation between markers of disease severity – such as FEV1[528] and exacerbation frequency[46] – and quality of life measures. However, this correlation is modest, reinforcing the need to specifically measure quality of life in order to thoroughly assess the effect of

an intervention. However, due to many inter-relating factors that contribute to overall quality of life, it is unrealistic to expect quality of life to be 'measurable' by a single instrument. The use of multiple tools that assess different aspect of quality of life is attractive, although the use of wide range of instruments can hamper comparison between studies.[529]

In a randomised controlled trial with repeated measures at baseline and follow-up, an instrument that is good at detecting change is important, and for this to be the case it should contain a substantial proportion of items that are sensitive to shifting with a change in the quality of life status of the participants studied. This sensitivity is highest when there are a minimum of items subject to 'floor' and 'ceiling' effects.[530] These effects occur when items and response options are poorly calibrated to the characteristics of the population studied, such that a high proportion of respondents fare 'worse' or 'better' than the available responses for worst or best performance. As an example of floor effect, a question about ability to participate in sports may be answered negatively by the vast majority of an elderly COPD population, and even with substantial improvement in health status would not be answered positively.

The two instruments used to measure quality of life in the SCATECOPD study are the St George's Respiratory Questionnaire for COPD patients (SQRQ-C) and the 5-level EQ-5D instrument provided by the EuroQol group (known as the the EQ-5D-5L). The former is a COPD-specific iteration of the St George's Respiratory questionnaire (SGRQ) consisting of 8 polytomous (Likert-style) questions and 32 dichotomous (predominantly true/false) questions.[531] It provides scores in three domains – symptoms, impacts and activities – as well as a total score, and has been used extensively in both descriptive and interventional studies.[532] While floor/ceiling effects have not been specifically studied for the SQRQ-C, they have been shown to be largely minimal for the SQRQ in a COPD population, with the exception of a notable ceiling effect for the impact domain.[533] The SQRQ-C has been found to be acceptable and straightforward to most patients[534] and has a minimal clinically important difference (MCID) of 4 units.[535]

In comparison to the SGRQ-C, the EQ-5L-5D instrument is not disease specific and is shorter, with 5 polytomous questions and an anchored visual analogue scale. The 5 domains assessed (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) were originally rated over three levels; expanded to 5 response levels in 2005. This 5-level version, or EQ-5D-5L, has become the dominant multi-attribute utility instrument used in studies concerned with economic evaluation of healthcare interventions.[536] Each of the 5 questions yields an integer score from 1 (no problems) to

5 (maximal problems), which define 3125 (5^5) different health states. Each state has been assigned an index value (also called a utility index), based upon responses from research participants who are asked to decide which of two health states they consider better, as well as to consider how much time in one health state they might be prepared to sacrifice to avoid a certain worse health state.[537] The highest value achievable is 1, and a state assigned a negative value is considered to be worse than being dead, although subsequent research suggests this does not reflect the experience or wishes of all respondents in such states.[538] Unique value sets have been created for participants from multiple different countries, to reflect differences in the importance given to aspects of quality of life,[539] as well as broad cultural differences in judgments about health states that are worse than death.[540]

The EQ-5D-5L index value has been found to be free from significant floor and ceiling effects in populations with chronic disease[541] and has a MCID of 0.051.[542] There is also a visual analogue scale component to the instrument, for which participants assess their current overall health from 0 to 100; this has a MCID of 6.9.

Physical performance can be assessed accurately and simply by measuring gait speed across a 4 metre flat, unobstructed course.[543] The patient is asked to perform two trials at their usual pace, using walking aids and supplemental oxygen as needed. The time taken to perform the fastest of two trials is used to calculate gait speed in m/s.[544] Besides being straightforward, safe and feasible in any setting, a slow 4-metre gait speed has been found to predict readmission and death following hospitalisation for ECOPD.[545] Importantly, gait speed is readily modifiable by rehabilitation and training so can be used as a measure of general functional improvement or deterioration over the recent past.[546] It is challenging, and probably unrealistic, to identify a universal cut-off to define a slow gait speed, due to variations in populations studied; speeds of 0.8,[543] 0.7[547] and 0.5 m/s[548] have all been recognised as defining a particularly slow-walking cohort with worse outcomes. The MCID for 4-metre gait speed has been calculated to be 0.11 m/s[549]; this can be simplified to 0.1 m/s given the precision with which gait speed is usually measured by stopwatch, and the correlation of an increase in velocity of this magnitude with an increase survival in a large pooled cohort study.[550]

4.3.5 Health costs and QALYs

Outcome 10: Report differences in health costs and estimated quality adjusted life years between the two study arms and assess feasibility of collecting health resource use data

If an improvement in outcome were to be seen in the group receiving the intervention, the question that would naturally follow would focus on the difference in healthcare costs between patients in the two arms of the study, so that a judgement about cost-effectiveness could be made. Cost data needs to be supplemented by quality of life data, including a quality of life state assigned to those patients who died, so that their health costs of zero from the point of death are not regarded as a positive effect. Given the design of the SCATECOPD study, the initial healthcare costs of patients in the intervention arm are expected to be higher, as for most randomised controlled studies. The extent to which the ratio of healthcare costs between the arms subsequently changes will depend on multiple factors, including any differences in adverse events between the arms – including costly hospital admissions – and the extent to which tests that are 'front-loaded' in the intervention arm end up being done later during the study period in the usual care arm. Details of the data collection and analysis plan for this aspect of the study are contained in section 4.7.

4.3.6 Right heart function

Outcomes 11-15: In the intervention group, examine the relationship between changes in right heart function between admission and stability and (E)COPD severity, comorbid cardiac disease and outcome

Echocardiography has been used to examine heart function during ECOPD, to make important links between poor ventricular function and outcome,[551] although relatively few studies have been conducted, with small sample sizes when compared with those carried out during periods of stability.[458,552] The right heart is of particular interest in patients with chronic lung diseases, including COPD, since, as has long been recognised, these patients are especially vulnerable to developing abnormalities of right heart structure and function, which may be accompanied by clinical signs such as jugular venous pressure elevation and peripheral oedema.[553] Dilatation and hypertrophy of the right ventricle, resulting from pulmonary disease and not due to left-sided heart disease, has come to define *cor pulmonale.*[554] This term remains in use despite being partially supplanted by other terminology such as right ventricular dysfunction or failure, and more specific descriptions of aberrant right ventricular structure and function such as an increased end diastolic volume or abnormal myocardial performance index. Pulmonary hypertension is regarded as an ever-present finding in right ventricular dysfunction due to COPD.[555] Accordingly, many studies have focussed on measuring pulmonary artery systolic pressure, assessed most accurately by right heart

catheterisation,[556] but most commonly by echocardiographic measurements of tricuspid regurgitation velocity alongside other right heart structural and functional parameters.[557]

Regardless of terminology, the most pertinent attribute of right ventricular dysfunction is that it is associated with significantly worse outcomes in patients who have COPD, including: increased mortality (by a factor of two in those with pulmonary artery pressure > 25mmHg[558]), increased risk for severe exacerbations[559] and, in those with reduced longitudinal systolic function, double the rate of adverse cardiovascular events.[552]

Despite these links to poor outcomes, the pathophysiological processes that lead to right ventricular abnormalities in COPD are not clearly delineated. Firstly, despite the focus on pulmonary hypertension, levels of pulmonary artery pressure elevation are only modest in COPD when compared with pulmonary hypertension of other causes, such as thromboembolic disease or primary pulmonary arterial hypertension.[560] The steeper increases in pulmonary circulation pressures seen when patients with COPD exercise may be an important factor contributing to right ventricular remodelling, however[561]; these increases also occur during acute exacerbation.[562] Secondly, recent studies have provided conflicting data on the effect of COPD on right ventricular size. Right ventricular dilatation has been the traditional paradigm for right ventricular failure in COPD, and indeed a recent investigation of right ventricular end diastolic volume during exacerbation reported higher mortality in those with a dilated right ventricle, who had a higher degree of exacerbation severity as measured by DECAF score and blood carbon dioxide concentration.[563] In contrast, cardiac MRI scanning of stable patients has associated more severe COPD with *smaller* right ventricular volumes, a state the authors termed 'cor pulmonale parvus'.[564] For a complete and correct description of the pathophysiology of right heart disease in COPD, this discrepancy requires resolution, perhaps by better characterisation of the COPD phenotypes involved in different right ventricular structure and function changes, but almost certainly through the studying of the same patients during exacerbation and after recovery. This has been done infrequently, and not with the correlation of clinical outcomes with trajectories of right ventricular dysfunction.[565] The echocardiographic evaluations performed during the SCATECOPD study therefore offer an opportunity to further understanding of right ventricular functional changes between exacerbation and stability and their correlation with background COPD and exacerbation severity.

4.4 Data collection

4.4.1 Baseline

For all consenting patients, data were entered onto paper source document worksheets using information from inpatient, outpatient and GP medical records, radiology and blood science reports, plus researcher observations and patient responses to questions. When complete, source document worksheet data was transcribed to a database held on a single password-protected PC. Source document worksheets are found in Appendix D. Specific considerations relating to data collection at baseline are listed here:

- **Most recent spirometry** – Most recent formal lung function reports were used preferentially, given these were accompanied by quality statements. In the absence of lung function laboratory testing, most recent GP recorded spirometry was used if it provided the ability to assess for obstruction and percentage of predicted FEV1. When recorded, the higher value of FVC or slow VC was used for calculation of FEV1/VC ratio in line with recommended practice[566]
- **Admission date/time** – The time of arrival to the emergency department (ED), rather than time of admission onto the ward, was used to accurately reflect time spent in hospital receiving treatment and account for variability in time spend in ED due to hospital bed availability; this convention was followed for recording subsequent admission information.
- **Symptoms and signs** – Presence or absence at presentation was ascertained from clerking documents plus findings of questions and examination by researcher
- **Initial observations** – The least favourable observations (i.e. those that summed to the highest national early warning [NEWS2] score) in the first 24 hours of admission were recorded. If more than 2 sets of observations had equally high scores, the set recorded earliest in admission was used.
- **Height and weight** – Obtained from mandatory nutritional assessment in majority of cases; if this was not performed then patients recollected height and weight were used.
- **Admission arterial blood gas (ABG)** – The least favourable ABG measured during the first 24h of admission was recorded, i.e. that with the lowest pH if decompensated type 2 respiratory failure was present, the highest $PaCO_2$ if compensated type 2 respiratory failure present, or the worst PaO_2 if type 1 respiratory failure alone was present. Fraction of inspired oxygen (FiO_2) was obtained from the notes of the clinician documenting the ABG; if not documented the observations at the time of ABG sampling were used. If only a venous

blood gas (VBG) was measured, the parameters were recorded and 'ABG not done' was indicated

- **Admission chest radiograph (CXR)** – The first CXR done during admission, regardless of projection, was assessed for the presence of abnormalities documented on the admission consultant ward round or subsequently identified by the reporting radiologist. Cardiothoracic ratio was measured in standard fashion by dividing the widest horizontal line drawn from right to left heart border by the widest horizontal line drawn from the right inner border of the thoracic cage to the left inner border of the thoracic cage.[567] Diaphragm height was also measured by drawing a transverse line across the thoracic cage from the costophrenic angle, and measuring the vertical distance to the apex of the right hemidiaphragm from this line.
- **Admission bloods** – The first sample taken was recorded for each parameter.
- **Admissions history** – This was obtained from a combination of hospital records and cross-referenced with patients' self-reported history (to ensure admissions elsewhere were accounted for). Exacerbation history was obtained from a combination of patient report, hospital and GP records and by records of rescue pack use.
- **Clinical scores** – eMRCD score was assessed from discussion with the patient about their physical function on a good day in the past 3 months. As emphasised in Table 11, a critical distinction in eMRCD scoring is between a score of 4 and 5a, the latter representing a patient too breathless to leave the house unaided (except by simple walking aids such as a stick or frame).[500] As much recruitment took place during the period of the COVID-19 pandemic, when clinically vulnerable patients were advised to shield, special attention was paid to scoring, to ensure that even if patients had not walked outside – or only walked from their front door to a car – due to shielding their eMRCD score was not inflated to 5a when, on a recent good day they could have left the house unaided. The PEARL score, used for randomisation stratification, was calculated according to the criteria stipulated in Table 10. The Rockwood clinical frailty score (CFS) was applied with the aid of a pictorial summary sheet, see figure 31.[568] Similar care applied to the distinction between scores of 5 and 6: since the latter is characterised by the need for 'help with all outside activities' it was ensured that this was not inflated by shielding behaviours such as less vulnerable family members doing shopping.

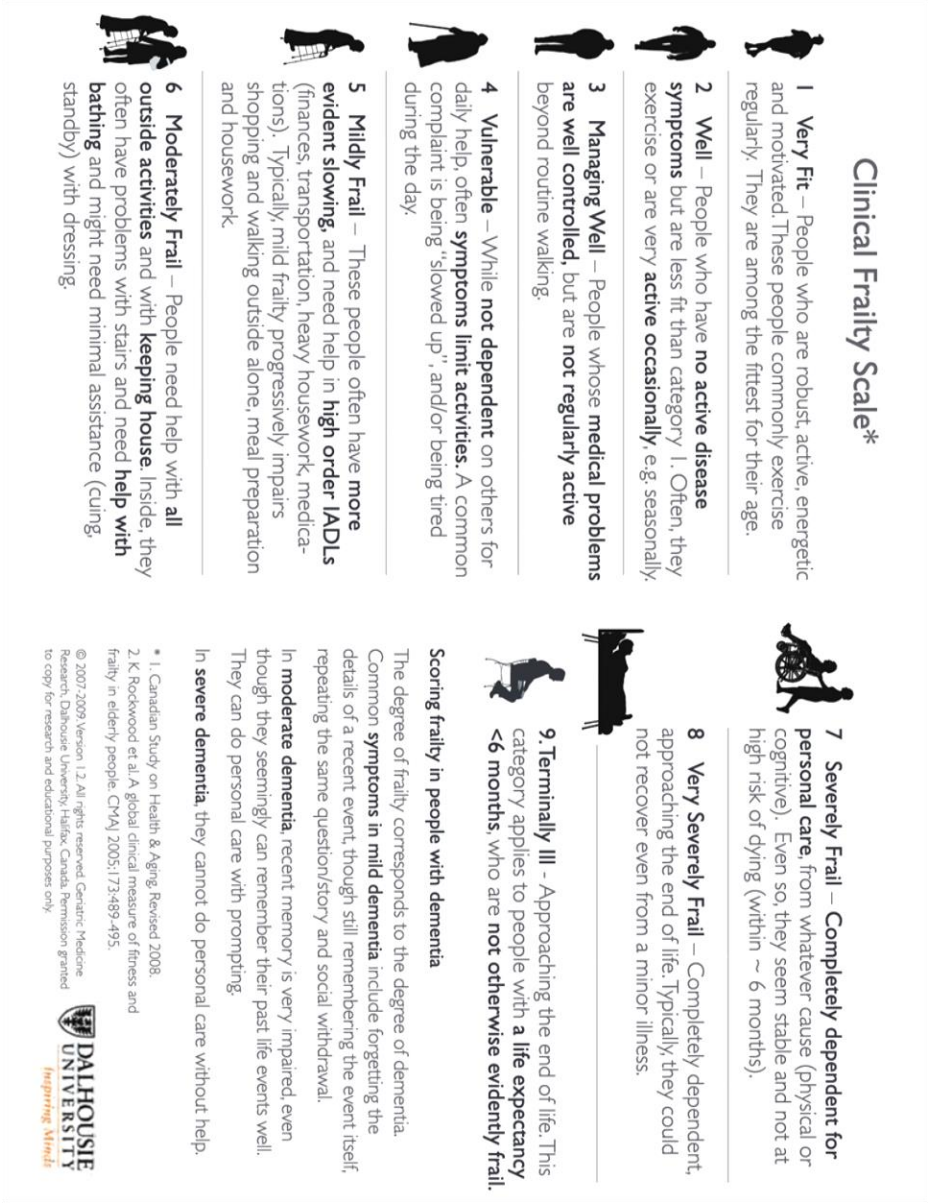


Figure 31: Pictorial aid for scoring the Rockwood clinical frailty score

- **CV comorbidities** – These were recorded based on medical notes up to the point of admission; any diagnoses made during admission were added after discharge. Heart failure diagnoses were regarded as present if recorded but no echocardiographic evidence was available. If, however, there was echocardiographic evidence of only normal cardiac function, these diagnoses were regarded as not being present, as further investigations had refuted the clinical diagnosis. If patients had a past echocardiogram demonstrating LV systolic dysfunction, but this had subsequently improved to within normal limits, this was regarded as an existing diagnosis of LVSD. The entity of heart failure with recovered ejection

fraction (abbreviated as HFrecEF) has been only widely recognised in recent years and was not included in guidelines until after the design of the SCATECOPD study; these patients have abnormal biomarkers and ongoing symptoms, heart failure hospitalisations, justifying the approach taken here.[569] Valve disease was only recorded if it was assessed as being moderate or severe.

- **Previous echocardiogram** – The most recent available prior to admission was recorded. If only reported details were available (for example, a clinic letter stating LV ejection fraction), this limited information was recorded.
- **Other comorbidities** – These were recorded in order to calculate the age-adjusted Charlson comorbidity index,[570] a validated method of measuring comorbidity that has been shown to predict mortality and readmission in multiple settings, including COPD,[571] and heart failure,[572] as well as hospitalisation with COVID-19[573] and all-cause acute admissions in elderly patients.[574] For the purposes of assessing for chronic kidney disease, the best recorded estimated glomerular filtration rate (eGFR) in the past 12 months was recorded, in line with the global KDIGO recommendations.[575] If no recent eGFR the baseline creatinine was taken as the best achieved during admission. If patients had no formal diagnosis of CKD but eGFR < 60 this diagnosis was recorded, with the stage as per KDIGO.
- **Spirometry** – Recorded as soon as patient felt able to complete the assessment, using a portable spirometer (Easy on-PC, ndd Medical Technologies), with quality graded according to American Thoracic Society (ATS)/ERS technical standards.[576] Slow vital capacity measurements were taken in order not to underestimate VC.
- **4-meter gait speed** – Assessed according to methodology discussed in section 4.3.2.3. Infection control requirements on the ward were respected, particularly in the earlier phase of recruitment when COVID-19 infection control measures were especially rigorous.

For patients in the intervention arm, data were collected from the SCA on an additional source document worksheet, as detailed in section 4.2.6. For patients in the usual care arm, the results of any cardiac tests done by the patients' care team were recorded. All diagnoses made, either via the SCA or by the attending teams, were recorded, along with any treatments indicated and any reasons why treatments were not started.

4.4.2 Follow-up

90 days

Patients were contacted after discharge to arrange face-to-face follow-up, scheduled at 90 days post-discharge +/- 10 days. If patients had recently had an exacerbation, follow-up was delayed until 4 weeks after the completion of steroids +/- antibiotics, following guideline recommendations to ensure spirometry was collected at clinical stability.[577] If successive or slow-resolving exacerbations took place, efforts were made not to delay review beyond 8 weeks wherever practical to avoid excessive follow-up delays.

All patients received reassessment of smoking status, functional status, COPD and CVD therapy, CVD diagnoses, quality of life (by SQRQ-C and EQ-5D-5L), 4-metre gait speed and spirometry, plus information about admission dates and times for COPD/CVD/other reasons. Data were also collected about healthcare resource use (both COPD and non-COPD) using a structured questionnaire comprising GP care, outpatient and acute secondary care, allied services, rehabilitation and residential care.

Patients in the intervention arm also received a repeat transthoracic echocardiogram – with the same dataset used as during admission and intravenous contrast administered if required – ECG and blood tests, including NT-proBNP and troponin T.

6 and 9 months

At these time points, telephone review was conducted to establish current COPD and CVD therapy and responses to the healthcare resource use questionnaire (HRUQ) covering the previous 3 months. Patients who were significantly unwell at the 6- or 9-month time point, for example due to hospitalisation with ECOPD, were recontacted as early as was reasonable after they had recovered.

12 months

Face-to-face review for reassessment of smoking status, functional status, COPD and CVD therapy, CVD diagnoses, quality of life (by SQRQ-C and EQ-5D-5L), 4-metre gait speed and spirometry, COPD/CVD/other admission dates and times and healthcare resource use.

The data collection schedules are summarised in the below tables:

	Baseline	90 days	6 months - telephone	9 months - telephone	12 months
Demographics, comorbidity	X	X			X
Medications	X	X	X	X	X
eMRCD	X	X			X
Spirometry & inspiratory capacity	X	X			X
NYHA class	X	X			
Rockwood clinical frailty scale	X				
COPD assessment	X				
Bedside observations	X				
ABG*	X				
ECG*	X				
Blood tests*	X				
4m gait speed	X	X			X
SGRQ-C	X	X			X
EQ-5D-5L	X	X			X
Exacerbation frequency	X	X	X	X	X
Hospital admissions / ED attendances		X	X	X	X
Primary & secondary NHS care visits		X	X	X	X
Mortality		X			X
Adverse Cardiovascular Events		X			X
* As performed by clinical team caring for patient					

Table 16: Schedule of assessments and tests for all patients in SCATECOPD study

	Baseline	90 days
12-lead ECG	X	X
Echocardiogram	X	X
Blood tests	X	X
24-hour ECG	X	
Cardiac CT	X	
Blood pressure assessment	X	

Table 17: Schedule of assessments and tests for patients in SCA arm of SCATECOPD study

4.4.3 Withdrawal and non-attendance

If a patient decided they no longer wanted to have face-to-face follow-up, this change in consent was recorded and they were offered telephone follow-up. Spirometry and gait speed data was not collected at 12 months from these patients, nor at 90 days if their consent status changed prior to

this time point. The follow-up tests scheduled at 90 days as part of the SCA, if applicable, were also not performed if non-attendance at face-to-face follow-up occurred at this time point. If a patient decided they did not want any further contact relating to the study, including telephone contact, this was also recorded and consent was sought for remote recording of admissions and mortality from their electronic records for calculation of DAOH, mortality and admission-related outcomes.

4.5 Diagnosis and treatment of conditions identified

4.5.1 Diagnostic criteria

Criteria for diagnosis of conditions identified by SCA were pre-specified according to relevant local, national and international guidelines with the consensus of local specialist clinicians. The diagnostic criteria, along with further specifics and the rationale for precise definitions used within the study, are listed below.

4.5.1.1 Heart failure with moderate-severe LV systolic impairment

Diagnostic criterion: LVEF < 45%

Further information: If LVEF was measurable by Simpson's biplane method this value was used for diagnosis. Alternatively, if Simpson's method could not be used due to poor endocardial border definition, despite the use of intravenous contrast, the sonographer's estimation of LVEF was used.

The LVEF cut-off of 45% was chosen to align diagnostic criteria with local guidelines for treatment, accepting that different societies have published diagnostic and treatment recommendations that use different values of LVEF. However, it was important that patients in the intervention arm of the study were assigned treatment based on echocardiographic markers in the same way as those in usual care, therefore the local cutoffs were used in preference.

LVEF < 40% was used by the local heart failure service as the criterion for initiation of combination heart failure treatment with novel agents (see section 4.5.2.1 below).

Additional clinical criteria were not required, as all patients had breathlessness and therefore satisfied the need for the presence of symptoms and/or signs for the identification of a clinical syndrome, rather than the isolated echocardiographic identification of abnormal ventricular function.

4.5.1.2 Heart failure without moderate-severe LV systolic impairment:

Diagnostic criteria: LVEF ≥ 45%, with echocardiography report of LV diastolic dysfunction

Further information: Once again, the local treatment cut-off thresholds were used to avoid complicating the categorisation of heart failure diagnosis. Diagnosis made if any evidence of diastolic dysfunction was noted the in echocardiography report. Sonographers used the BSE algorithm for the assessment of diastolic function. Although more complex definitions exist, such as those for HFpEF (see Section 2.2.1), this definition was chosen for its simplicity, to correspond with local guidelines regarding thresholds for treatment, and because it was anticipated that it would be difficult to reliably obtain the range of echocardiographic data required to make or refute more complex diagnoses such as ESC-defined HFpEF and HFmrEF.

4.5.1.3 Right-sided heart failure

Diagnostic criteria: Overall assessment of RV impairment at TTE, with peripheral oedema on examination

Further information: The function of the right heart is more challenging to measure than the left, chiefly because the RV has a more irregular shape and contracts in a more complex way. Simple measures of one-dimensional shortening do not accurately describe function. Several measurements are used to describe right heart function, including the distance moved by the tricuspid valve towards the RV apex during systole (the tricuspid annular plane systolic excursion, or TAPSE), the peak velocity of the tricuspid valve as it moves apically in systole (referred to as S'), the percentage reduction in the internal area of the right ventricle between diastole and systole (the fractional area change, or FAC), and the velocity of regurgitation through the tricuspid valve (TR velocity), from which an estimate of the pulmonary artery systolic pressure can be derived from the modified Bernoulli formula, as can an estimate of the overall probability of pulmonary hypertension.[578]

TAPSE, as a linear M-mode measurement, is relatively straightforward to capture and measurable in most cases, including in COPD population.[579] Nevertheless, its interpretation is variable: the threshold for abnormally low TAPSE is variously defined, between 1.8 cm[578] and 1.5 cm[580]. The local definition, < 1.6 cm, was used in interpreting measurements taken in this study.

S' and FAC both rely on adequate views, of the lateral annulus of the tricuspid valve and of the endocardial border, respectively, which makes their use challenging in patients with COPD, particularly those with marked emphysema.[581]

Tricuspid regurgitation is not always measurable, and can be normal in the presence of RV impairment.[582] The preference of guideline development groups is for the use of pulmonary hypertension *probability* over numerical estimates of PASP[504,578] – this categorical variable is

derived from the TR velocity measurement in combination with other measurements from the cardiac chambers and great vessels. This approach was taken to the TR velocity measurements acquired in the study.

As summarised in Table 18, the various methods for assessing right heart function all have limitations as tools for diagnosing right heart failure. Accordingly, while the above quantitative assessments were made wherever possible, the pragmatic decision was made to use the *overall assessment of RV function* made by the sonographer on the basis of these objective measurements (where obtainable), alongside subjective assessments such as the quality of radial ventricular contraction observed, as the criterion with which to diagnose right heart failure. In addition, patients had to have evidence of peripheral oedema on examination: this distinguishes the echocardiographic finding of RV impairment from the clinical syndrome of right-sided heart failure.

Measure	Definition	Measurement technique: view (modality); notes	Normal range*	Pitfalls/problems	Advantages
TAPSE	Displacement of the lateral TV annulus towards the RV apex during systole	A4C (M-mode); cursor aligned with lateral tricuspid annulus	<1.6cm	Assesses longitudinal function only; can be normal in setting of radial dysfunction	Simple, prognostic in pulmonary hypertension[583]
Tricuspid s'	Peak velocity of the tricuspid annulus during displacement towards the RV apex in systole	A4C (pulsed wave tissue Doppler); aligned with basal RV free wall and lateral tricuspid annulus	≥9 cm/s	Assumes function of a single segment represents function entire RV[584]	Better detects reduced RVEF, as measured by MRI, than TAPSE[585]
Fractional area change (FAC)	Percentage change in right ventricular area from end-diastole to end-systole	A4C (2D); RV endocardial border manually traced: lateral TV annulus along free wall to apex, along interventricular septum to medial TV annulus	≥30% (male) ≥35% (female)	Requires good image quality; neglects contribution of the RV outflow tract to overall systolic function[584]	Provides a quantitative measure that incorporates radial function
Estimated pulmonary artery systolic pressure (PASP)	Calculated from peak TR velocity: PASP = (4 x TRV_{max}^2) + RAP	A4C (continuous wave Doppler); measured across the tricuspid valve to determine peak TR velocity	≤ 30 mmHg	Eccentric jets lead to incomplete Doppler envelopes and underestimation of TR velocity and hence PASP; requires RAP estimation; absent TR does not exclude PH[504]; low precision[586]	Continuous variable; accurate on a population level; good correlation with invasive mPAP values[586]
Pulmonary artery hypertension probability	Based upon TRV_{max} in conjunction with other markers involving chamber sizes, RVOT acceleration, PR, IVC diameter	PSAX (2D, pulsed wave and continuous wave Doppler), A4C (2D), subcostal (2D M-mode); required to assess TRV_{max} plus all additional signs	N/A	Categorical variable therefore detail lost from data; insensitive in mild PH[587]	Better aligns with role of echocardiography as screening tool for PH
Overall assessment of RV function	Synthesis of longitudinal and radial function assessments	A4C (2D) for qualitative assessment of radial function; as above for quantitative longitudinal measurements	N/A	Qualitative assessment, inter-operator variability and reduced specificity[588]; categorical data	Highly specific for low RVEF by MRI[588]; ascertainable from low quality views (c.f. FAC)

*Locally accepted definition (others exist, see text). Abbreviations: A4C – apical 4-chamber view; 2D – 2-dimentional; TRV_{max} – peak tricuspid regurgitation velocity; RAP – right atrial pressure; RVOT – right ventricular outflow tract; PR – pulmonary regurgitation; PSAX – parasternal short axis; PH – pulmonary hypertension; TV -tricuspid valve

Table 18: methods of assessment of RV function

4.5.1.4 Moderate-severe coronary artery disease

Diagnostic criteria: CACS ≥ 100 on cardiac CT scan, or previous myocardial infarction/coronary revascularisation.

Further information: Coronary artery calcification, as measured by non-contrast CT scan using the Agatston system, has been demonstrated to be highly correlated with coronary artery plaque burden, and to be independently associated with incident adverse cardiovascular events.[589] The median annual incidence of such events is 16 times higher for asymptomatic patients in the highest CAC categories[590]: 1.6% vs. 0.1% for patients with a CACS of ≥400vs 0. Accordingly, CACS is an effective non-invasive method with which to diagnose coronary artery disease; the Agatston score cut-off of 100 was selected to define moderate to severe CAD (as opposed to mild or absent disease), as this has been recommended as the threshold above which aspirin should be prescribed for primary prevention,[590] based on the balance of risk and benefit from prospective observational data.[591]

Patients who had had a previous myocardial infarction or coronary revascularisation were also considered to have CAD. A historical diagnosis of angina was not included in this definition as the circumstances under which this diagnosis was made were anticipated to be unclear and it is known that, in the majority of cases, it is not associated with significant CAD on further investigation.[592]

4.5.1.5 Atrial fibrillation

Diagnostic criteria: Any episode of AF detected clinically, seen on 12-lead ECG, or present for ≥5 minutes on 24-hour ECG

Further information: As stated in Chapter 2 (Section 2.2.3), it appears that very short events of asymptomatic AF are not associated with adverse outcomes,[177] and that a threshold of ≥5 minutes confers a significantly increased risk of stroke. Therefore, if threshold was surpassed on 24-hour ECG monitoring, this was considered to satisfy a diagnosis of AF. Additionally, if AF was seen on a 10-second 12-lead ECG recording, or detected clinically, it was considered to be present at supra-threshold levels and the diagnosis was made.

4.1.5.6 Hypertension

Diagnostic criteria:

New diagnosis of hypertension: Blood pressure (BP) ≥ 180/120 mmHg on two occasions (either value); or BP ≥ 140/90 mmHg on two occasions in last 24h of admission,

subsequently confirmed by ambulatory BP monitoring

Uncontrolled hypertension: Known hypertension, with BP ≥ 140/90 mmHg on two occasions in last 24h of admission, or BP medication uptitrated by clinical team during admission

Further information: These recommendations are based on the NICE guideline for hypertension in adults.[593] The final 24 hours of admission was selected for evaluation of blood pressure since this is the period when patients should be most clinically stable. Ambulatory BP monitoring was requested from the local physiology department and the standard threshold of a daytime average of ≥ 135/85 mmHg applied for diagnosis of hypertension.

4.5.1.7 Type 2 diabetes

Diagnostic criteria:

New diagnosis of type 2 diabetes: $HbA_{1C} \geq 48$ mmol/mol confirmed on repeat

Uncontrolled type 2 diabetes: $HbA_{1C} \geq 58$ mmol/mol confirmed on repeat in patients with known T2DM

Further information:

These thresholds were based on the NICE guideline for type 2 diabetes in adults[594] and advice from local diabetes specialists. There was a recognition that in some cases glycaemic control may have deteriorated due to the physiological stress of a prolonged illness or because of corticosteroid treatment,[595] hence the need for confirmatory samples and ongoing review of glycaemic control post-discharge (see management summaries below).

4.5.2 Management summaries

For each diagnosis made as a result of the SCA, recommended treatment approaches were summarised, based on relevant local, national and international guidelines and agreed with local specialists.

Treatment of diagnosed conditions was carried out by the treating hospital team and continued by the patients GP and specialist services (e.g. community heart failure service) if appropriate. Treating clinicians were not instructed on management decisions; rather, management summaries were produced and disseminated to the patients' GPs when new diagnoses were made, with the intention of providing a framework for a consistent response to new diagnoses, and streamlining the primary care workload associated with the additional diagnoses made by the SCA. In this subsection, specific aspects of management are highlighted for each diagnosis; the management summaries produced

for the study are included in full in Appendix C. As stated in section 4.2.7, for patients in usual care management of existing comorbidities, and any diagnosed during admission, was at the discretion of their usual treating teams.

4.5.2.1 Heart failure with moderate-severe LV systolic impairment

Referral to the heart failure service was recommended for supervision of ongoing care. Beta-blocker and ACE-inhibitor introduction and titration was recommended, following NICE and ESC guidelines[596,597] and local policy. Diuresis with furosemide was advised where pulmonary or peripheral oedema was identified, as was renal function monitoring where appropriate (e.g. with use of renin-angiotensin system antagonist or diuretic therapy). The local heart failure service used an LVEF threshold of <40% to initiate treatment with sacubitril-valsartan, SGLT2 inhibitor and mineralocorticoid inhibitor alongside beta-blocker treatment.

4.5.2.2 Heart failure without moderate-severe LV systolic impairmentt

For these patients, diuresis and treatment of important comorbidities such as hypertension, atrial fibrillation, diabetes and CAD was recommended, following the framework detailed in the management summaries for these conditions. Although evidence has emerged for the role of SGLT2 inihbitors in patients with higher ejection fractions,[130,131] this was published after the finalisation of the management summaries for the SCATECOPD study and was therefore not included in the management framework.

4.5.2.3 Right-sided heart failure

The recommendations were the same as for heart failure without moderate-severe LV systolic impairment.

4.5.2.4 Moderate-severe coronary artery disease

It was recommended that patients were prescribed aspirin 75mg daily, or clopidogrel if intolerant or allergic to aspirin. Co-prescription of proton-pump inhibitor was recommended for patients aged over 75 and/or with a history of gastrointestinal bleeding, peptic ulceration or severe gastro-oesophageal reflux disease. Additionally, atorvastatin 20mg daily was recommended for this group, with liver function test monitoring. Atorvastatin 20mg daily was also recommended for patients who

had a CACS of 1-100, or a QRISK3 score of over 10%. A higher dose of atorvastatin, 80mg daily, was recommended for patients who had experienced an adverse cardiovascular event such as MI or stroke, or experienced such an event during the study period, in line with NICE guidance.[598]

4.5.2.5 Atrial fibrillation

Recommendations were made to assess individual stroke and bleeding risk to guide use of anticoagulation, and to control heart rate to ≤110bpm at rest, following NICE and ESC guidelines.[599,600]

4.5.2.6 Hypertension

Treatment initiation was recommended if BP was ≥ 180/120 mmHg on two occasions, but not until confirmation by ambulatory blood pressure monitoring if below this threshold. Agents recommended were as stipulated in NICE and ESC/ESH guidelines.[593,601] Review and monitoring recommendations were also provided.

4.5.2.7 Type 2 diabetes

The need for shared decision making regarding Hb_{A1C} targets and management decisions was emphasised, as was the need for ongoing supervision via primary or secondary care diabetes services. The additional benefits of SGLT2 inhibitor therapy in patients with comorbid heart disease was emphasised although, as for heart failure at higher ejection fractions, prescription recommendations changed following study set-up to recommend these medications more prominently. In 2022 these medications became first-line alongside metformin for patients with comorbid heart disease or a QRISK score predicting a greater than 10% risk of stroke or MI over 10 years.[602] This would have impacted all of the 32% of patients who had diabetes in the SCA arm, in whom elevated QRISK scores were ubiquitous.

4.6 Statistical Methods

4.6.1 General principles and methods

The study design and plan for data analysis was created with the collaboration of a biostatistician, Dr Keith Gray and uploaded to the ISRCTN registry. The statistical analysis plan was finalised by a second statistician, Dr Eduwin Pakpahan (after Dr Gray changed post) and also uploaded to ISRCTN.

All statistical tests used were two sided and the critical alpha was set at 5%. 95% confidence intervals were calculated where appropriate.

4.6.2 Assessment of DAOH

The plan for analysis of DAOH was for assessment of sample distribution and testing for difference between the SCA and usual care groups using Student's t-test or Mann-Whitney U test as appropriate. Stepwise Poisson regression analysis (with robust standard errors in the case of overdispersion) was planned to examine the association between the number of days spent alive outside of a hospital and the treatment (SCA vs. usual care), adjusting for various appropriate demographic variables (such as age, sex, COPD severity, comorbidity and frailty).

4.6.3 Assessment of other outcome measures

The plan for analysis of other collected data including that relating to other outcome measures was as follows:

- Present baseline characteristics and follow-up measurements with suitable measures of central tendency and spread for continuous data (mean and standard deviation for parametric data; median and inter-quartile range for non-parametric data).
- Present proportions for categorical data (including binary data).
- Present descriptive data for the whole cohort and for each study arm, with tests for difference between the study arms carried out using appropriate tests: Student's t-test for comparing means; Mann-Whitney U test for non parametric data; Fisher's exact test for categorical data.
- Carry out tests for change between time points using: paired Student's t-test to compare means; for non-parametric data, Wilcoxon signed rank test; for categorical data, McNemar's test.
- Carry out multiple comparisons between distributions, where appropriate, using repeated measures analysis of variance (ANOVA) with Bonferroni correction for post-hoc tests, or, for non-parametric data, Kruskal-Wallis test.
- Assess time to event outcomes, such as time to readmission or death, by the Kaplan-Meier method, with differences tested by the log-rank test.

- Analyse quality of life using the area under the curve method as discussed in Section 4.7.3, with change in quality of life per unit time compared between the study arms using Student's t-test or Mann-Whitney U test as appropriate.
- Present data from cardiac tests performed in the SCA arm according to the principles above, with associations between cardiac test results and outcomes tested using the above range of statistical methods, as appropriate to the distributions.
- Assess correlations between bivariate continuous data using Pearson correlation coefficient.
- Assess diagnostic tests using diagnostic performance statistics and area under receiver-operator curve analysis.
- Support the assessment of the feasibility of the key outcomes of interest listed in the objectives (section 4.2.2) for use as primary outcomes in future study, by using observed differences to calculate sample sizes that would be required to adequately power definitive trials.

The statistical methods used for the cost effectiveness analysis are presented separately, in section 4.7.

4.6.4 Data handling and software

Data recorded on source document worksheets was transcribed to a Microsoft Excel database. The accuracy of this process was checked through data verification carried out by an independent clinical researcher, who assessed the accuracy of transcription for the first 10 of records transcribed. As accuracy was high (99.79%), and with the agreement of the trial steering committee, this process was deemed acceptable. 10% of the subsequent records were then randomly selected by the same independent researcher and assessed, with accuracy remaining high (99.93%).

Statistical analyses were carried out using SPSS Statistics version 28 (IBM), Stata version 17 (StataCorp) and Prism version 10 (GraphPad).

4.7 Economic evaluation

This evaluation is directed at meeting the study objectives to collect healthcare resource use data to report differences in health costs and quality adjusted life years between the study arms, and to assess the feasibility of collecting healthcare resource use data to carry out an economic evaluation of the intervention in a future RCT. The results of the economic evaluation are intended to guide

subsequent pre-trial modelling for future studies. An independent health economist (Professor Jo Gray, Northumbria University) contributed to this aspect of study design and analysis, and was a member of the Trial Steering Committee.

4.7.1 Measurement of health effects

Healthcare quality of life was measured using the EQ-5D-5L tool, discussed above in subsection 4.3.2. EQ-5D-5L responses were converted to utility indices (UI) using the UK value set and the crosswalk method published by Van Hout[603] and preferred by NICE.[604] The utility index ranges from 1 (no problems in any health domains) to -0.594 (extreme problems in all health domains) in the UK value set. Mean change in quality of life during the study period was calculated from the three UI values collected at baseline, 90-day and 12-month follow-up.

The plan for the two main reasons for encountering missing quality of life data was as follows:

1. *Death during follow-up*

   Patients who died were assigned a UI of 0 at their data of death. This approach has precedent[605,606] and has been shown to counteract the bias of EQ-5D-5L scores upwards that occurs without this adjustment.[607]
2. *Non-attendance at active follow-up*

   For initial analysis, patients who did not attend active follow-up were excluded from the analysis as complete quality of life data was not available. However, the likelihood is that this data is *not missing completely at random*: the odds of follow-up non-attendance may be expected to increase as patients deteriorate and die, which is associated with worsening quality of life. By contrast, but also with non-random implications, the odds of follow-up non-attendance may increase if patients feel very well and feel no further need to prioritise involvement with the study. Therefore, excluding patients without data has the potential to bias results. As a result, analysis was also carried out after multiple imputation of missing data, with sensitivity analysis to explore the effect of missing data on the conclusions.[608]

4.7.2 Measurement of healthcare resource use

Healthcare resource use was collected from records held by local hospital trusts and GP practices, as well as patient healthcare resource use questionnaires (HRUQs) completed with the researcher at each follow-up point. No healthcare use occurring after the 365th post-discharge day was counted. For patients that died or did not attend active follow-up, only hospital admission information could

be gathered, as the patient was unable to complete the HRUQ. As hospital costs were by far the greatest contributor to healthcare resource use, and loss to follow-up through death was balanced across the arms, these patients were included in the final analysis.

Costs were assigned to the index admission, subsequent hospital admissions, outpatient care (including tests) and primary care encounters, using latest NHS reference costs,[609] Unit Costs of Health and Social Care,[610] the NHS drugs tariff[611] and local costs for SCA investigations as advised by the local research and development department. Full details of prices associated with healthcare use are found in Appendix E.

4.7.3 Calculation of QALYs and incremental cost-effectiveness ratio

Quality adjusted life years (QALYs) were calculated from the EQ-5D-5L UI, with adjustment for baseline UI to mitigate the impact of small baseline quality of life imbalances on subsequent estimates of incremental cost-effectiveness ratio (ICER).[612] For patients with significantly delayed 90-day follow-up (defined as follow-up occurring more than 15 days after the 90th post-discharge day), the UI recorded at the later time point was adjusted, assuming a linear change in UI from baseline to 90 days and to the delayed time point. In the graphical example below, a patient whose UI increased from 0.5 at baseline to 0.8 at a delayed follow-up at 120 days has a change in UI of +0.0025 per day (0.3/120). Their UI at 90 days was calculated at (0.5 + 0.0025*90) = 0.725. This allowed QALY calculation, using area under the curve method, to be unbiased by delayed follow-up. No such adjustment was necessary for costs, as these were simply summed over the 12 months of follow up.

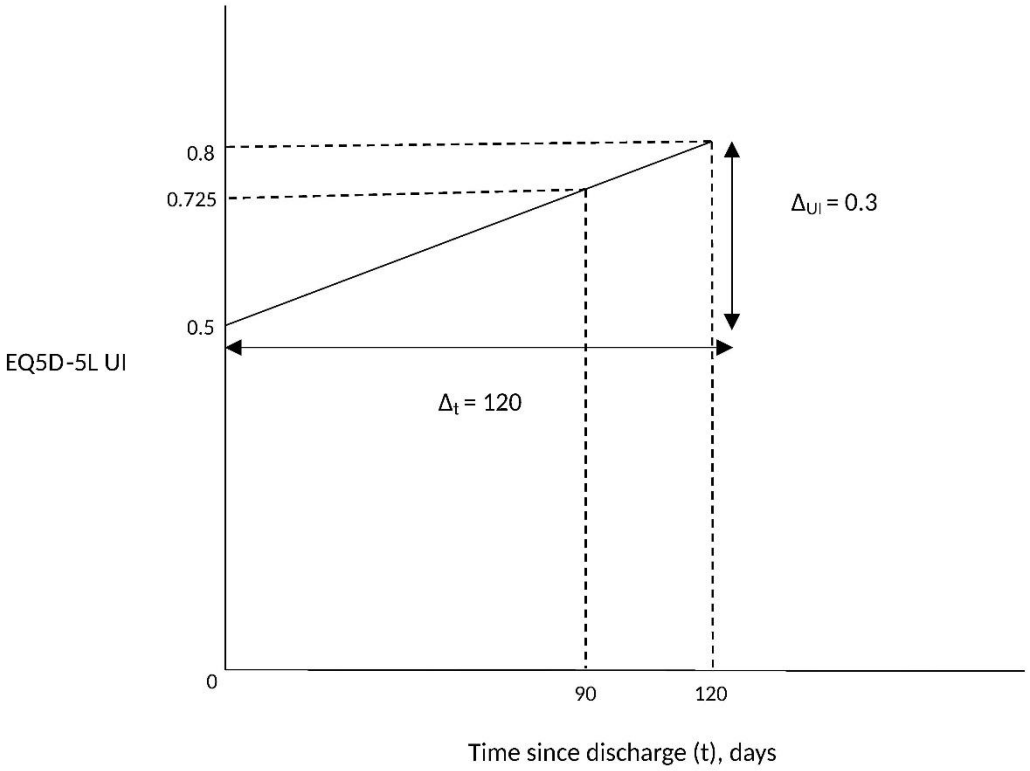


Figure 32: Method for adjustment of delayed 90-day EQ5D-5L UI scores

The incremental cost effectiveness ratio – synonymous in this case with the cost per QALY – was calculated by dividing the cost difference between the study arms by the difference in QALYs. The distribution of the ICER was constructed using bootstrapping: taking 10000 samples with replacement from the QALY and cost data. This distribution was used to calculate the probability of the SCA being cost-effective at increasing willingness to pay thresholds.

4.8 Governance

4.8.1 Funding

This research was funded by Northumbria Healthcare NHS Foundation Trust (sponsor), Chiesi Limited, and Menarini Pharmaceutica. No organisation had any role in the study design, execution and analysis, or decision to publish the results.

4.8.2 Ethical approval

The study was referred for Research Ethics Committee (REC) approval via the Integrated Research Application System (IRAS) with project ID 277817. REC favourable opinion was received in November

2020 and HRA and HCRW approval was given in November 2020 with REC reference 20/ES/0112. An IRAS progress report was submitted to the HRA in March 2023 and the end of study form in February 2024.

4.8.3 Registrations

The study was registered on the ISRCTN registry with the plain language title “Does a detailed assessment for heart disease help patients who have been admitted to hospital with a flare-up of chronic obstructive pulmonary disease (COPD)?” and registry number ISRCTN26935612. This registry page was updated regularly with the protocol, study timeline and publication information.
The study was adopted by the National Institute for Health Research (NIHR) portfolio in December 2020 with the central portfolio management system (CPMS) ID 47350.

4.8.3 Local approvals

Caldicott approval was given locally for data storage and transfer in December 2020 with local reference number C3505. Approval for local research and development department support was given in December 2020 with local reference number NHCT0205.

4.8.4 Trial steering committee

Four trial steering committee (TSC) meetings, chaired by an independent researcher external to the study centre, took place, in April 2021, September 2021, June 2022 and March 2023. Recruitment progress, changes in patient consent status, deaths, follow-up progress and practicalities of trial conduct were discussed. Protocol amendments were discussed and agreed; these are listed in the following subsection.

4.8.6 Protocol amendments

Four amendments were made via IRAS to the protocol since REC approval; all were non-substantial (category C); i.e. not requiring study-wide review.

1. December 2020 – Minor changes made to patient information sheet following advice from REC regarding wording; patient study ID removed from consent form on advice of REC.

2. May 2021 – Following discussion at TSC meeting, CACS to be performed on patients receiving SCA only if not done in past 6 months, as score unlikely to change in that time therefore additional irradiation not justified. Definition of stability following ECOPD altered from 6 weeks to 4 weeks after completion of course of steroids for ECOPD, in line with other COPD studies[613] and to make timely follow-up more practical.
3. November 2021 – Following discussion at TSC meeting, protocol amended in relation to 90 day follow up: to avoid excessive delay in cases of recurrent exacerbation, 90 day review conducted – when practical – after delay has exceeded 8 weeks, regardless of recency of exacerbation. This was to balance need for stability for accurate spirometry and quality of life assessments with avoidance of excessive delay in patients who take multiple courses of steroids for ECOPD symptoms.
4. May 2022 – Recruitment target reduced from 120 to a projected 114 patients due to need to finish recruitment by end of May 2022 due to both slower-than-expected recruitment and the time-limited employment status of research fellow (eventual recruitment total achieved: 115 patients).

4.9 COVID-19 precautions

All research activity adhered to the Northumbria Healthcare NHS Foundation Trust infection control procedures active at the time. Patients were contacted prior to face-to-face follow-up appointment to ensure they were no showing symptoms of COVID-19 infection. Necessary personal protective equipment (PPE) was worn by members of the research team as advised by Public Health England and the Trust infection control policies. For hospital follow-up, a separate hospital entrance to the research and development department was available, minimising patient exposure to healthcare professionals, other patients and hospital visitors.

Chapter 5: Results – baseline demographics and clinical assessments

5.1 Chapter introduction

Chapters 5-7 contain the results of the pilot randomised trial described in detail in the preceding chapter. The results have been divided into chapters as follows:

- Chapter 5 contains descriptions of the demographics and clinical status of the cohort at recruitment, and the results of investigations done at recruitment and follow-up.
- Chapter 6 contains results pertinent to the main objectives of the study, namely assessing the effect of SCA on DAOH and other outcome measures including mortality, readmissions and quality of life and carrying out an economic evaluation
- Chapter 7 contains detailed results of the cardiac investigations done for patients in the intervention arm

159 patients were identified as suitable for recruitment as they met inclusion/exclusion criteria; 42 declined to participate and in 2 it transpired that exclusion criteria were met. 115 patients were recruited to the study; 57 were randomised to the intervention arm and 58 to usual care. The recruitment target was revised from 120 due to slower-than-anticipated recruitment, primarily caused by the reduced rate of admissions for ECOPD during the second and subsequent waves of the COVID-19 pandemic.

5.2 Findings at baseline assessment

The characteristics of patients in the two study arms at baseline are summarised below. Throughout, the mean and standard deviation (SD) is presented unless stated, and comparisons between arms made as pre-specified in section 4.6. Corrections for multiple comparisons have not been carried out for simple comparisons of descriptive data.

5.2.1 Demographics and baseline morbidity

The cohort had a mean age of 72 years, range 53 to 87. There was a preponderance of female patients, concordant with recent national trends in COPD admissions.[614] Almost all were living at home, with only 1 in 7 receiving formal care. Approximately 4 in 10 were currently smoking, in line with rates reported in latest national audit data.[615] The mean most recent predicted percent FEV1 was on the borderline between moderate and severe airflow obstruction, and the cohort had been

highly impacted by previous COPD admissions, with nearly a quarter having previously suffered a very severe exacerbation necessitating the use of NIV. Patients were profoundly affected by COPD: 43.5% of patients were unable to leave the house due to breathlessness, and another 40% were unable to walk more than 100 yards or a few minutes on the level, per the recorded eMRCD scores. Additionally, the majority of patients in the study had mild to moderate frailty.

Prior to study entry, many patients had been diagnosed with conditions that predispose to heart disease, such as hypertension (47%) and diabetes (30%), but a relatively lower proportion had established diagnoses of heart disease. For example, only 3.5% had an established diagnosis of moderate to severe LVSD, a lower rate than would be expected to be present, based on the results of the meta-analysis in Chapter 3. A substantial proportion of patients had already suffered acute atherosclerotic cardiovascular events: 14% had a history of MI and 19% a history of stroke or TIA. Age-adjusted Charlson comorbidity index (CCI) scores showed a high burden of comorbidities across the population.[616,617]

There were no statistically significant differences between the study arms in terms of demographics, COPD severity or the prevalence of comorbidities, although a noticably higher proportion of patients in the usual care arm had a co-existent diagnosis of asthma. Additionally, the interquartile range for CCI scores encompassed higher values in the intervention arm.

	Whole cohort n=115	**Usual care n=58**	**SCA n=57**	p value (no between-arm difference)
Sociodemographics				
Age, y	72.0 (6.44)	71.6 (6.34)	72.6 (6.54)	0.403
Sex, % female	58.3	56.9	59.6	0.851
Residence, %:				
Home	94.8	93.1	96.5	0.618
Sheltered Accommodation	3.5	5.2	1.8	
Residential Home	0.9	0.0	1.8	
Nursing Home	0.9	1.7	0.0	
Formal carers	13.9	12.1	15.8	0.601
Current smoking, %	38.3	39.7	36.8	0.848
PYH, median (IQR)	45 (20)	50 (23)	45 (20)	0.441

COPD severity				
BMI	25.4 (7.0)	24.8 (5.9)	25.9 (7.9)	0.431
Preadmission FEV1 (% predicted)	49.1 (18.3)	48.0 (17.1)	50.2 (19.5)	0.532
eMRCD, median (IQR)	4 (4-5a)	4 (4-5a)	4 (4-5a)	0.230
PEARL score, median (IQR)	4 (1-5)	4 (1-5)	4 (1-5)	0.291
Patient reported ECOPD past year, median (IQR)	3 (1-5)	3 (1.75-5)	3 (1-5)	0.941
ECOPD admissions in past year, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.690
Previous NIV for ECOPD, %	22.6	24.1	21.1	0.824
LTOT, %	13.0	15.5	10.5	0.581
Home NIV, %	1.7	3.4	0.0	0.496
Rockwood CFS, median (IQR)	5 (5-6)	5 (5-6)	5 (5-6)	0.657
Secondary care for COPD, %	76.5	75.9	77.2	1.000
Known cardiovascular comorbidities, %				
Moderate-severe LVSD	3.5	1.7	5.3	0.364
Heart failure without moderate-severe LVSD	7.8	8.6	7.0	0.743
Right-sided heart failure	5.2	6.9	3.5	0.679
Myocardial infarction	13.9	13.8	14.0	1.000
Atrial fibrillation	7.8	8.6	7.0	1.000
Angina	13.0	8.6	17.5	0.177
Hypertension	47.0	43.1	50.9	0.457
High cholesterol	10.4	12.1	8.8	0.762
Stroke/Transient ischaemic attack	19.1	19.0	19.3	1.000
Peripheral vascular disease	11.3	8.6	14.0	0.393
Diabetes	29.6	27.6	31.6	0.686
Chronic kidney disease	20.0	17.2	22.8	0.492
Other comorbidities				
Asthma, %	6.1	10.3	1.8	0.114
Bronchiectasis, %	14.8	15.5	14.0	1.000
OSA, %	5.2	5.2	5.3	1.000
Charlson comorbidity index, median (IQR)	2 (1-4)	2 (1-4)	3 (2-4)	0.175
Age-adjusted Charlson comorbidity index, median (IQR)	5 (4-7)	5 (4-6)	5 (4-7)	0.181

Table 19: Demographic, COPD severity and comorbidity data at baseline

5.2.2 Exacerbation characteristics

Exacerbations were generally of low to moderate risk for in-hospital mortality, as measured by DECAF scores, for which the median score was 2 (IQR 1-2). 49.6% were low risk (DECAF score 0-1), 32.3% intermediate risk (DECAF score 2), and 18.3% high risk (DECAF score 3+). This is consistent with the low in-hospital mortality observed for recruited patients (1.7%).

NIV was used in around a fifth of cases, higher than the rate of 10-15% reported by recent national audit.[615] Median length of stay was 6 days, slightly higher than the national median of 4 days, most likely because of the inclusion criteria: patients had to be stable, and not imminently prepared for discharge, in order to be suitable for eligibility assessment. There was a low rate of identified microbiological causes for exacerbation: only 6% had a positive sputum culture result, which is likely due sputum cultures being not being sent in a large proportion of admissions. Additionally, sputum culture sensitivity may have been reduced by pre-admission antibiotic use. This finding might also indicate a high proportion of admissions precipitated by non-bacterial infectious causes, such as viral infection (detected in 9%), or other factors such as comorbid heart disease, anxiety and social isolation.

	Whole cohort n=115	**UC n=58**	**SCA n=57**	p value (no between-arm difference)
ECOPD markers				
Consolidation, %	22.6	20.7	24.6	0.661
Acidosis (pH <7.3), %	10.4	12.1	8.8	0.762
Eosinophils (x10^9/L), median (IQR)	0.05 (0.01-0.17)	0.06 (0.02-0.19)	0.05 (0.01-0.17)	0.320
DECAF score, median (IQR)	2 (1-2)	2 (0-2)	2 (1-2)	0.880
Symptom, %:				
Increased dyspnoea	100	100	100	-
Increased sputum volume	37.4	34.5	40.4	0.566
Increased sputum purulence	53.9	48.3	59.6	0.263
2+/3 cardinal symptoms	60.9	58.6	63.2	0.703
CRP (mg, L), median (IQR)	22 (6-77)	22.5 (8-66)	19 (4-113)	0.151
NIV, %	21.7	22.4	21.1	1.000
Length of stay (days), median (IQR)	6 (3-9)	4 (3-9)	6 (3-8)	0.559

Inpatient events				
Sputum culture positive, %	6.1	5.2	7.0	0.717
Viral PCR positive, %	8.7	6.9	10.5	0.528
Acute kidney injury, %	10.4	12.1	8.8	0.762
Any antibiotics, %	69.6	72.4	66.7	0.547
IV antibiotics, %	41.7	47.9	43.9	0.707
DNACPR status, %:				
New DNACPR	21.7	24.1	19.3	0.855
Existing DNACPR	27.0	25.9	28.1	
No DNACPR at discharge	51.3	50	52.6	
Died during admission, n	2	2	0	0.496

Table 20: Markers of ECOPD severity and inpatient events

5.2.3 In-hospital investigations

The investigations detailed below were part of routine care and undertaken at the discretion of the treating clinical team. Blood gas analysis was done in 90% of cases, although several patients had analysis of venous blood only, reducing the proportion that had arterial blood gas analysis to 72%. A third of these patients demonstrated decompensated type 2 respiratory failure (24% of the total cohort: in line with the proportion receiving NIV).

ECGs from admission were not available in 3 patients; incident reporting to the clinical teams was used to highlight this non-standard practice. The most common ECG rhythm was sinus rhythm, with a mean heart rate of 98bpm. Rhythm abnormalities occurred infrequently: 7.1% had atrial fibrillation and 1 patient had a paced rhythm. 1 in 8 patients had intraventricular conduction delay, suggesting underlying structural or ischaemic heart disease. Overall, 6.3% displayed overt features of acute ischaemia, with this proportion being higher in the intervention arm.

In the majority, the admission chest X-ray was done using the AP projection, as is common when patients are clinically unstable. As a result, the cardiothoracic ratio, which was elevated above 0.5 in most patients, cannot be interpreted as indicating with certainty that cardiomegaly was widely prevalent. Selected blood test results reveal that troponin and NTpro-BNP tests were ordered as part of routine care in around 10% of cases, and were almost always abnormal when tested.

There were no statistically significant differences between study arms, although there were some noticeable numerical disparities between the arms. Firstly, although proportions with type 2

respiratory failure were similar, a higher percentage of patients in usual care (17.5%, versus 2.3% in SCA) had no respiratory failure on their admission ABG. Secondly, a higher proportion of patients in SCA had pulmonary congestion reported on their admission chest X-ray. Although X-ray findings have only low sensitivity and moderate specificity for detecting pulmonary oedema,[618] this does imply that there may have been a greater number of patients with acute heart failure in this group. Tempering this, a similar proportion had NT-proBNP tested, with a comparable range of value recorded, suggesting that there was not a difference in the number with overt signs of heart failure on initial assessment.

	Whole cohort n=115	**Usual care** **n=58**	**SCA** **n=57**	p value (no between-arm difference)
Blood gas analysis*				
ABG done (vs. VBG), %	79.8	75.5	84.3	0.331
pH, median (IQR)	7.38 (0.09)	7.39 (0.08)	7.38 (0.11)	0.984
$HCO3^-$ (mmol/L),	29.7 (5.8)	30.0 (5.8)	29.3 (5.8)	0.583
Respiratory failure on ABG, %:	*n=83*	*n=40*	*n=43*	
None	9.6	17.5	2.3	
Type 1[#]	24.1	17.5	30.2	0.096
Type 2, compensated	32.5	32.5	32.6	
Type 2, decompensated	33.7	32.5	34.9	
ECG[†]				
Rate (min^{-1})	97.9 (21.3)	100.0 (22.1)	95.8 (20.5)	0.301
QRS axis (°)	50.3 (53.7)	47.0 (53.8)	53.6 (54.0)	0.518
Rhythm, %:				
Sinus	92.0	91.1	92.9	1.000
Atrial fibrillation/flutter	7.1	7.1	7.1	
Paced	0.9	1.8	0.0	
Acute ischaemia, %	6.3	3.6	8.9	0.438
Conduction delay, %	12.5	12.5	12.5	1.000

Chest X-ray‡				
PA projection, %	46.1	44.8	47.4	0.852
Cardiothoracic ratio	0.51 (0.08)	0.51 (0.08)	0.51 (0.08)	0.702
Diaphragm height¶ (cm),	35.4 (12.5)	34.7 (13.8)	36.2 (11.1)	0.523
Effusion, %	13.0	10.3	15.8	0.420
Pulmonary congestion, %	13.0	6.9	19.3	0.057
Blood tests‡				
eGFR ml/min/1.73m^2 §	83.0 (66-90)	87 (66-90)	80 (62.5-90)	0.270
eGFR impaired (<60), %	18.3	13.8	22.8	0.236
Troponin T tested, %	9.6	10.3	8.8◊	1.000
Troponin T (ng/L), median (IQR)	24 (17-43)	39 (19-170)	21 (12.5-24)	0.126
Troponin T raised (>14 ng/L), %	81.8	83.3	80.0	1.000
NT-proBNP tested, %	8.7	8.6	8.8	1.000
NT-proBNP (ng/L), median (IQR)	700 (389-1923)	696 (426-1395)	1731 (315-4498)	0.841
NT-proBNP raised (>300 ng/L), %	90.0	100.0	80.0	1.000
*Performed in 104 (51 SCA, 53 UC) †Performed in 112 (56 SCA, 56 UC) ‡Performed in all # PaO_2 <8.0kPa or receiving supplemental O_2 ¶ Vertical distance between right costophrenic angle and dome of diaphragm §Taken as 90ml/min/1.73m^2 if reported as >90 ◊ tested in remaining patients after recruitment				

Table 21: Results of standard inpatient investigations

5.2.4 COPD and cardiovascular disease therapy

Most patients were on maximal inhaled therapy for COPD; a minority were prescribed further adjunctive therapies or treatments for respiratory failure. COPD therapy was balanced across the study arms. The most prescribed heart disease medications were statins (63%), aspirin (32%) and ACE-inhibitors (32%). As expected, since randomisation was stratified by the presence of heart disease, there was no difference in cardiovascular therapy between the study arms.

	Whole cohort n=115	**Usual care** **n=58**	**SCA** **n=57**	p value (no between-arm difference)
COPD drug therapy				
Inhaled therapy				
LABA+LAMA+ICS	81.7	75.9	87.8	0.153
LABA+LAMA	14.8	17.2	12.2	
LABA+ICS	1.7	3.4	0.0	
None	1.7	3.4	0.0	
Adjunctive therapy				
Theophylline	6.1	3.4	8.8	0.272
Macrolide	25.2	22.4	28.1	0.525
Carbocisteine	48.7	46.6	50.1	0.710
Oral corticosteroid	9.6	12.1	7.0	0.528
Treatment of respiratory failure				
LTOT	13.0	15.5	10.5	0.581
Home NIV	1.7	3.4	0.0	0.496
Cardiovascular disease drug therapy				
Aspirin	32.2	29.3	35.1	0.553
Dual antiplatelet therapy	2.6	1.7	3.5	0.618
Anticoagulation	9.6	12.0	7.0	0.528
Beta-blocker	20.9	22.4	19.3	0.819
ACE-inhibitor/ARB	32.1	25.9	38.6	0.166
Statin	62.6	60.3	64.9	0.701
Other antihypertensive drug	27.0	24.1	29.8	0.534
Antidiabetic drug (inc. insulin)	15.7	15.5	15.8	1.000
Mineralocorticoid receptor antagonist	1.7	1.7	1.8	1.000
Sacubitril-valsartan	0	0	0	-
SGLT2-inhibitor	0.9	0	1.8	0.496

Table 22: Therapy at baseline

5.3 Findings on follow-up

5.3.1 Loss to follow-up

Patients were lost at each of the 4 stages of follow-up, due to death, non-attendance and inability to be contacted, as tabulated below and displayed in Table 23. Of note, 8 patients did not attend some degree of follow-up between discharge and first review. There were no such events later in the study, although 2 patients proved to be uncontactable for final review. In many cases, non-attendance was because patients remained very unwell after discharge and felt further participation in the study would be too onerous. There was not a noticeably higher rate of non-attendance in the SCA arm, which might have been seen if the intervention caused patients to feel significantly more burdened by the additional investigations and treatments involved.

	All (n=115)	Usual care (n=58)	SCA (n=57)
90 days*			
Died	12	7	5
Declined hospital follow-up	-	-	4
Did not attend face-to-face follow-up	3	1	2
Did not attend any active follow-up	5	4	1
n remaining (full follow-up)	96	46	50
6 months			
Died	4	3	1
n remaining (full follow-up)	93	44	49
9 months			
Died	7	3	4
n remaining (full follow-up)	86	41	45
12 months			
Died	6	2	4
Uncontactable	2	2	0
n remaining (full follow-up)	80	38	42
4 patients (2 usual care, 2 SCA) non-attended before subsequently dying during follow-up hence 'n remaining (full follow-up)' does not always fall by number of deaths at each time point **This refers to completion of 90-day follow-up review (cf. 90 days post discharge): this was delayed for unwell patients, hence disparity with 90-day mortality rate*			

Table 23: Reasons for loss to follow up. Full follow-up means all data could be gathered, including spirometry, gait speed and all questionnaire-based data, but does not refer to the 90-day investigations that were part of SCA

No patient withdrew consent for their hospital records to be accessed until the end of the follow-up period for the purposes of analysing admissions and mortality. The CONSORT diagram summarises progress through the study to analysis of DAOH:

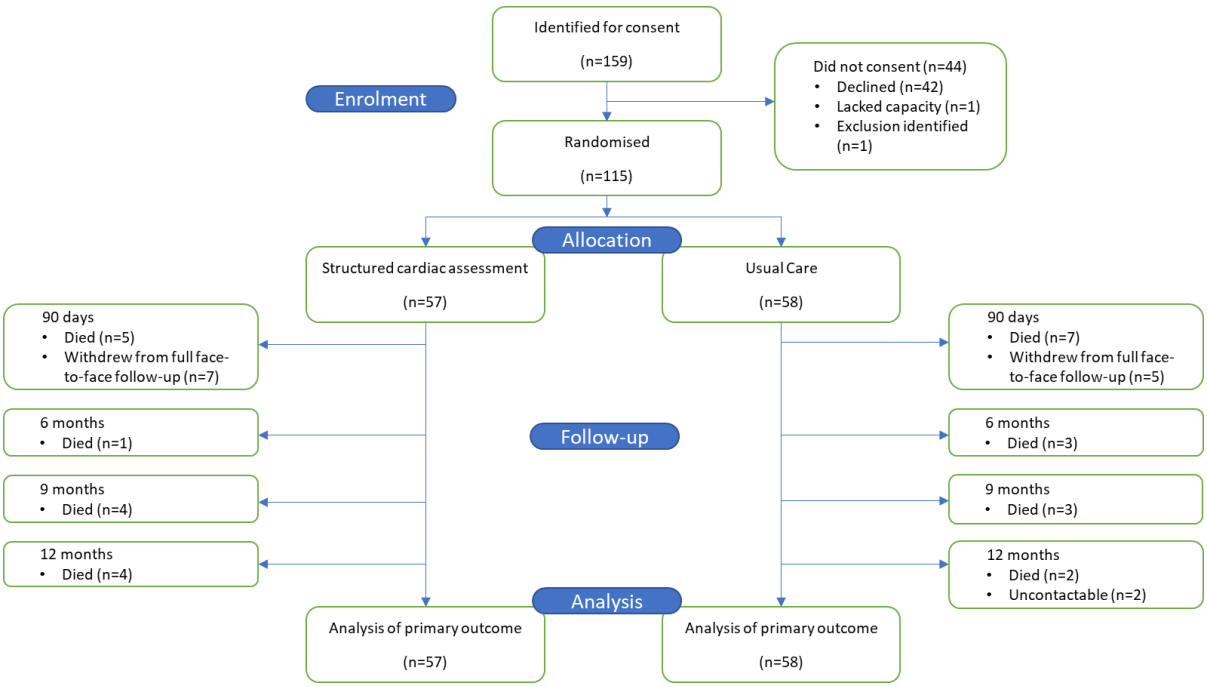


Figure 33: Consort diagram for the SCATECOPD study

5.3.2 *Spirometry*

Spirometry assessments were conducted during index admission and in patients who attended face-to-face assessment. Two patients were unable to complete baseline spirometry: one was too unwell and never recovered, one declined to perform the test.

Summary descriptive data for spirometry at baseline, 90 days and 12 months is tabulated below. The distribution of percent predicted values failed tests of normality for FEV1 at each time point, although skewness and kurtosis values were not above 1 and histograms approximated the normal distribution with a slight positive skew. Mean (SD) values have therefore been used for consistency, and were not significantly different at baseline.

The mean percent predicted FEV1 recorded at admission was noticeably lower than the mean most recent historical value (33% vs 49%), indicating a combination of acute and chronic decline between measurements to a state of severe airflow obstruction. The follow-up mean FEV1 results were also below the historical values, again likely reflecting expected decline between time points and irreversible loss of lung function following a severe exacerbation.

During admission	**Whole cohort n=113**	**Usual care n=56**	**SCA n=57**	p value (no between-arm difference)
FEV1 (% predicted)	33.3 (14.5)	32.5 14.2)	34.1 (14.8)	0.551
VC (% predicted)	65.6 (18.1)	63.3 (17.9)	67.9 (18.2)	0.182
Inspiratory capacity (% predicted)*	62.4 (20.3)	61.5 (20.3)	63.3 (20.4)	0.657
90 days	**Whole cohort n=93**	**Usual care n=44**	**SCA n=49**	
FEV1 (% predicted)	40.0 (19.1)	39.4 (19.5)	40.5 (18.9)	
VC (% predicted)	74.1 (19.2)	71.6 (18.1)	76.4 (20.2)	
Inspiratory capacity (% predicted)*	65.3 (20.4)	65.2 (21.2)	65.4 (19.9)	
12 months	**Whole cohort n=75**	**Usual care n=35**	**SCA n=40**	
FEV1 (% predicted)	40.6 (19.6)	42.3 (20.0)	39.2 (19.3)	
VC (% predicted)	74.1 (19.0)	73.6 (17.5)	74.6 (20.4)	
Inspiratory capacity (% predicted)*	67.7 (18.3)	69.1 (17.4)	66.6 (19.2)	
Missing at baseline in 7 usual care, 6 SCA; at 90d in 2 usual care, 2 SCA; at 12m in 2 usual care, 0 SCA				

Table 24: Results of spirometry assessments at baseline and follow-up

For patients who provided spirometry at 3 time points, a repeated measures ANOVA was used to test for a changes in mean predicted values during follow-up, for the whole cohort initially. A major limitation of this analysis is the quantity of missing data; a linear mixed-effects model would be an alternative and more robust analysis method.

Percent predicted FEV1 and VC were significantly different between time points ($F=18.435$, $p<0.001$; $F=10.139$, $p<0.001$ respectively), with a significant improvement from baseline to 90d (FEV1 95% CI 3.7% – 10.8%, VC 95% CI 2.9% - 11.9%) and no significant change from 90d to 12m. Percent predicted inspiratory capacity showed the same pattern of change between time points but this change was not significant by repeated measures ANOVA ($F=2.001$, $p=0.145$).

Plots of means are presented, with truncated y-axes for clarity, and results of pairwise comparisons (with Bonferroni correction; ns = not significant, * = $p < 0.05$, ** = $p < 0.001$).

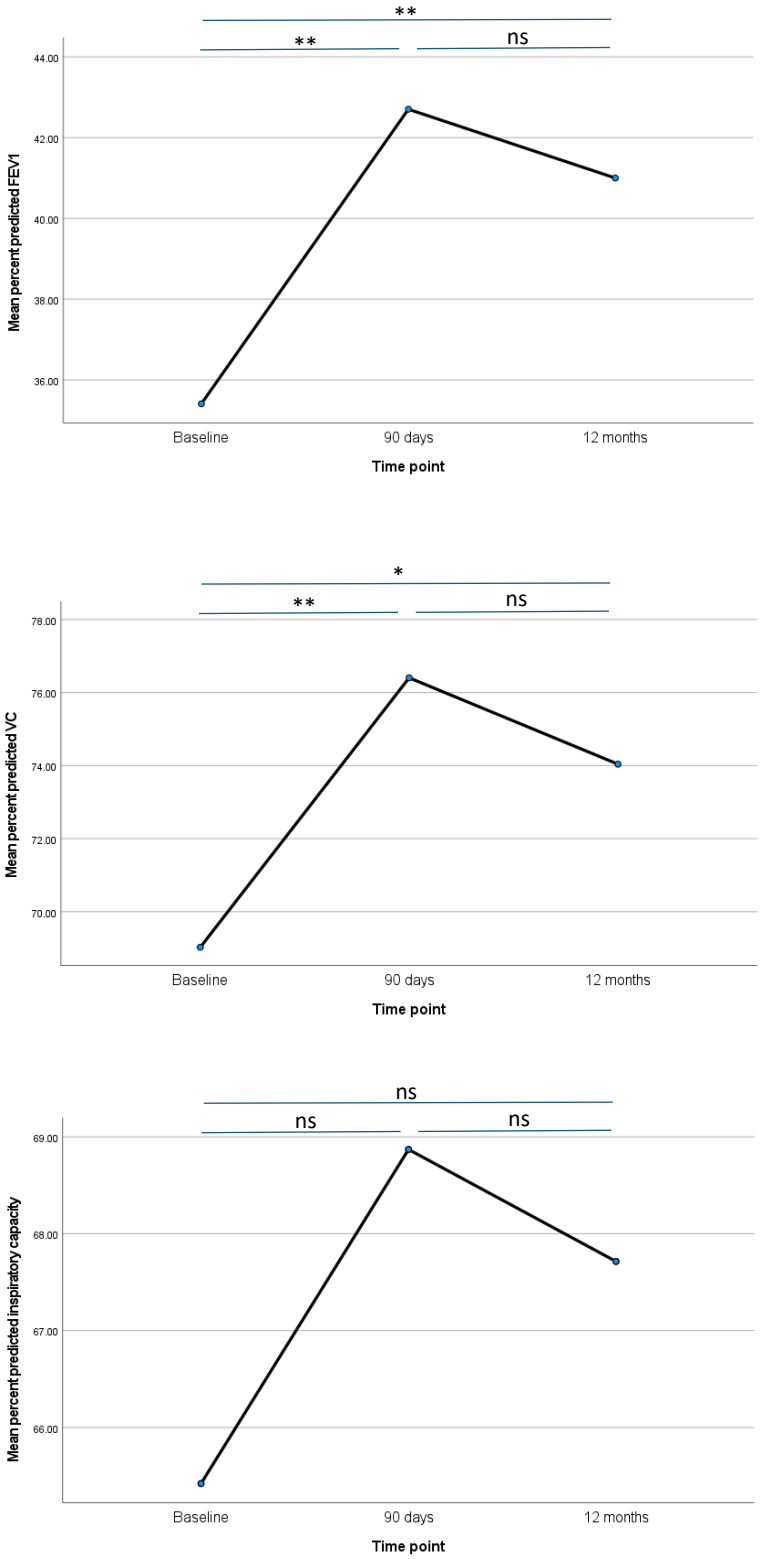


Figure 34: Mean spirometric measures at baseline and follow-up

A repeated measures ANOVA examining the between-subject effect of study arm showed that this had no significant effect on change in mean percent predicted FEV1, FVC or inspiratory capacity (F=0.541, p=0.465; F=0.002, p=0.964; F=1.038, p=0.312 respectively).

5.4 Chapter conclusion

In this chapter the characteristics of the cohort and their progress through the study were reported. The patients recruited were, in the majority, living with frailty and highly impactful COPD, but had low levels of previously diagnosed major heart disease. Mortality was high within the study, this being the major contributor to loss to follow-up. In the following chapter, the results of outcome assessments, as prespecified in the study objectives, are discussed.

Chapter 6: Results – Clinical outcomes and economic evaluation

6.1 Introduction

This chapter contains results pertinent to the main study objectives: assessing the effect of SCA on DAOH and other important clinical outcome measures, including mortality, readmissions and quality of life. As this was a pilot study, these are best interpreted as descriptive associations rather than definitive rate ratios. In section 6.4 the results of the economic evaluation are presented.

6.2 DAOH

6.2.1 Comparison between arms

The distribution of days alive outside hospital was highly left-skewed, with a range from 0-365 and 34.8% of patients having the maximum value of 365 (i.e. survival throughout follow-up without any admissions that crossed midnight).

Histograms and summary data for each study arm demonstrate this skewness:

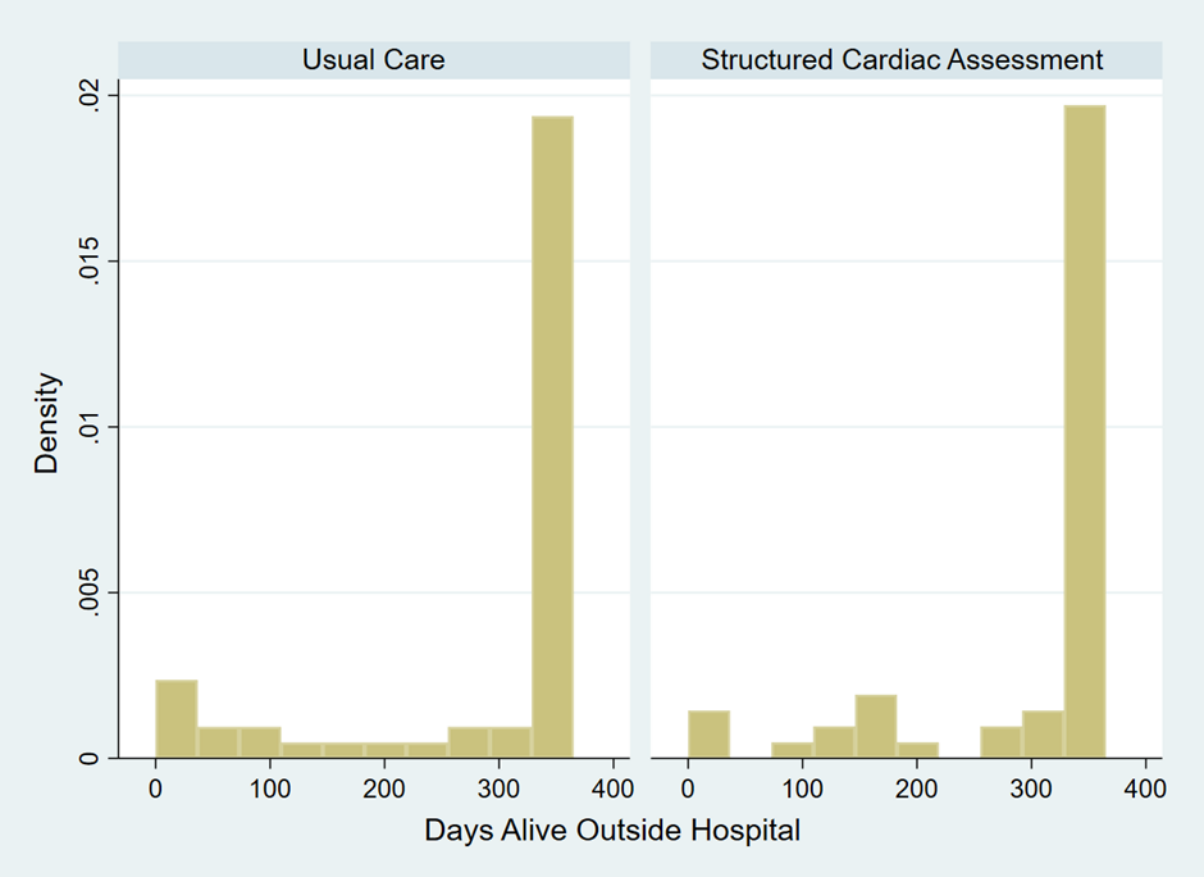


Figure 35: Histograms of DAOH for each study arm

	Whole cohort (n=115)	Usual care (n=58)	SCA (n=57)
Mean (SD)	298.6 (111.4)	292.2 (120.4)	305.4 (102.0)
Median (IQR)	356 (63)	356 (80.8)	356 (52.5)
Range	0-365	0-365	10-365

Table 25: Summary descriptive data for DAOH

T-test comparison of means was inappropriate given the distributions observed. There was no significant difference between median DAOH across the two study arms (p=0.977, MWU test).

Exploratory analyses were conducted using methodology employed previously for handling DAOH data[522,619].

First, DAOH was categorised as high (median or above) and low (below the median) and distribution of high and low DAOH between the arms tabulated.

	DAOH category		
	Low (<356)	High (≥356)	*Totals*
Usual care	28	30	*58*
SCA	27	30	*57*
Totals	*55*	*60*	

Table 26: Contingency table of DAOH category and study arm

As immediately apparent on inspection of the contingency table, there was no relationship between study arm and DAOH category (Fisher's exact test p=1.000).

Second, DAOH was categorised into tertiles: high, medium and low. The high DAOH tertile was composed of 38 patients who had DAOH 364 or 365. The medium and low DAOH tertiles consisted of 39 patients with DAOH 343-363 and 38 patients with DAOH ≤342 respectively.

	DAOH tertile			
	Low (≤342)	Medium (343-363)	High (≥364)	*Totals*
Usual care	19	19	20	*58*
SCA	19	20	18	*57*
Totals	*38*	*39*	*38*	

Table 27: Contingency table of DAOH tertile and study arm

Once again, was no relationship between study arms and DAOH category (Fisher's exact test p=0.972).

An exploratory regression analysis was carried out to estimate effects of relevant explanatory variables on the dependent variable of DAOH. Stepwise Poisson regression was used as DAOH can be considered a count variable, although, notably, events reducing DAOH such as exacerbations do not occur independently, and DAOH has an upper bound of 365. Selected model outputs are presented in the below table. Overdispersion was present in the distribution of DAOH (that is, the variance was significantly higher than the mean); robust standard errors were therefore used.

	Poisson regression models (n=115)				
Explanatory variables	M1 Coefficient (SE)	M2 Coefficient (SE)	M3 Coefficient (SE)	M4 Coefficient (SE)	M5 Coefficient (SE)
Study arm (SCA=1)	0.079 (0.06)	0.046 (0.07)	0.044 (0.07)		0.082 (0.07)
Sex (male=1)	-0.120 (0.08)	-0.126 (0.08)	-0.111 (0.08)	-0.104 (0.07)	-0.106 (0.07)
Age (y)	0.006 (0.01)	-0.03 (0.01)	-0.003 (0.01)		
FEV1 (% predicted)	0.000 (0.00)	0.000 (0.00)			
Diaphragm height (cm)	0.003 (0.00)	0.004 (0.00)			
HOT (used=1)	0.073 (0.08)	-0.019 (0.08)			
Admissions in past year	-0.027* (0.01)	-0.043* (0.01)		-0.032* (0.01)	-0.033** (0.01)
Clinical frailty score	-0.075 (0.06)			-0.101** (0.04)	-0.104** (0.04)
eMRCD score	-0.036 (0.06)				
DECAF score	-0.009 (0.04)			-0.036 (0.03)	
CCI (age-adjusted)‡	-0.041 (0.03)				-0.034 (0.02)
Constant	5.981*** (0.44)	5.834***(0.39)	5.911***(0.37)	6.361***(0.17)	6.465***(0.17)
AIC	6792.335	7306.080	7717.321	7008.813	6892.590

* p <0.05 ** p <0.01 *** p <0.001 AIC: Akaike information criterion; HOT = home oxygen therapy

Table 28: Results of Poisson regression analysis

The regression analysis showed that study arm had no significant effect on DAOH in any model. The optimal model, given its lower number of covariates and lower estimates of prediction error as measured by AIC, is model 5, in which both all-cause admissions in the previous year and clinical frailty score were the variables that had the most significant effect on DAOH. Alternative methods for modelling this data could be applied, including a negative binomial model or a two-part model that might better handle the marked skewness observed in the distribution of DAOH.[620]

6.2.2 Comparison with other outcome measures

Because outcomes measures collected included DAOH, which is novel over this duration in this population, and more conventional measures such as mortality, readmissions and quality of life, an opportunity was present to evaluate the relationship between DAOH and other outcome measures.

There was a close relationship between high DAOH scores and mortality, with a median DAOH of 138 in those who died during follow-up and 362 in those who survived throughout ($p<0.001$, MWU test). Histograms demonstrate almost complete separation between the ranges of DAOH for those who died and those who survived.

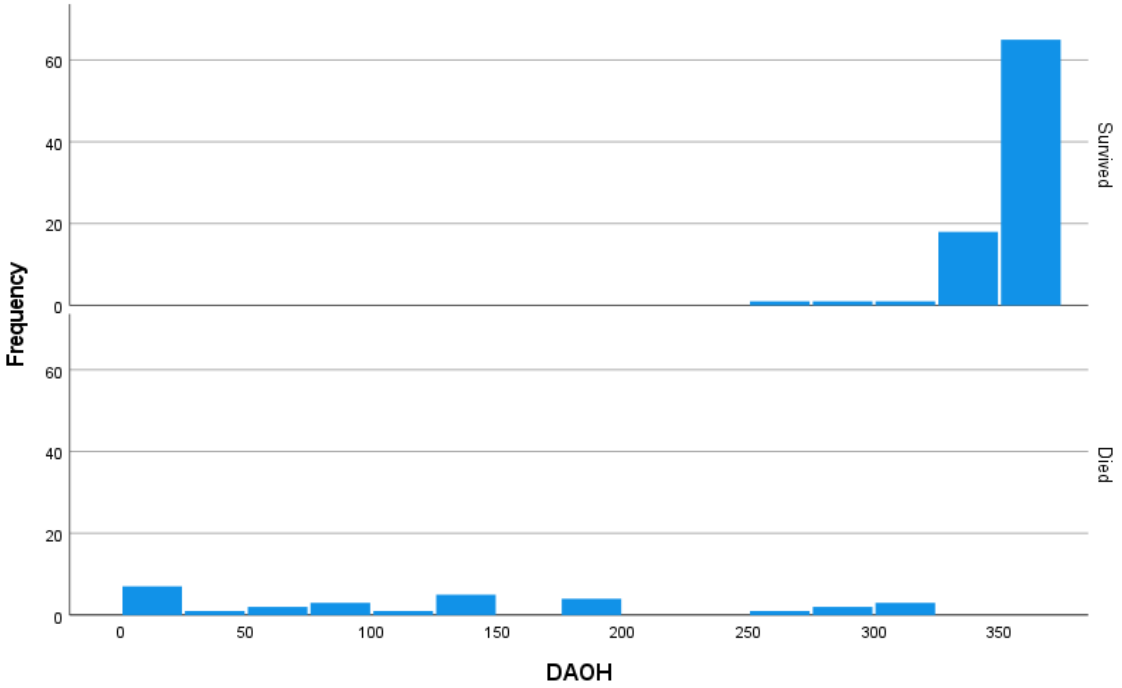


Figure 36: Histograms: DAOH for patients who survived throughout follow-up (upper) and died during follow-up (lower)

Number of readmissions was also negatively correlated with DAOH (Spearman's correlation coefficient -0.620, $p<0.001$), although visual inspection of a scatter plot reveals a substantially weaker relationship than that seen with mortality, with very low goodness of fit ($R^2 = 0.037$).

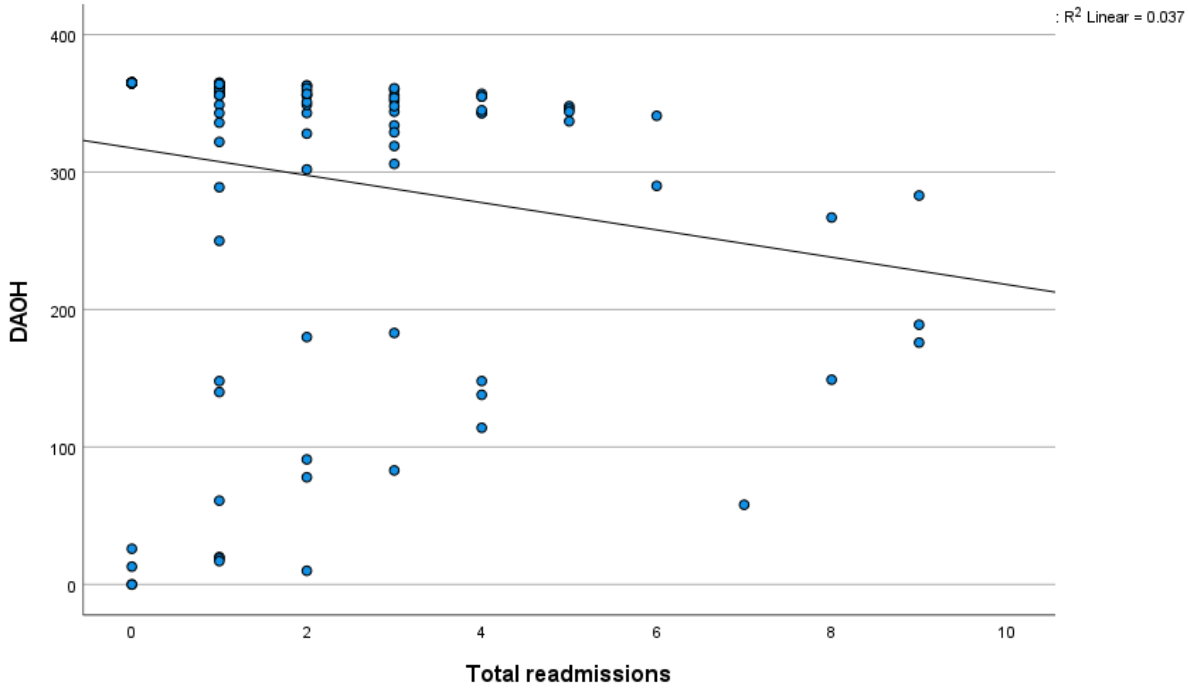


Figure 37: Scatter plot: Number of readmissions vs DAOH

Lower DAOH scores would be expected to correspond to greater increases (i.e. worsening) in the SGRQ-C score, as repeated readmissions should lead to increased symptom burden and impact on activities. Inspection of the scatterplot reveals that if DAOH was under approximately 280 a substantial majority of patients recorded worsening of SQRQ-C during follow-up. This may provide a 'rule-of-thumb' for the magnitude of reduction of DAOH that corresponds to a high probability of a reduction in quality of life. However, a test of correlation between DAOH and change in SGRQ-C was not significant (Pearson correlation coefficient -0.88, p=0.364).

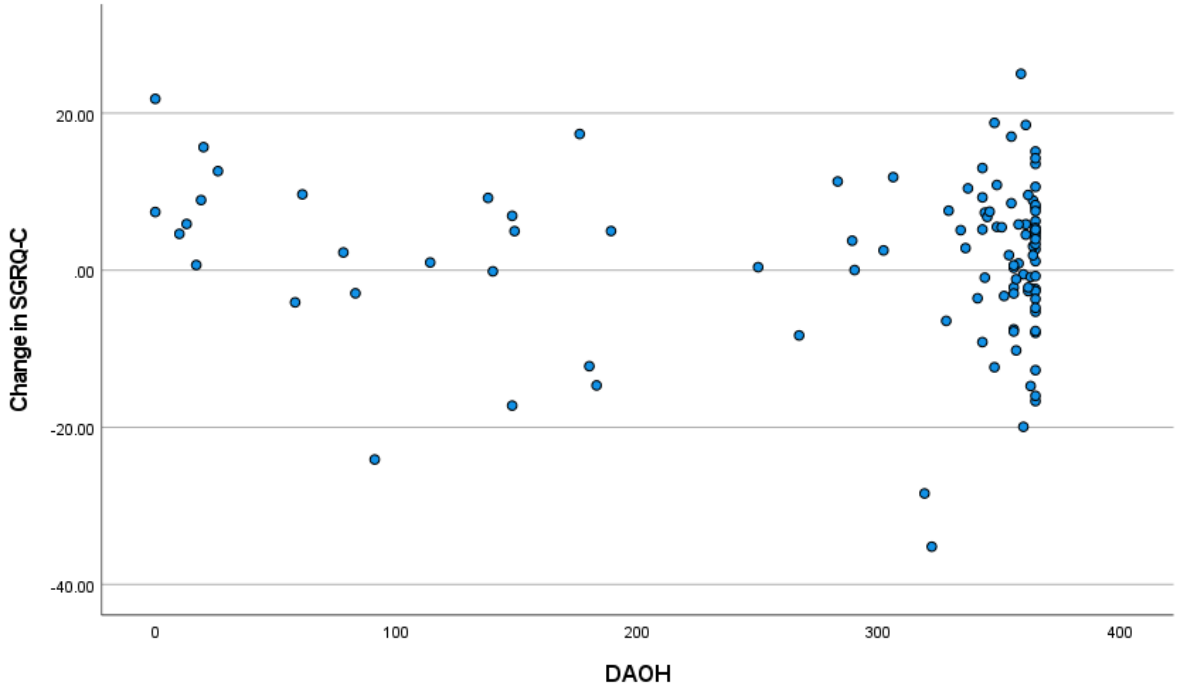


Figure 38: Scatter plot: DAOH vs change in SGRQ-C per unit time

6.2.3 DAOH as an outcome measure

Favourable aspects of DAOH as an outcome measure in the study included the fact that it could be obtained for all participants, and that a robust formula was derived to enable its calculation from discharge, admission and (if relevant) death dates, in a manner that would be amenable to scaling for a multicentre study due to its simplicity. However, a major limitation was the highly skewed nature of the distributions obtained, with a third of patients recording maximum values for DAOH. This may be a function of the study timescale; further discussion of potential modifications and future research avenues relating to DAOH as an outcome measure is contained in Chapter 8.

6.3 Other important outcome measures

As specified in the study protocol and listed in section 4.3, several additional outcome results were assessed. This section includes a comparison of outcome results between study arms as well as evaluation of their utility as outcome measures and relationship to DAOH, as contained in the study objectives.

The below table contains a summary of the secondary outcome results and reveals that the measures that differed significantly between arms were:

- The proportion that had a new diagnosis of heart disease during admission, which was significantly higher in the SCA arm (see section 6.3.6);
- The proportion that had undertreated heart disease after completion of the SCA and at 90 days, which was significantly lower in the SCA arm (see section 6.3.7).

	Usual care (n=58)	**SCA (n=57)**	**p value***
Days alive outside hospital, mean (SD)	292.2 (120.4)	305.4 (102.0)	0.526
Days alive outside hospital, median (IQR)	356 (80.8)	356 (52.5)	0.977
Mortality at 90d, % (n)	8.6 (5)	5.3 (3)	0.717
Mortality at 12m, % (n)	25.8 (15)	24.5 (14)	1.000
Median survival without readmission, days	111	120	0.814
90d readmission rate, % (n)	43.1 (25)	45.6 (26)	0.852
Number of admissions at 90d, median (IQR)	0 (0-1)	0 (0-1)	0.633
12m readmission rate, % (n)	63.8 (37)	73.7 (42)	0.316
Number of admissions at 12m, median (IQR)	1 (0-3)	1 (0-3)	0.593
COPD exacerbations at 90d, median (IQR)	1 (0-1.25)	1 (0-2)	0.212
COPD exacerbations at 12m, median (IQR))	2.5 (0.75-6)	2.5 (1-6)	0.596
Adverse CV events at 90d, % (n)	8.6 (5)	8.8 (5)	1.000
Adverse CV events at 12m, % (n)	17.2 (10)	10.5 (6)	0.420
New diagnosis of heart disease following admission, % (n,N)	19.0 (11/58)	73.7 (42/57)	**<0.001**
New diagnosis of heart disease at 90d, % (n,N)	3.6 (2/56)	5.3 (3/57)	1.000
New diagnosis of heart disease at 12m, % (n,N)	3.9 (2/51)	0.0 (0/52)	0.501
Total with heart disease§ at admission, % (n/N)	17.2 (10/58)	19.3 (11/57)	0.813
Undertreated heart disease at admission, % (n/N)	50.0 (5/10)	45.5 (5/11)	1.000
Total with heart disease§ at completion of SCA, % (n/N)	19.6 (11/56)	82.5 (47/57)	**<0.001**
Undertreated heart disease at completion of SCA, % (n/N)	63.6 (7/11)	25.5 (12/47)	**0.029**
Total with heart disease at 90d, % (n/N)	18.0 (9/50)	80.8 (42/52)	**<0.001**
Undertreated heart disease at 90d, % (n/N)	44.4 (4/9)	31.0 (13/42)	0.056
Total with heart disease at 12m, % (n/N)	14.6 (6/41)	83.7 (36/43)	**<0.001**
Undertreated heart disease at 12m, % (n/N)	50.0 (3/5)	19.4 (7/36)	0.135
Change in 4-metre gait speed at 90d, $m.s^{-1}$ mean (s.d)	0.03 (0.30)	-0.002 (0.32)	0.592
Change in 4-meter gait speed at 12m, $m.s^{-1}$ mean (s.d)	-0.107 (0.36)	-0.100 (0.34)	0.931
Mean change in QoL over 12m (measured by SGRQ-C)	2.24 (10.45)	1.02 (9.90)	0.553

* difference between arms; statistical tests as per section 4.6
§ MI, CAD (CACS > 100/CT or invasive angiographic evidence of CAD), LVEF < 45%

Table 29: Summary of key outcome measure results

6.3.1 Mortality

In the whole cohort there were 29 deaths during follow up, yielding a mortality rate of 25.2%. 15 deaths occurred in usual care arm, 14 in the SCA arm. 8 deaths occurred before 90d after discharge (7.0%), 5 in the usual care arm, 3 in the SCA arm.

Time to death was analysed by the Kaplan-Meier method. The trajectory of survival curves was similar for each arm. There was no significant difference in the survival distributions (Log rank test p=0.783)

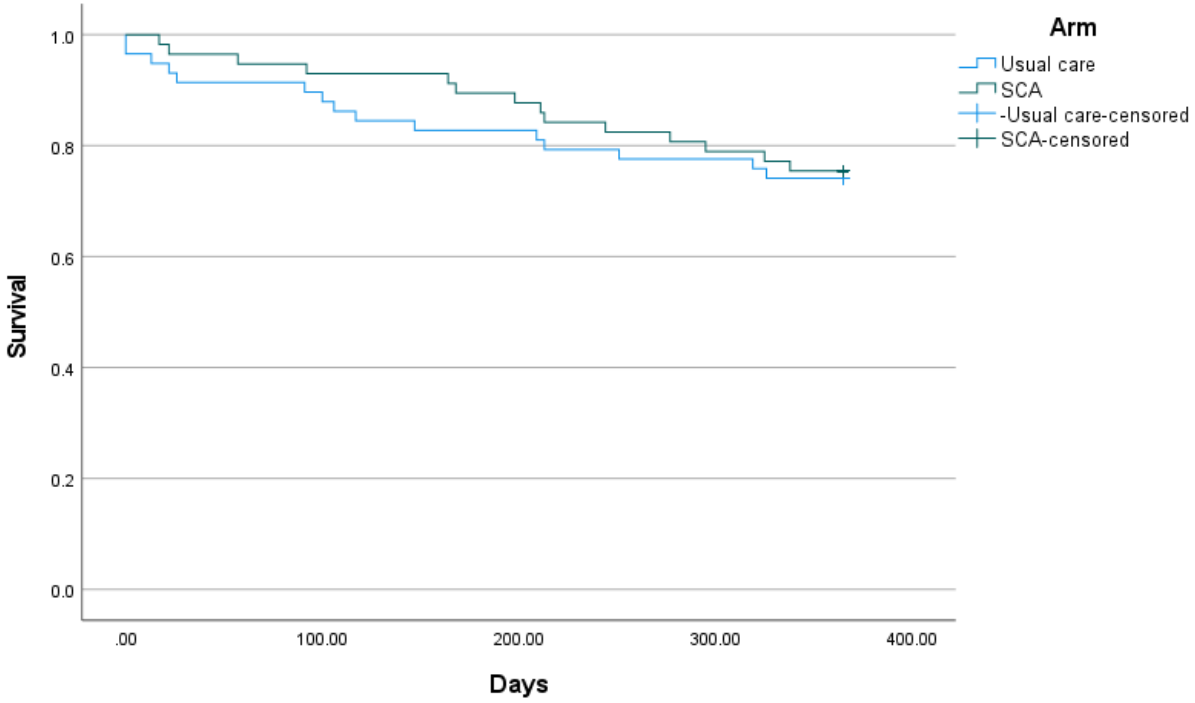


Figure 39: Kaplan-Meier plot: mortality

Adjudication of the cause of death was carried out in all cases, by two consultants, specialising in respiratory medicine and cardiology, who were independent to the study and blinded to allocation. They used the available electronic patient records capturing admissions and outpatient encounters at the study sites, death certificate information and paramedic records, as well as further information from the patient's GP practice where this could be obtained.

Following the adjudication process, the causes of death were determined to be as shown in Table 30.

	Whole cohort (n=115)	Usual care (n=58)	SCA (n=57)
Total deaths	**29**	**15**	**14**
COPD	18	9	11
Cardiovascular disease	5	4	1
Other causes*	4	2	2
* COVID-19, oropharyngeal cancer, ureteric cancer, pancreatitis			

Table 30: Results of mortality adjudication

COPD proved to be the predominant cause of death and occurred at equal frequency between arms. A numerical difference was apparent in the number of deaths from cardiovascular disease, however with this cohort size and length of follow-up insufficient numbers were available for further analysis to be appropriate. Nevertheless, cardiovascular mortality emerges as a potential outcome measure for investigation in future studies (see Chapter 8 for further discussion).

6.3.2 Readmissions

Readmissions were commonplace, consistent with previous national audit data.[50] By 90 days after discharge, almost half of patients had been readmitted, and one in 6 had already experienced multiple readmissions. By 12 months, two thirds of patients had been readmission, and almost half had experienced multiple readmissions, meaning that, including their index admission, they had at least three hospital admissions in a one year period. The percentage of patients that were readmitted for any cause by 90 days and 12 months is shown in Table 31.

	All (n=115)	Usual Care (n=58)	SCA (n=57)	p value
Any admission by 90 days (%)	44.3	43.1	45.6	0.852
Multiple admissions by 90 days (%)	16.5	13.8	19.3	0.462
Any admission by 12 months (%)	68.7	63.8	73.7	0.316
Multiple admissions by 12 months (%)	43.5	39.7	47.3	0.455

Table 31: (Multiple) admissions at 90 days and 12 months

The readmission rate at 90 days was 0.72 admissions per patient in the usual care arm and 0.84 admissions per patient in the SCA arm. The readmission rate at 12 months was 1.88 admissions per patient in the usual care arm and 1.91 admissions per patient in the SCA arm, although the histograms of the data presented below show significant skewness. Regardless, there was no

significant difference in admission rates between the arms (p=0.852 at 90 days, 0.593 at 12 months, MWU test).

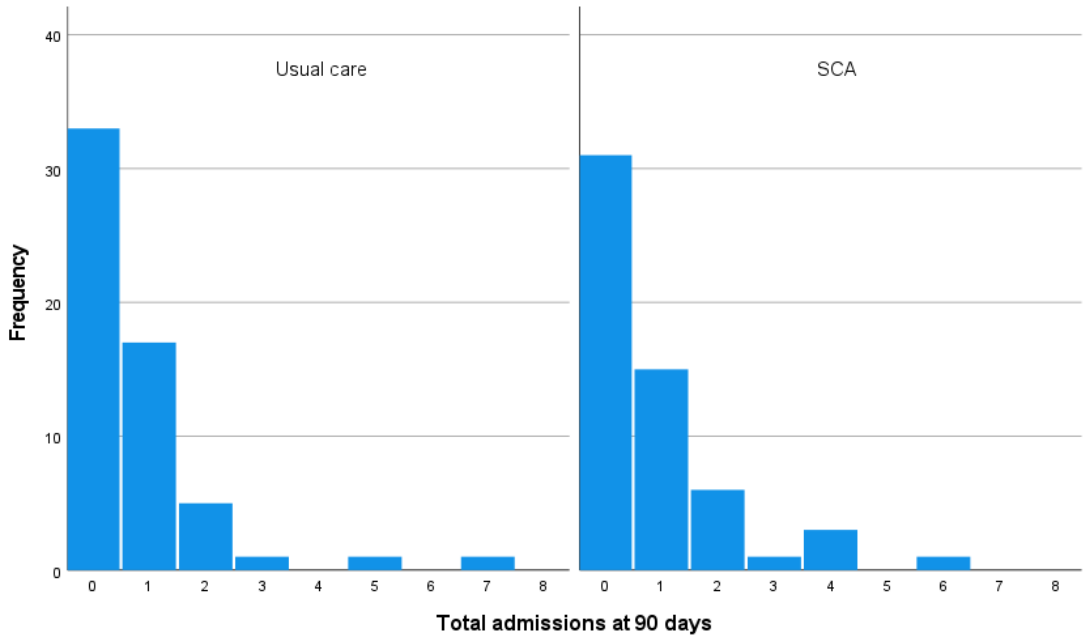


Figure 40: Histograms of total admissions at 90 days

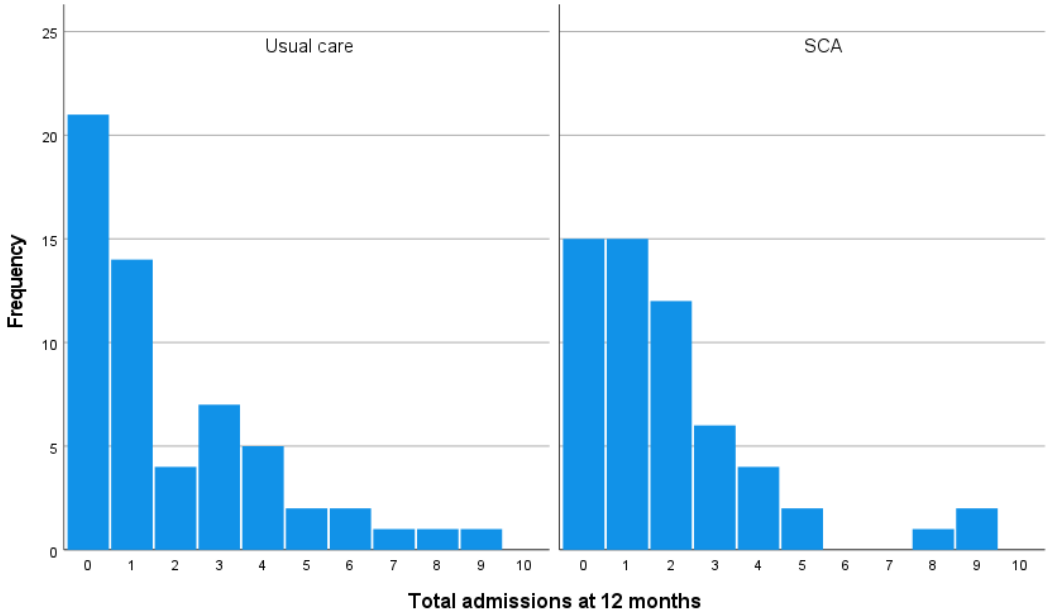


Figure 41: Histograms of total admissions at 12 months

The high event rate seen with readmissions in this pilot study lends it suitability as an outcome measure, particularly in a study of limited participant numbers and follow-up duration. Little difference was observed between arms; contributory to this may be the fact that the final outcome of readmission is influenced by multiple interacting variables beyond baseline cardio-respiratory health and the magnitude of acute deterioration, including other comorbidities, social support, coping strategies, healthcare accessibility and health beliefs. This is discussed further in Chapter 8.

6.3.3 Time to readmission or death without readmission

Time to readmission or death without readmission was analysed by the Kaplan-Meier method. The second component of this composite outcome is important to avoid the illogical eventuality where patients who die without readmission appear to survive, and is in line with previous studies.[498] The survival curves for the two study arms crossed. There are several potential reasons for this. Firstly, there may be no difference in survival between the arms, and the crossing of the curves is an incidental phenomenon. Conversely, it may be that the hazard ratio with respect to the SCA arm truly varied throughout the study: it was less than 1 in the early phase of follow-up and greater than 1 in the later phase. This concept is discussed further in chapter 8 along with further implications of the crossed survival curves.

The log-rank test was used to compare the probability of survival without readmission throughout follow-up between the arms, and yielded a p-value of 0.814, far above the critical alpha. Therefore, although this test is reported to have some loss of power in cases were the hazards of events change significantly over time ,[621] the conclusion that study arm had no effect on admission-free survival over the course of one year appears secure.

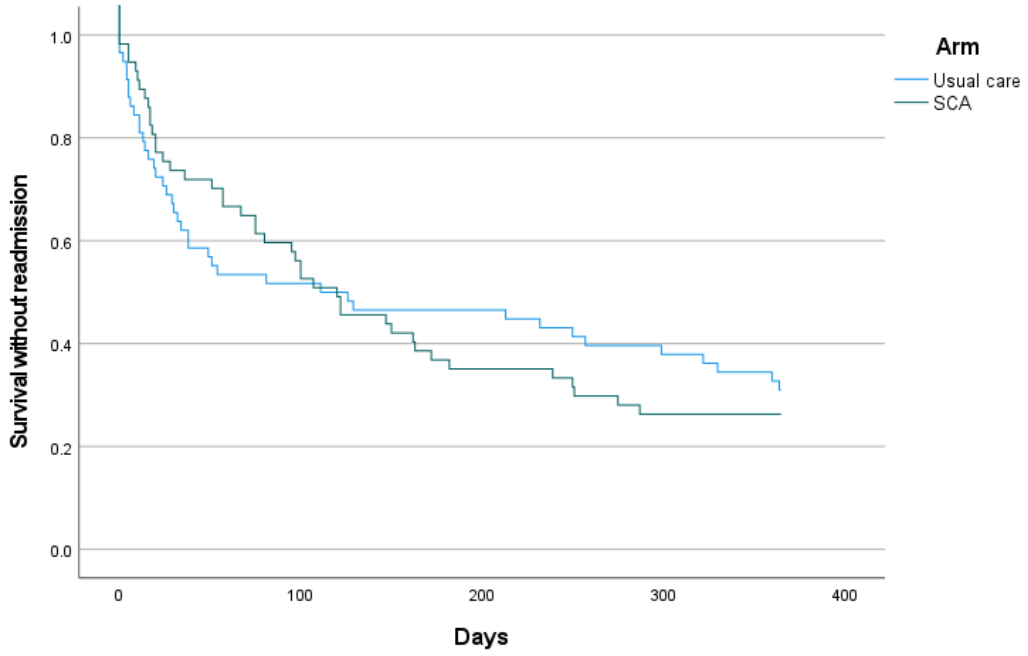


Figure 42: Kaplan-Meier plot: survival without readmission (or death without readmission)

The outcome measure of time to readmission (or death without readmission) has the positive attribute that the outcome occurred often, and was observed in over half of patients, making the median time to event reportable. The early separation of curves implies there may be an effect of SCA on preventing early readmissions, which would be of substantial benefit to patients even if subsequent events mean the survival curves subsequently reach parity, given the deleterious effect of rapid readmission on recovery of musculoskeletal conditioning and functional performance and, in a 64-month observational study, mortality over several years beyond the index early readmission.[622] Accordingly, the rate of early – e.g. 30 or 90 day – readmission (or death without readmission) emerges from this analysis as an outcome measure that merits consideration in further evaluation of the structured cardiac assessment.

6.3.3.4 Time to readmission or death without readmission according to diagnosis and treatment status

In the above analysis, it was recognised that, following the application of the SCA to half of a cohort of patients admitted with ECOPD, patient could be divided based on what was known, post-hoc, about their diagnosis and treatment status with respect to major cardiac comorbidities, defined in this case as left ventricular dysfunction (i.e. LVEF < 45%), myocardial infarction, and coronary artery

disease of a degree where pharmacological, percutaneous or surgical intervention was warranted (for CAD diagnosed by cardiac CT, the threshold for this was set at an Agatston score of ≥400). Four groups were therefore created:

1) Patients who had **known treated** heart disease: these had either pre-existing heart disease and were on correct, guideline-based treatment (defined below), or those who had heart disease identified during admission – whether by SCA or ad hoc application of tests in the usual care arm – and were subsequently initiated on appropriate therapy (n=31);
2) Patients who had **known undertreated** heart disease: if one of the above conditions was present pre-admission, or uncovered during admission, but one or more elements of appropriate pharmacological treatment was not being taken during the follow-up period (n=15);
3) Patients who were **known to have no heart disease** were those who had undergone the SCA, and this had uncovered none of the conditions above (n=20);
4) Patients who **no known heart disease** were those without a pre-existing diagnosis of the above conditions, but who did not undergo the SCA, hence up-to-date knowledge of their cardiac comorbidity status was lacking (n=47).

Appropriate treatment was defined as:

- For patients with left ventricular dysfunction: if LVEF <45%, treatment with beta-blocker and ACE-inhibitor (or ARB), as per the SCATECOPD management summary; if LVEF <40%, involvement of the specialist heart failure service for introduction of more intensive therapies including angiotensin receptor-neprilysin inhibitor, SGLT2-inhibitor and mineralocorticoid receptor antagonist drugs.
- For myocardial infarction: statin, ACE-inhibitor (or ARB) and antiplatelet therapy (with dual antiplatelet and beta-blocker therapy for one year post-event)
- For CABG and post-PCI for stable coronary artery disease: aspirin and statin

Survival without readmission was assessed for the first 90-days following discharge (NB: group numbers above sum to 113 as the two patients who died before discharge were not included in this analysis).

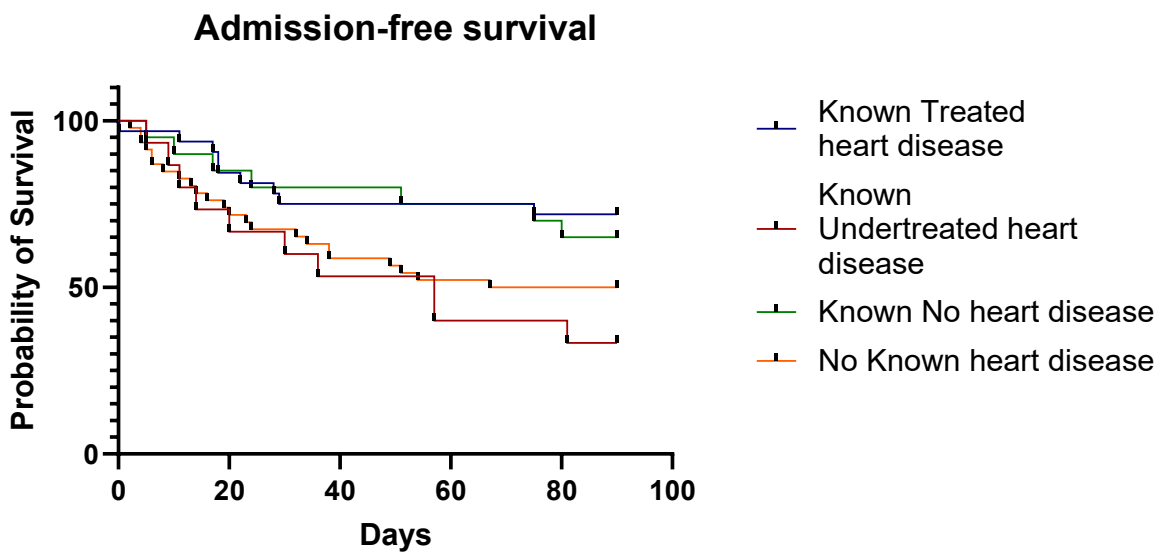


Figure 43: Survival curves showing percentage without any-cause readmission (or death without readmission) for patients in the four diagnosis/treatment groups over 90 days

Survival curves separated, with patients who had heart disease that was treated appropriately (the **known treated** group) appearing to have equivalent survival as patients who were **known to have no heart disease** (see Figure 44). By contrast, the group of patients with **no known heart disease** followed a similar trajectory to those with **known undertreated** heart disease; conceivably because both groups contained a similar, substantial proportion of patients who were undertreated, due to underdiagnosis in the 'no known' group. The log-rank test with the hypothesis that there was no between-group difference across the four arms returned a p-value of 0.06 (post-hoc testing was not carried out). This analysis was presented at the winter British Thoracic Society (BTS) conference in 2022 (see Appendix A for details).

Once all follow-up had been completed, the analysis was extended to 365 days. Extending beyond the first follow-up point introduces complexity, as patients could potentially move groups based on additional diagnoses made, and also as a result of changes in medication use during the time period. It was elected not to increase the complexity of the analysis by introducing additional groups to account for this, particularly given the small numbers of patients involved. Therefore the survival analysis was conducted based on the diagnosis and treatment status assigned based on the first 90 days of follow-up – see Figure 44.

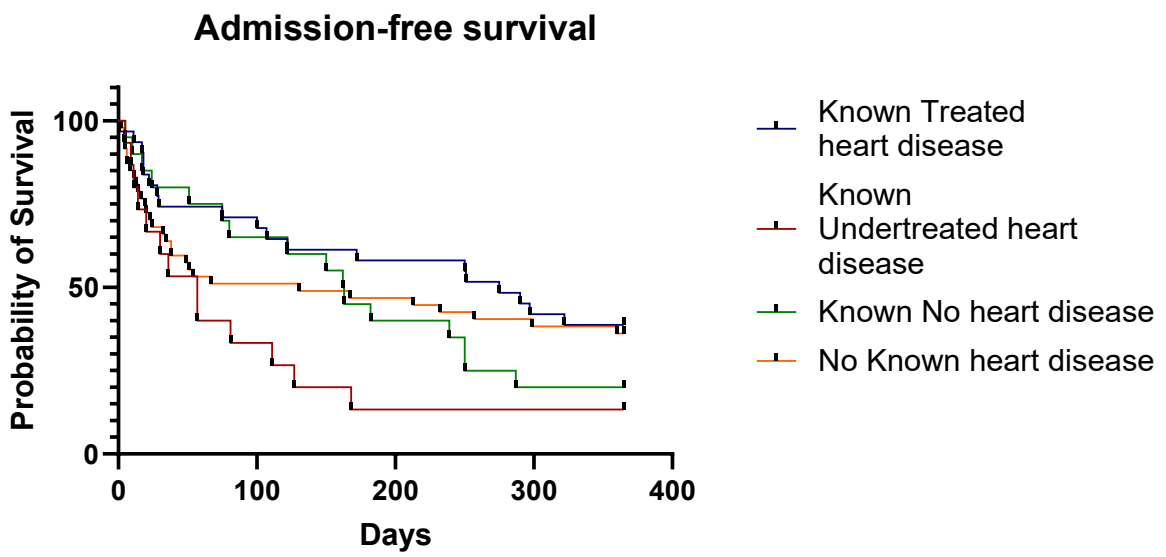


Figure 44: Survival curves showing percentage without any-cause readmission (or death without readmission) for patients in the four diagnosis/treatment groups over 365 days

Inspection of the curved reveals that the early separation between the known treated/known no heart disease groups and the known undertreated/no known heart disease groups attenuated with time. The p-value from the log-rank test for difference between groups decreased to 0.103. Again, no post-hoc tests were conducted. A separation between the two groups with known heart disease was observed, with the group that had undertreated disease having poorer admission-free survival: median time to event 57 days, compared with 275 days for those with treated heart disease. It should be remembered that these groups contained patients from both the SCA and usual care arms (in Known Treated, 20 from SCA and 5 from UC; in Known Undertreated, 10 from SCA, 5 from UC). The reasons for undertreatment in the SCA patients were, in the majority of cases, intolerance or patient choice not to take recommended medications.

The trajectories for the groups without known heart disease crossed, after the initial period where the admission-free survival appeared lower in those who had not a structured cardiac assessment to exclude disease. This could represent ultimately equal outcomes for these two groups, after an initial post-exacerbation period where risk was higher for those with undiagnosed (and hence undertreated) heart disease; small numbers and the exploratory nature of this analysis mean this remains speculative.

In conclusion, an analysis of time to readmission (or death without readmission) stratified by diagnostic and treatment status with respect to heart disease, suggested that the cohort of patients who had adequately treated heart disease had a comparable clinical trajectory to those without

heart disease, but those with known, but undertreated disease had the highest probability of readmission at 90 days and one year. This should provide clinicians with an urgent impetus to reduce undertreatment of heart disease for patients with COPD.

6.3.4 COPD exacerbation rates

Exacerbation rates were assessed from patient self-report – complemented by primary and secondary care records – at 90-day, 6-month, 9-month and 12-month review. For those that did not survive, or did not attend active follow-up, exacerbation rates were not available, therefore only surviving, follow-up-attending patients could be included for this outcome.

Importantly, because the 90-day review took place at stability, this was often delayed by several weeks, meaning that the period covered up to that point was variable between patients. Although the same stability condition applied to the timing of the 12-month review, this was less commonly delayed because the overall exacerbation rate had often reduced by this point, and only exacerbations up to the 365th day following discharge were counted.

Severe exacerbations (requiring admission) and very severe exacerbations (requiring NIV) were also recorded: because admissions dates were available for these no allowances needed to be made for the timing of review or for patients that died or non-attended. Distributions were all right-skewed (see Figure 45 and Figure 46); median (IQR) exacerbation rates are shown in Table 32 along with the number of patients contributing data.

	Whole cohort	**Usual care**	**SCA**	p value (no between-arm difference)
Exacerbations recorded at 90d review	1 (0-2) *(n=98)*	1 (0-2) *(n=47)*	1 (0-2) *(n=51)*	0.591
Severe exacerbations at 90d	0 (0-1) *(n=115)*	0 (0-1) *(n=58)*	0 (0-1) *(n=57)*	0.766
Exacerbations at 12m	4 (2-6) *(n=81)*	4 (2-7) *(n=39)*	4 (2-5) *(n=42)*	0.496
Severe exacerbations at 12m	0 (0-2) *(n=115)*	0 (0-2.25) *(n=58)*	0 (0-1.5) *(n=57)*	0.761
MWU test used for all comparisons				

Table 32: Exacerbation rates at 90 days and 12 months

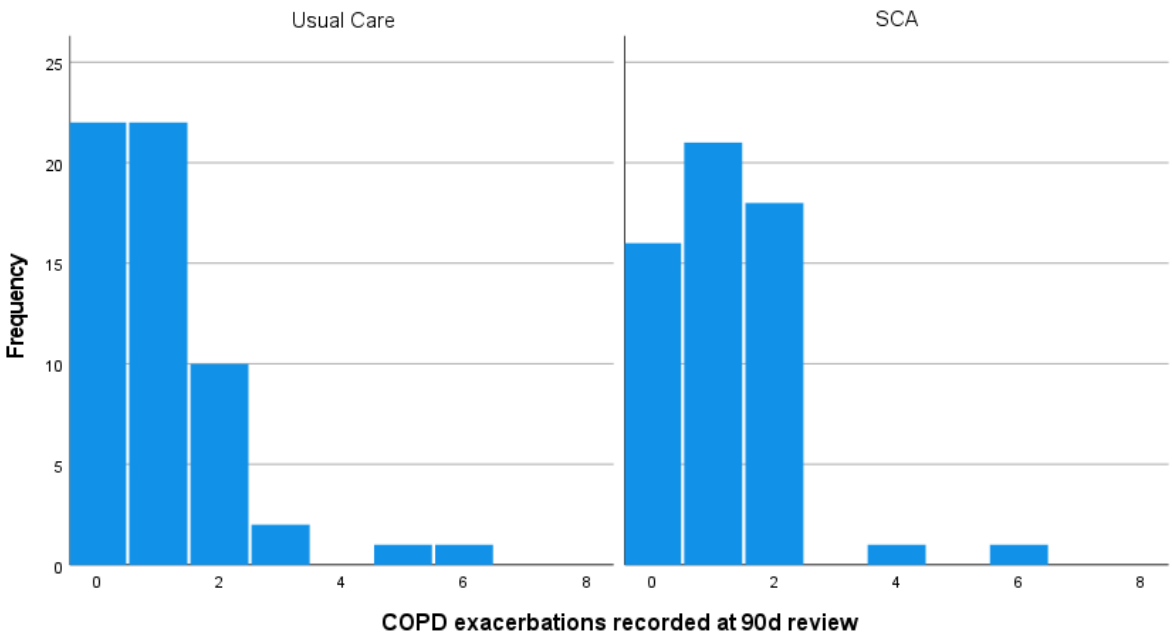


Figure 45:Histograms: COPD exacerbations at 90 days

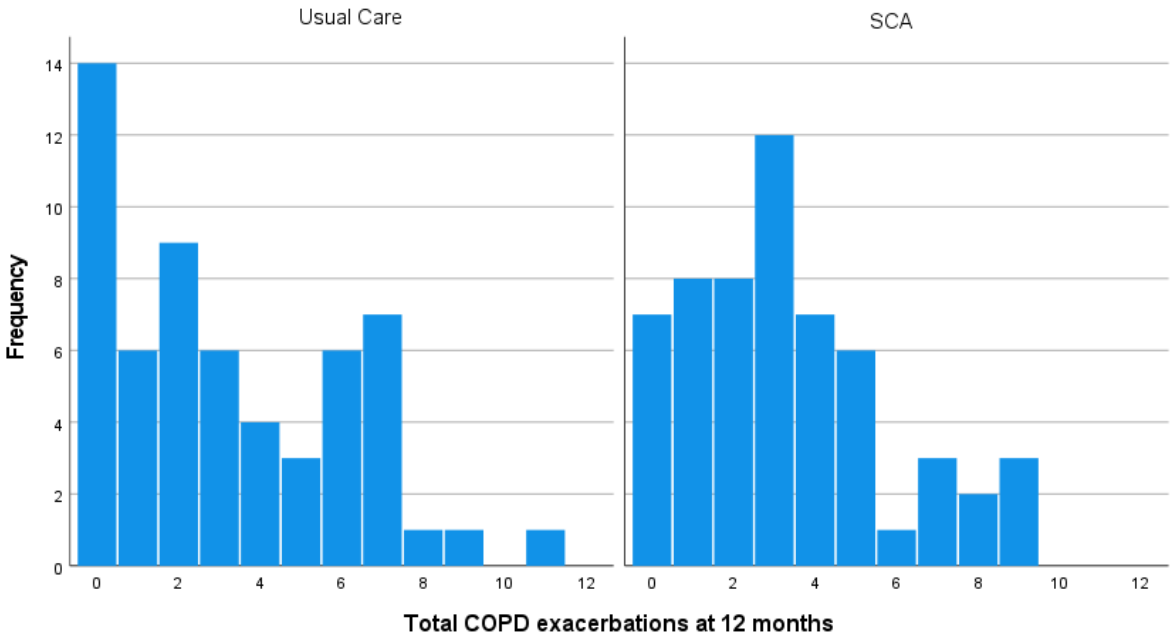


Figure 46: Histograms: exacerbations at 12 months

Only 6 patients had at least one very severe exacerbation (defined by an NIV episode) in the first 90 days after discharge, 3 in each arm, therefore this data was not analysed further. Given the close relationship between mortality and very severe exacerbations, time to event analysis was conducted on this variable at 12 months, as well as on the rates of severe exacerbations for the same reason.

This revealed no difference in survival without a very severe exacerbation between the two study arms (log rank p=0.998)

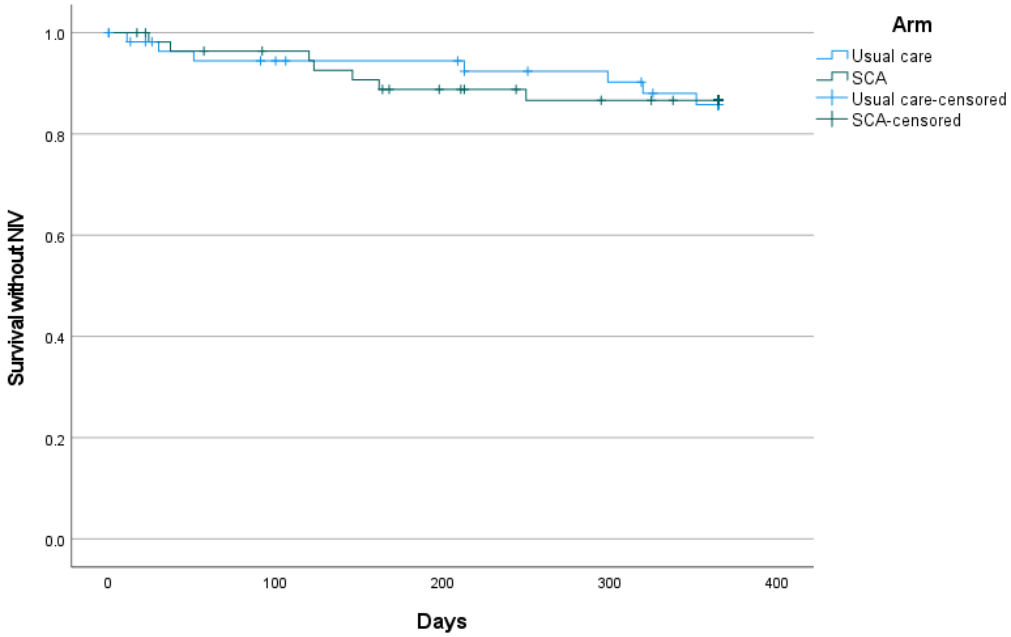


Figure 47: Kaplan-Meier plot: survival without NIV

Likewise, there was no difference in survival without a severe COPD admission between the arms (log-rank p=0.715).

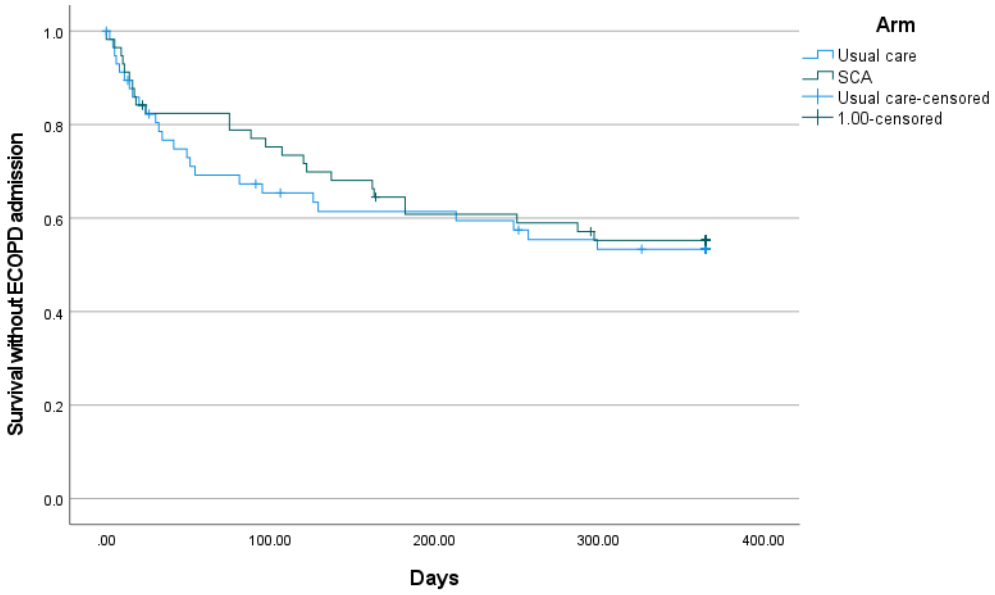


Figure 48: Kaplan-Meier plot: survival without a severe ECOPD

This second set of survival curves resembles that derived from the analysis of all-cause readmission or death, which follows from the fact that ECOPD was the commonest reason for patients to be readmitted. Likewise, it demonstrates a degree of early separation followed by return to parity. If this is a true signal it could follow from the fact that better assessment and treatment of heart disease for patients receiving the SCA reduced symptoms of breathlessness and chest discomfort caused by these conditions, which might otherwise have led to hospital admission and been incorrectly labelled as ECOPD.

6.3.5 Adverse cardiovascular events

The composite endpoint of the occurrence of myocardial infarction, stroke or death from cardiovascular cause (confirmed by mortality adjudication) was assessed at 90 days and 12 months following discharge, with time to event analysis also conducted.

The following adverse cardiovascular events occurred:

	Whole cohort *(n=115)*	**Usual care** *(n=58)*	**SCA** *(n=57)*	p value (no between-arm difference)†
Prior to 90 days				
MI	7	3	4	
Stroke	1	1	0	
CV death	3	2	1	
Any ACE*	**10**	**5**	**5**	**1.000**
By 12 months				
MI	11	6	5	
Stroke	1	1	0	
CV death	5	4	1	
Any ACE	**16**	**10**	**6**	**0.420**
* 1 usual care patient experienced both MI and subsequent CV death † Fisher's exact test				

Table 33: Adverse cardiovascular events

Cumulative incidence of ACE was compared between the study arms by the Kaplan-Meier method. Figure 49 demonstrates separation of the curves, with higher cumulative incidence of ACE in the usual care arm, although this was not statistically significant (log-rank p=0.286).

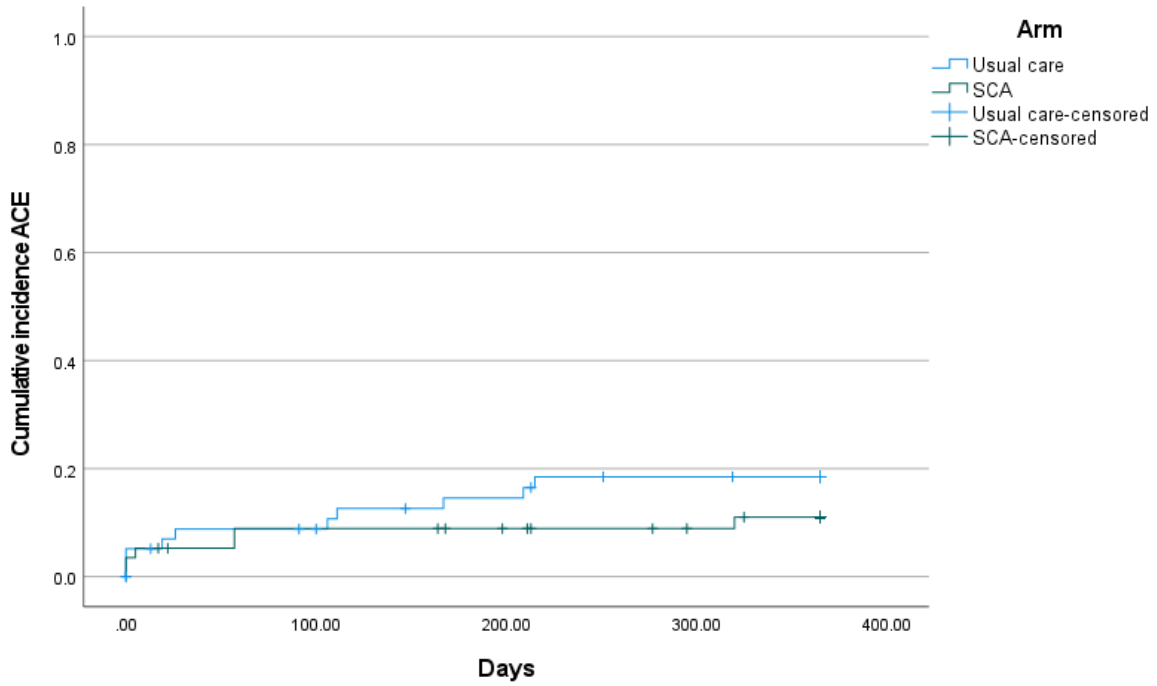


Figure 49:Kaplan-Meier plot: cumulative incidence of ACE

This difference between arms has high biological plausibility given the most common new diagnosis made was coronary artery disease above the threshold for treatment with antiplatelet medications (see next subsection), and the known high post-exacerbation risk for MI and stroke. However, this finding is based on only a very small number of events and a study involving the observation of a greater number of patient-years would be required to assess this outcome definitively.

Since the design of this study, the concept of cardiopulmonary risk has been developed, with the aim of focussing COPD management towards proactively targetting the twin major sources of mortality: exacerbations and adverse cardiovascular events.[623] The definition of a *cardiopulmonary event* has not been definitively standardised, with one group using a broad composite outcome of all-cause death and hospitalisation for either acute respiratory or cardiovascular reasons,[624] while others reported individual components including moderate ECOPD events, and a cardiovascular event outcome that including worsening of known cardiac conditions.[625] As a post hoc, exploratory analysis, time to first serious cardiopulmonary (CP) event was compared between arms, defining a CP event as an admission with ECOPD or occurrence of ACE, as already defined previously for this study.

Survival curves separated and remained so throughout follow-up, with a mean time to first CP event in the usual care arm of 192 days (95% CI 150 – 233), compared with 236 days (196 – 274) in SCA (see Figure 50). This difference was not statistically significant (log-rank test p=0.229).

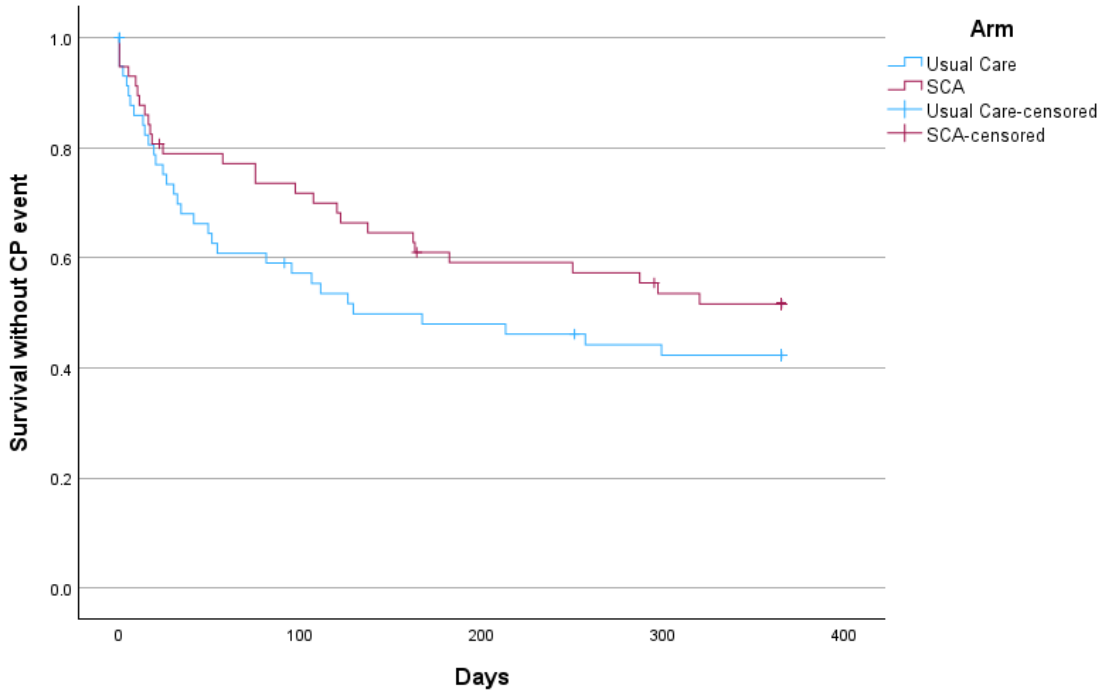


Figure 50: Time to first cardiopulmonary event according to study arm.

While a post-hoc and exploratory analysis, the distinct and preserved separation of the survival curves, along with the emerging recognition of the importance of overall cardiopulmonary risk, suggest that cardiopulmonary event rate would be an important outcome measure to consider for a definitive trial of SCA.

6.3.6 New diagnosis of cardiovascular disease

Diagnoses made during admission were recorded in each arm, based both on the results of the SCA and on tests and evaluations made as part of usual care. Heart failure was defined according to the definitions used to prompt treatment changes, as stated in Chapter 4. A substantially higher rate of diagnoses was seen in SCA. In this group, by completion of SCA, 42 patients (73.7%) received a new cardiovascular disease diagnosis; 8.8% were found to have moderate-severe LVSD, 22.8% to have heart failure without LVSD and 59.6% to have moderate-severe CAD. In the UC group, 11 (19%)

received a new diagnosis (p for difference from SCA <0.001). A single patient in the UC group, post-randomisation, experienced an ischaemic stroke during admission (this category is included in the below tables as it is classified as a cardiovascular disease, although screening for cerebrovascular disease was not included within the SCA).

	UC n=58	SCA n=57
Heart failure		
Moderate-severe LVSD	2 (3.4%)	5 (8.8%)
HF without moderate-severe LVSD	4 (6.9%)	13 (22.8%)
Right sided heart failure	2 (3.4%)	8 (14.0%)
Myocardial infarction	2 (3.4%)	2 (3.5%)
Atrial fibrillation	2 (3.4%)	1 (1.8%)
Mild coronary artery disease (CACS 1-100)*	0	11 (19.3%)
Moderate-severe coronary artery disease (CACS >100)*	0	34 (59.6%)
Uncontrolled hypertension†	0	14 (24.6%)
Uncontrolled diabetes	1 (1.7%)	8 (14.1%)
Stroke/TIA	1 (1.7%)	0

*Table 34: New diagnoses made during admission, number (%). *Without pre-admission diagnosis of MI; †BP above target range at discharge or BP assessment, or antihypertensives increased during admission. Patients can have more than one new diagnosis*

Between discharge and 90-day review, and between 90-day review and 12 months, diagnoses continued to be made, albeit at a diminishing rate. Of note, 7 new diagnoses of heart failure without moderate-severe LVSD and 3 of right-sided heart failure were made in the SCA arm on the basis of the 90-day follow-up echocardiogram. There was not a substantial degree of new diagnosis during follow-up for patients in usual care arm, suggesting that patients who did not have cardiovascular disease diagnosed during the index admission did not have tests later in their clinical care and their heart disease remained undiagnosed.

	Discharge to 90-day review		90-day review to 12 months	
	UC n=56*	SCA n=57	UC n=51*	SCA n=52*
Heart failure				
Moderate-severe LVSD	1	1	0	0
HF without moderate-severe LVSD	0	7	2	0
Right sided heart failure	0	2	1	0
Myocardial infarction	1	1	1	0
Atrial fibrillation	0	1	0	0
Coronary artery disease	0	0	1	0
Hypertension	0	0	1	0
Diabetes	0	0	0	1
Stroke/TIA	0	0	0	0

*Table 35: New diagnoses made during follow-up. * 2 patients did not survive beyond discharge; 5 patients in SCA arm and 7 patients in UC arm died prior to 90-day review*

The significantly increased rates of diagnosis of new cardiovascular disease in the SCA arm supports the hypothesis that applying the structured cardiovascular assessment to patients admitted with ECOPD results in the identification of a substantial quantity of undiagnosed disease. The detailed results of the cardiovascular investigations and their interpretation for the purposes of diagnosis are presented in Chapter 7.

6.3.7 Undertreated heart disease

At 90-day, 6-month, 9-month and 12-month follow-up, use of medications in major drug classes relating to heart disease was ascertained. As presented in section 5.2.4, rates of prescription were not different at baseline. In the usual care arm, there was not a substantial alteration in the proportion of patients prescribed medications for heart disease over the full follow-up period. This is represented in the below table, where intensifying colours are used on a logarithmic scale to emphasise sizeable changes. Intensification is seen in the SCA arm for use of antiplatelets and beta-blockers. In both arms, the proportion of patients prescribed more novel agents for heart failure, such as sacubitril-valsartan and SGLT2i inhibitors, increased – to a greater degree in the SCA arm – then decreased, reflecting new diagnosis and treatment of severe LVSD and then subsequent mortality in this subgroup.

Usual Care	Antiplatelet	DAPT	Anti-coagulant	Beta-blocker	ACEi/ARB	Statin	Other anti-HTN drug	Anti-DM drug	MRA	Sacubitril-valsartan	SGLT2i
Baseline *n=58*	17	1	7	13	15	35	14	9	1	0	0
Discharge *n=56*	15	2	10	15	13	33	12	10	1	0	1
90 days *n=50*	12	2	7	12	15	31	9	9	2	1	2
6 months *n=48*	12	2	6	13	15	31	8	9	2	1	1
9 months *n=45*	11	1	6	12	15	31	9	9	2	1	1
12 months *n=41*	8	2	7	9	10	28	6	9	1	0	0
SCA	Antiplatelet	DAPT	Anti-coagulant	Beta-blocker	ACE-i/ARB	Statin	Other anti-HTN drug	Anti-DM drug	MRA	Sacubitril-valsartan	SGLT2i
Baseline *n=57*	20	2	4	11	22	37	17	9	1	0	1
Discharge *n=57*	22	4	5	17	21	38	12	9	2	2	3
90 days *n=52*	32	3	5	16	16	41	9	10	3	3	1
6 months *n=50*	30	3	4	14	17	39	9	10	3	3	1
9 months *n=47*	29	2	5	15	17	37	8	9	4	3	1
12 months *n=43*	30	2	4	13	17	35	8	9	2	2	1
Each cell contains the number taking the medication class; shaded by percentage of the represented as follows:											
	0%	0-5%	5-15%	15-30%	30-60%	60%+					

Table 36: Medication use during study, by arm

Undertreatment was defined as a lack of prescription, for any reason, of guideline-recommended treatments for the major heart diseases listed below; or, where patients stated, lack of self-administration of medications that were currently prescribed at the time of review. The diagnostic criteria and treatments match those stipulated in the management summaries described in Chapter 4 (see Appendix C for full summaries), with the key points summarised below:

Diagnosis	Definition	Treatment
Myocardial infarction	Historic MI: recorded clinical diagnosis MI during inpatient admission: Final diagnosis reached by clinical team, supported by troponin rise and ischaemic ECG changes	• Aspirin (or equivalent); DAPT for 1 year • ACE-inhibitor/ARB* • Beta-blocker in first year • Statin
Coronary artery disease	Agatston score 100+ or intervention for coronary artery disease; no diagnosis of MI	• Aspirin (or equivalent) • Statin
Heart failure with moderate-severe LVSD	LVEF <45%	• Beta-blocker • ACE-inhibitor/ARB *Plus, if LVEF <40%* • Management by heart failure service including use of MRA/ARNI/SGLT2i

Table 37: Criteria for diagnosis of heart disease and for adequate treatment

The rates of diagnosis and undertreatment are summarised in Table 38. Patients who survived and attended face-to-face or telephone review (required for confirmation of compliance with prescribed medications) are included at each review point.

At baseline, around half of patients in the whole cohort were not being treated adequately for heart disease diagnosed prior to their index admission. After the SCA, not only did the proportion of patients with diagnosed heart disease increase considerably, but the proportion that were undertreated fell significantly as most patients were, successfully initiated on treatments. Subsequently, the proportion of patients with known but undertreated heart disease in each arm fell slightly, due to the combined effects of attrition in under-treated cases and initiation of treatments after a delay following discharge: undertreatment rates reduced from 64% to 50% by study end in the usual care arm, and 26% to 19% in the SCA arm, although p-values for difference between the arms from Fisher's exact test were not significant at later time points.

	Whole cohort		UC		SCA		P*
	Diagnosed	Under-treated	Diagnosed	Under-treated	Diagnosed	Under-treated	
Pre-admission	*n=115*		*n=58*		*n=57*		1.000
Any diagnosis	**21**	**10**	**10**	**5**	**11**	**5**	
Mod-Sev LVSD	4	2	1	0	3	2	
MI	16	8	8	5	8	3	
CAD	2	1	1	0	1	1	
Hospital discharge†	*n=113*		*n=56*		*n=57*		
Any diagnosis	**58**	**19**	**11**	**7**	**47**	**12**	0.029
Mod-Sev LVSD	10	2	3	1	8	1	
MI	20	10	10	7	10	3	
CAD	35	22	0	-	35	8	
90-day review	*n=102*		*n=50*		*n=52*		
Any diagnosis	**51**	**17**	**9**	**4**	**42**	**13**	0.056
Mod-Sev LVSD	10	3	4	2	6	1	
MI	15	7	7	4	8	3	
CAD	32	10	0	-	32	10	
12 months	*n=84*		*n=41*		*n=43*		
Any diagnosis	**42**	**10**	**6**	**3**	**36**	**7**	0.135
Mod-Sev LVSD	7	2	3	2	4	0	
MI	12	4	4	2	7	1	
CAD	30	6	0	-	30	6	

* Difference in overall undertreatment rates between arms; Fisher's exact test
† In 3 cases, cardiac CT was performed after discharge

Table 38: Rates of diagnosis and undertreatment of heart disease throughout study evolution

Randomisation was carried out stratified by presence of known heart disease, and it can be assumed that heart disease was present to an equal degree in each study arm. Therefore, the undertreatment rates reported here for the usual care group represent considerable under-estimates of the true rates for this arm of the trial.

The reasons for undertreatment were recorded for patients who had medication started or recommended as part of the outcome of the structured cardiac assessment and are detailed in Appendix F. Of note, all three incidences of non-treatment with ACE-inhibitor (or equivalent) when indicated were due to hypotension on treatment, and 5 of the 17 patients newly prescribed statins stopped or declined them due to personal choice.

The rate of undertreatment is an important outcome as, notwithstanding that better understanding the causes of patients' symptoms leads to more accurate management, it is the delivery of treatment of heart disease with evidence-based therapies that is the primary mechanism by which a

structured cardiac assessment would improve key outcomes for patients. However, as highlighted, the full extent of undertreatment is difficult to measure in a control arm containing patients that do not receive a full cardiac assessment. Furthermore, it is laborious to assess: in this pilot study there were several patients who were prescribed medications such as statins and aspirin but were not actually taking them through personal choice. Direct questioning at each time point of the study was required to establish true (under)treatment rates, an undertaking that would be challenging in a larger multi-centre study.

6.3.8 4-metre gait speed

Gait speed was calculated from the fastest of two trials completed, or the sole trial if only one was completed. If patients were unable to walk 4 metres or had died by the time of review, they were assigned a score of zero, since change in gait speed was the focus of investigation. If patients did not attend face-to-face follow-up, they were excluded from the analysis. One patient had an above knee amputation and therefore was excluded from all gait speed analyses.

For the whole cohort, histograms of the changes in gait speed approximated normal distributions, with the mean change being positive between baseline and 90 days and baseline to 12 months, and negative from 90 days to 12 months. This is interpreted as representing recovery from hospitalisation to a baseline functional state, with further subsequent deterioration over the following 9 months.

Gait speeds were generally slow at baseline, with mean around 0.5 ms^{-1}, in keeping with previously published data collected during admission for ECOPD.[626] The mean gait speed among those that were able to record values at stability was lower than that seen in other studies: 0.68 (SD 0.23) ms^{-1} at 90 days in this cohort, vs, for example, 0.91 (0.24) ms^{-1} in a cohort attending outpatient clinics,[627] highlighting a particularly high degree of mobility impairment in recruited patients.

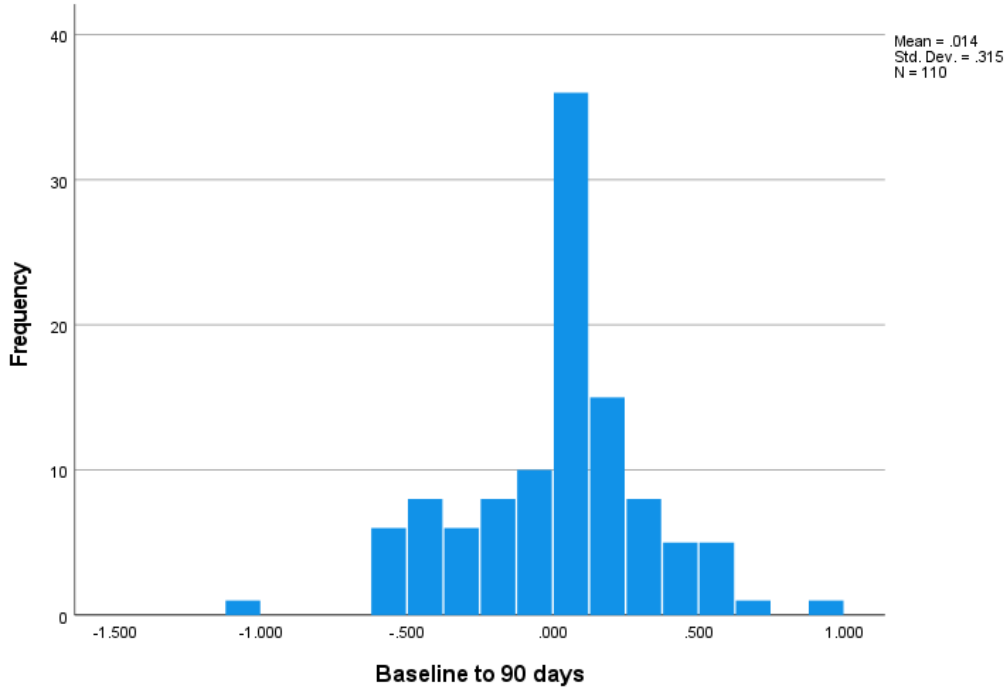


Figure 51: Change in 4 metre gait speed from baseline to 90-day follow-up

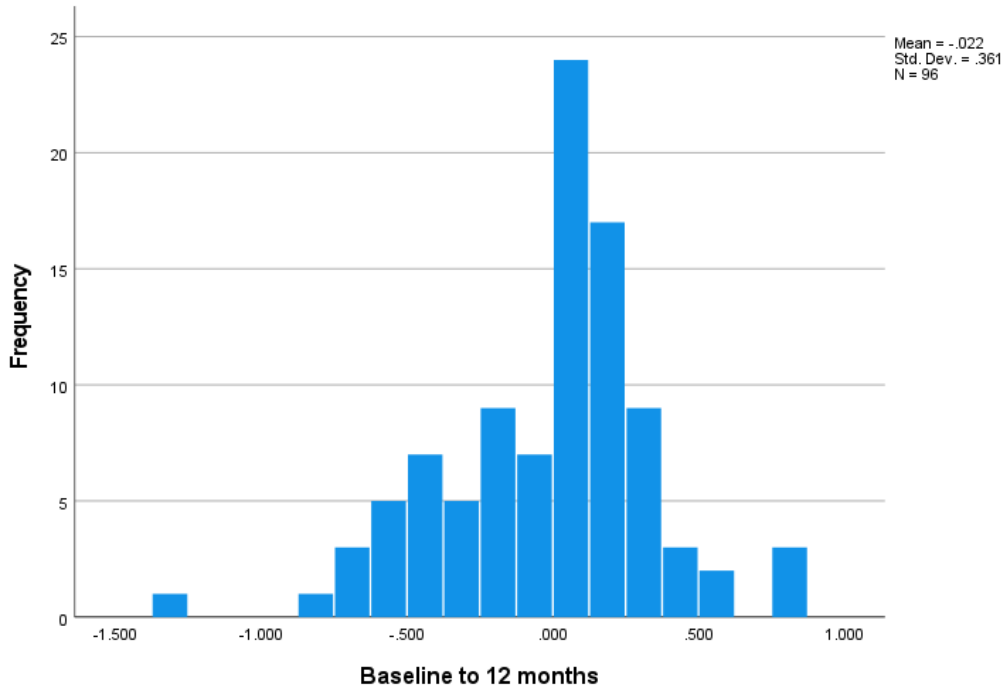


Figure 52: Change in 4 metre gait speed from Baseline to 12-month follow up

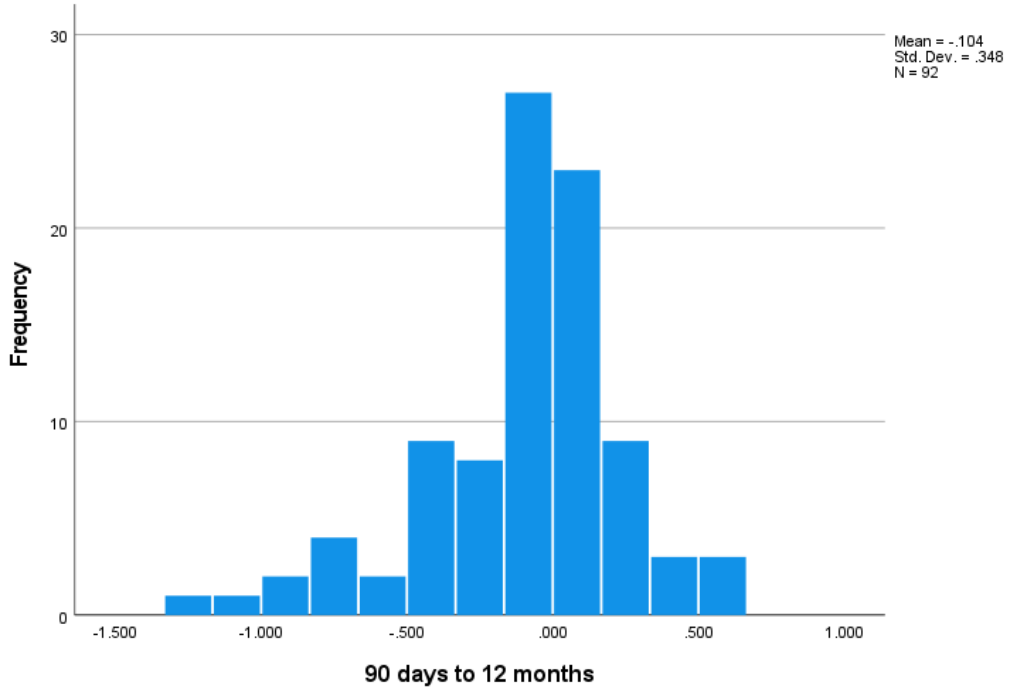


Figure 53: Change in 4 metre gait-speed from 90-day to 12-month follow-up

Examining the two study arms, the mean gait speed (ms^{-1}) was slightly higher in the usual care arm at each time point:

	Usual care	SCA
Baseline	0.541 (0.276)	0.505 (0.307)
90 days	0.570 (0.352)	0.564 (0.311)
12 months	0.614 (0.342)	0.530 (0.363)

Table 39: Mean gait speed (m/s) at each assessment point

The mean gait speed appeared to increase between 90 days and 12 months in the usual care arms yet decrease in the SCA arm. However, inspection of box-plots for the two study arms reveals little difference in the trajectory of the median gait speed.

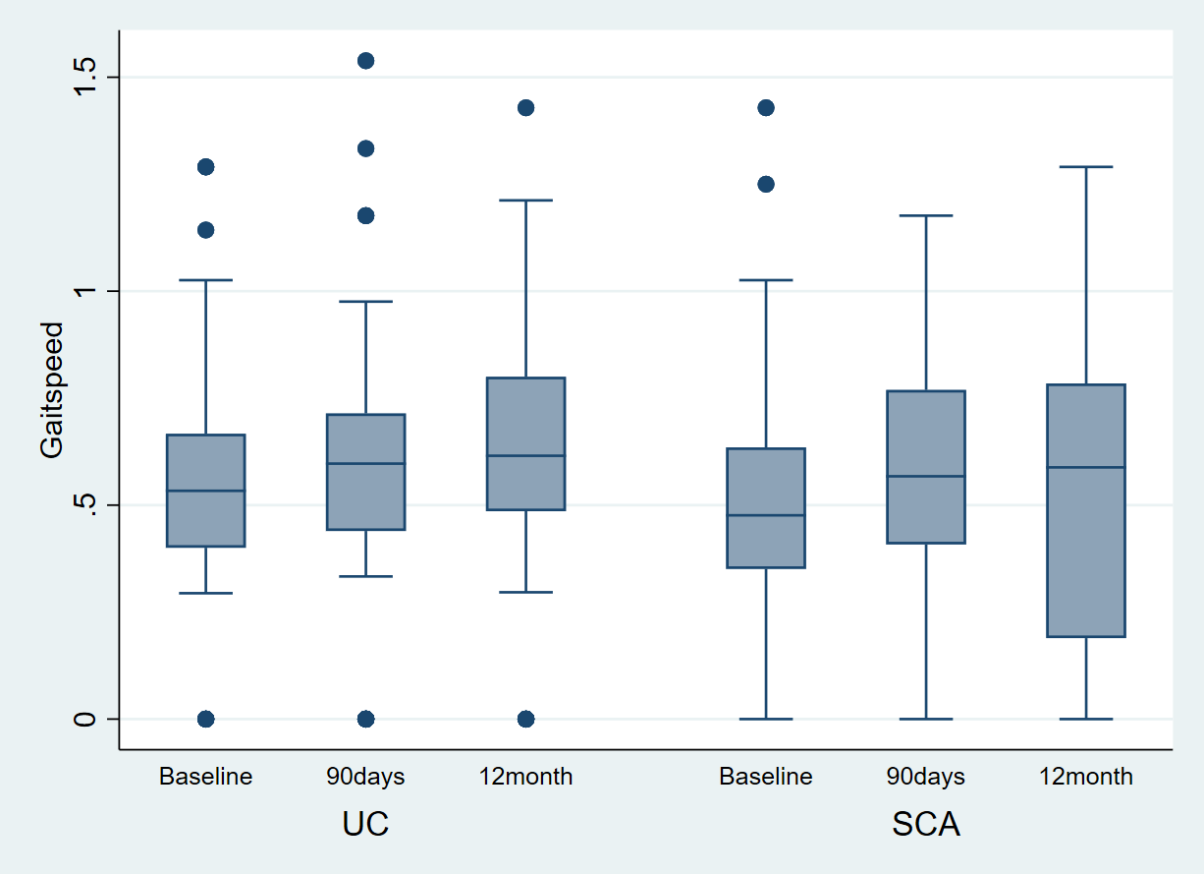


Figure 54: Box plots of 4 metre gait speed at each assessment point

A repeated measures ANOVA was used to compare the effect of study arm on gait speed; no statistically significant difference was found (p=0.310).

Given the apparent difference between the arms shown in Figure 54 from the 90-day to 12-month time point, the change in gait speed during this interval was explored further by categorising the patients according to gait speed changes above, within and below the minimal clinically important difference, taken to be 0.1ms^{-1} in line with previously published work in similar populations.[549,628]

Gait speed change	**Usual care, % (n)**	**SCA, % (n)**	*Totals*
Increase > MCID	37.8 (10)	27.7 (13)	23
Within MCID	40.0 (18)	31.9 (15)	33
Decrease > MCID	22.2 (17)	40.4 (19)	36
Totals	45	47	92

Table 40: Contingency table of gait speed change category (90 days to 12 months) and study arm

There was no significant difference in the relative proportions in the different gait speed categories between the arm (p=0.722, Fisher's exact test).

There were difficulties with measuring gait speed as an outcome, including the need to assess patients face-to-face and maintain infection control precautions for hospitalised patients. In the study centre, side rooms were large, allowing room for gait speed to measured for patients isolated for reasons such as suspected or proven Covid-19, but at other sites this would present a challenge.

6.3.9 Quality of life (St George's Respiratory Questionnaire for COPD)

SGRQ-C scores were converted to percentage values, with 100% representing the highest possible score and hence the worst measurable quality of life (QoL). The change in the area under the Total SGRQ-C score vs. time curve was calculated and change per unit time determined for patients that attended follow-up (if patients died, they were assigned the worst quality of life scores at the time of death).

The distribution of change in total SGRQ-C score per unit time approximated a normal distribution with a mean value above 1, corresponding to overall worsening of quality of life during study follow up.

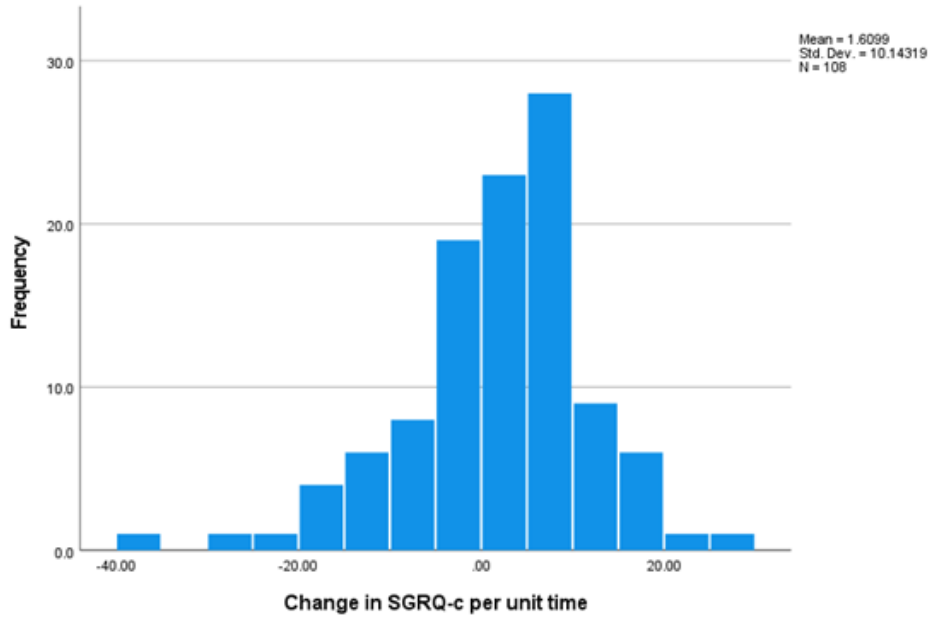


Figure 55: Histogram: change in SQRQ-C per unit time (whole cohort)

Mean change (SD) in QoL in the SCA arm was consistent with very slight worsening during follow up,

at 1.02 (9.90); in the usual care arm the mean change was 2.24 (10.45); this difference was not significant (p=0.533).

Meaningful changes in quality of life - i.e. those greater than the accepted MCID of 4 units - were examined, with patients divided into those with an overall favourable, unfavourable or neutral quality of life change during follow up.

QoL change	**Usual care, % (n)**	**SCA, % (n)**	*Totals*
Favourable	19.2 (10)	23.2 (13)	23
Neutral	28.8 (15)	35.7 (20)	35
Unfavourable	51.9 (27)	41.1 (23)	50
Totals	52	56	108

Table 41: Contingency table: Quality of life change category and study arm

The contingency table reveals that the SCA arm had a slightly higher proportion of patients with favourable QoL change, and a slightly lower proportion with unfavourable QoL change, although the difference was non-significant (p=0.539, Fisher's exact test).

As for 4-metre gait speed, quality of life assessment required patients to attend follow-up with the investigator, but had the advantage of being accessible by telephone follow-up. The broad variance in quality of life change during the study means that very large numbers of patients per arm would be required in order to power a study to detect a difference (using this tool), if one was truly conferred by the use of the SCA.

6.4 Economic analysis

The final objective of the study discussed in this chapter is the assessment of the feasibility of collecting healthcare resource use data to carry out an economic evaluation of the intervention in a future RCT.

The SCATECOPD study compared two study arms: in one, no alteration was made to usual care for, and following, hospitalisation with ECOPD, whereas the SCA arm involved additional tests and intensification of treatment in many cases.

Consequently, analysis of the cost difference between the intervention and usual care arms is essential for a comprehensive assessment of the impact of the intervention through a definitive study. This cost difference must then be set against the difference in quality of life between the

study arms for an overall assessment of the cost-effectiveness of the intervention. This is particularly important if the intervention is being considered as a potential part of an increasingly resource-pressured healthcare system, such as the NHS.

The results of the cost effectiveness analysis are the focus of this section, with the primary procedure being the use of collected healthcare resource use and quality of life data to estimate the incremental cost effectiveness ratio of the intervention compared with usual care.

As per the study objectives, the feasibility of collecting service-user data for economic evaluation in a future randomised controlled trial of a similar intervention is also considered, along with suggested practical modifications to the process based on experiences in the present study.

6.4.1 Quality of life (EQ5D5L)

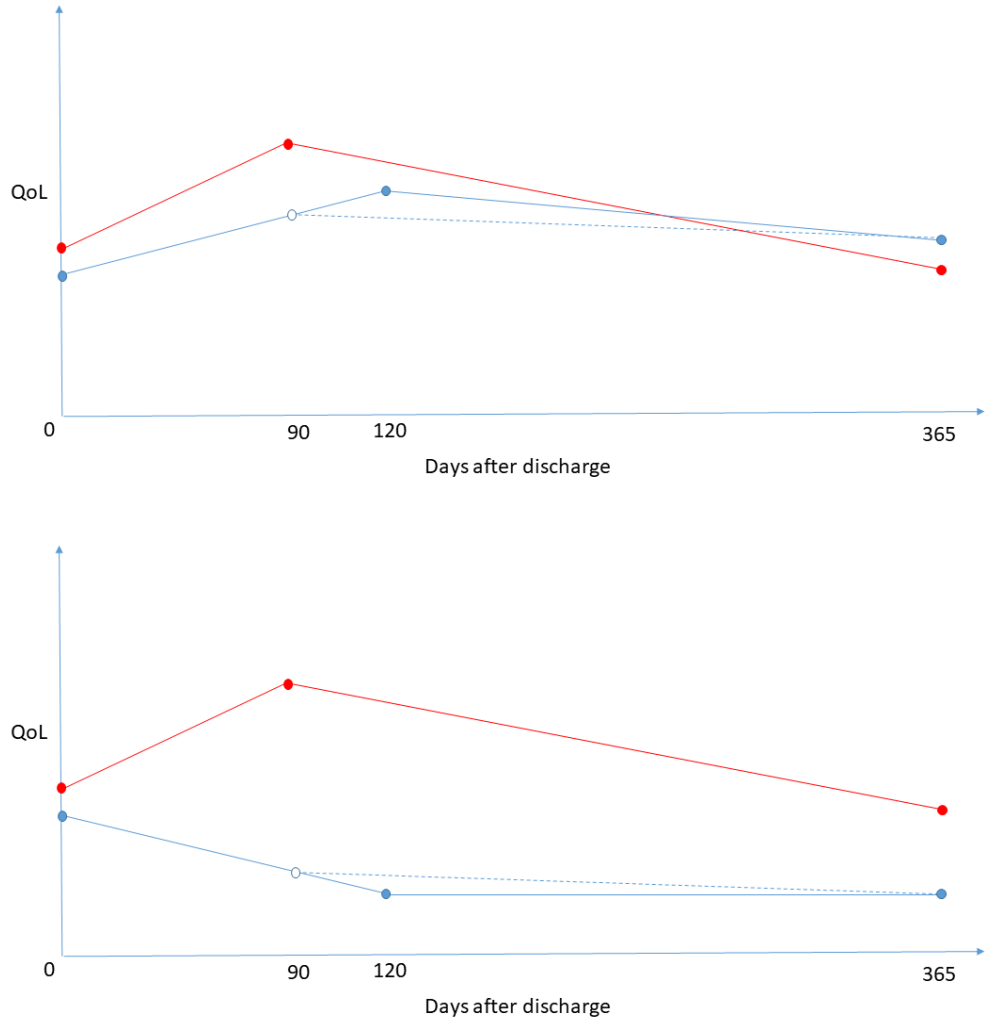
The health effects of participation in either the usual care or SCA arm of the study were assessed by measurement of health-related quality of life.

An analysis of quality of life change during study follow-up has already been presented in section 6.3.9. This was based on responses to the St George's Respiratory Questionnaire for COPD, which is a valuable and precise tool for assessing COPD-related quality of life but is not recommended for cost effectiveness analysis. Therefore, the EQ-5D-5L instrument was used to assess overall health-related quality of life at baseline, 90-day follow-up and 12-month follow up, as preferred by NICE for cost effectiveness analysis.[629] This could only be performed for patients attended telephone follow-up, reducing the number of patients contributing to the cost-effectiveness analysis to 108 (56 in the SCA arm, 52 in usual care).

As stated in section 6.3.4, follow-up at 90 days was often delayed due to recent COPD exacerbation; in 23 cases (21%) this delay was more than 15 days and in 19 (18%) it was over a month. This meant that quality of life was not assessed at the same time interval following discharge for all patients. This was, however considered an appropriate method for assessing the baseline quality of life attained by patients following their index hospital admission, since assessing EQ-5D-5L during or immediately after a subsequent exacerbation, would not be an accurate reflection of baseline status (particularly in the domains of mobility, self-care and usual activities). However, to avoid delayed follow-up influencing the area under the curve used for quality of life change calculation, utility indices derived from follow-up appointments delayed more than 15 days were adjusted back to the their value projected at 90 days. The methodology and effect of this is described in section 4.7.3; the consequences of not performing the justment are illustrated below (Figure 56).

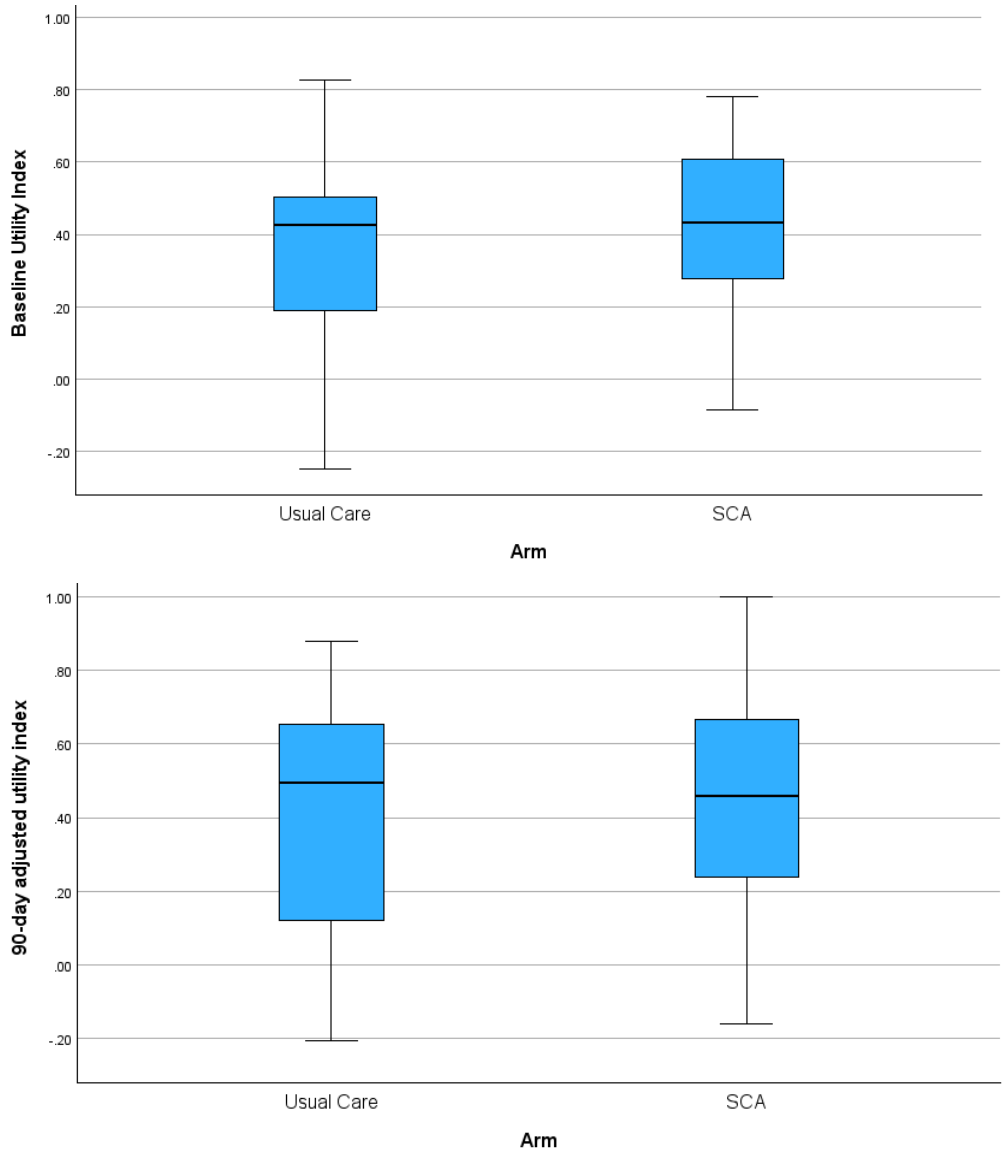
Figure 56: Illustration of the effect of delayed 90-day follow-up on the area under the curve of the quality of life-time graph. Solid circles represent quality of life scores obtained during study participation; unfilled circles represent adjusted values. QoL – quality of life.

In both cases, the red line represents a patient followed up at precisely 90 days, who experienced improvement in QoL post-admission and subsequent deterioration at 1 year. The blue lines represent patients with delayed follow up, for whom QoL scores were adjusted in proportion to the duration of delay to obtain an adjusted QoL score for 90 days post discharge. In the upper graph, a patient was followed up at 120 days and also showed improved QoL; for this patient the area under the curve would be greater without adjustment. In the lower graph, a patient whose QoL deteriorated following admission would have a smaller area under the curve without adjustment.



This process was also applied for patients whose 1-year follow-up was delayed for more than 15 days; although not illustrated above, the same principles were applied to adjust quality of life scores in proportion to the duration of delay.

Distribution of EQ5D5L utility index scores was normal at baseline, with an increasing tendency towards right skew during follow-up, as increasing numbers of patients attained scores of 0 due to mortality. Box plots of EQ5D5L utility index scores are presented below.



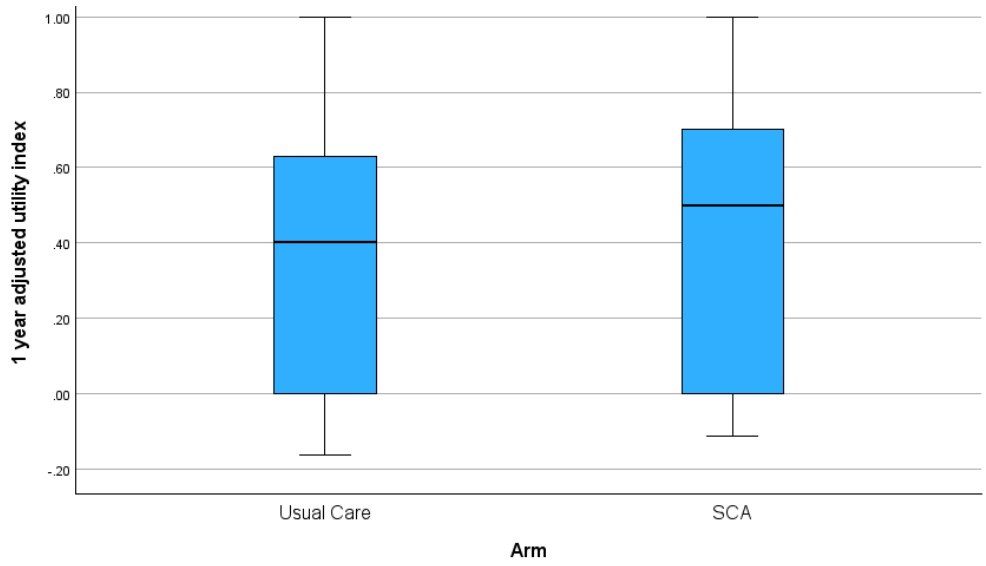


Figure 57: Box plots of EQ5D5L utility index at baseline (top, previous page), 90 days (bottom, previous page) and 1 year (this page); values adjusted if delayed at follow up

Mean UI at baseline, 90-days and 1 year, is presented in table 42:

EQ5D5L UI [mean (SD)]	Usual Care n=52	SCA n=56	P value (t-test)
Baseline	0.378 (0.27)	0.429 (0.20)	0.266
90-day	0.429 (0.31)	0.449 (0.27)	0.730
1-year	0.386 (0.34)	0.418 (0.32)	0.613

Table 42: mean (SD) UI at baseline, 90 days and 1-year (UI adjusted at follow-up if delayed)

The greatest between-arm difference in mean EQ5D5L UI was at baseline - the score was notably higher in the SCA arm – although this was not significant. The ranges displayed in the box plots (Figure 57) and the standard deviations calculated indicate a broad spread of quality of life scores throughout the study. In both arms, the trend was for UI to increase slightly at 90 days and then decrease once again to a similar value at 1-year as that seen at baseline.

6.4.2 Healthcare resource use

Healthcare resource use was enumerated for each participant from the details of their inpatient admission, subsequent admissions, outpatient attendances and investigations, and community healthcare use.

As for the assessment of quality of life presented in the previous subsection, this could only be accurately completed for patients who attended telephone follow-up; accordingly, the same 108 patients (52 in usual care, 56 in SCA) were used in this analysis.

Costs were assigned to the recorded resource use using values published by the NHS (reference costs 2022/23) for hospital admissions, procedures and investigations and the Personal Social Services Research Unit (2021) for visits to primary care, allied health professionals such as physiotherapists, and outpatient clinics.[630,631]

For both total costs and each costs subcategory, the distributions observed were, consistent with previous research into variation in healthcare utilisation, significantly right-skewed, with a small number of outlying patients accounting for very large individual health costs. This is demonstrated in the histograms for total costs presented in Figure 58.

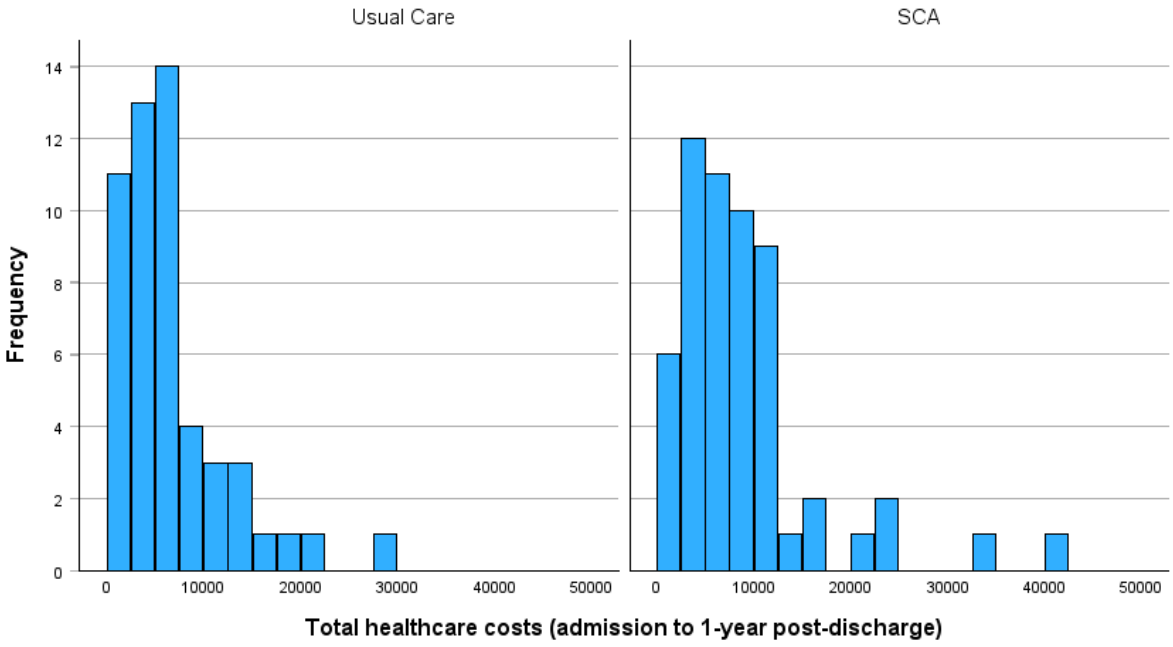


Figure 58: Histograms of total healthcare costs at 1 year

Median total and subcategorised costs in each study arm are presented in Table 43, along with results of the non-parametric test for difference.

	Usual Care n=52	SCA n=56	P value (MWU test)
Index admission costs	1100 (1650)	1650 (1787.50)	0.783
Index procedure costs	0 (83)	250.22 (0)	<0.001
Post-discharge hospital costs	1100 (4675)	1803 (5912.50)	0.322
Post-discharge investigations*	82.17 (240.50)	0 (152.92)	0.168
Outpatient clinic costs	274 (513.75)	411 (513.75)	0.065
Primary care and AHP costs	1109.97 (1661.62)	1467.17 (1703.75)	0.223
Total costs	5714.03 (5100.40)	7269.42 (6790.81)	0.053

Table 43: Median (IQR) costs (in £) by arm, including index admission and 365 days of follow-up.

In almost all subcategories, the median cost was higher in the intervention arm. However, with the exception of the index procedure costs category, this difference did not reach statistical significance. The median total cost was £1555.39 higher in the SCA arm; the p value returned by the Mann-Whitney U test for a difference in distributions between arms was 0.053.

6.4.3 Quality adjusted life years and incremental cost per QALY

UI values were used to calculate QALYs by the area-under-the-curve method. Histograms displaying the distribution of QALYs in each study arm are contained in Figure 59.

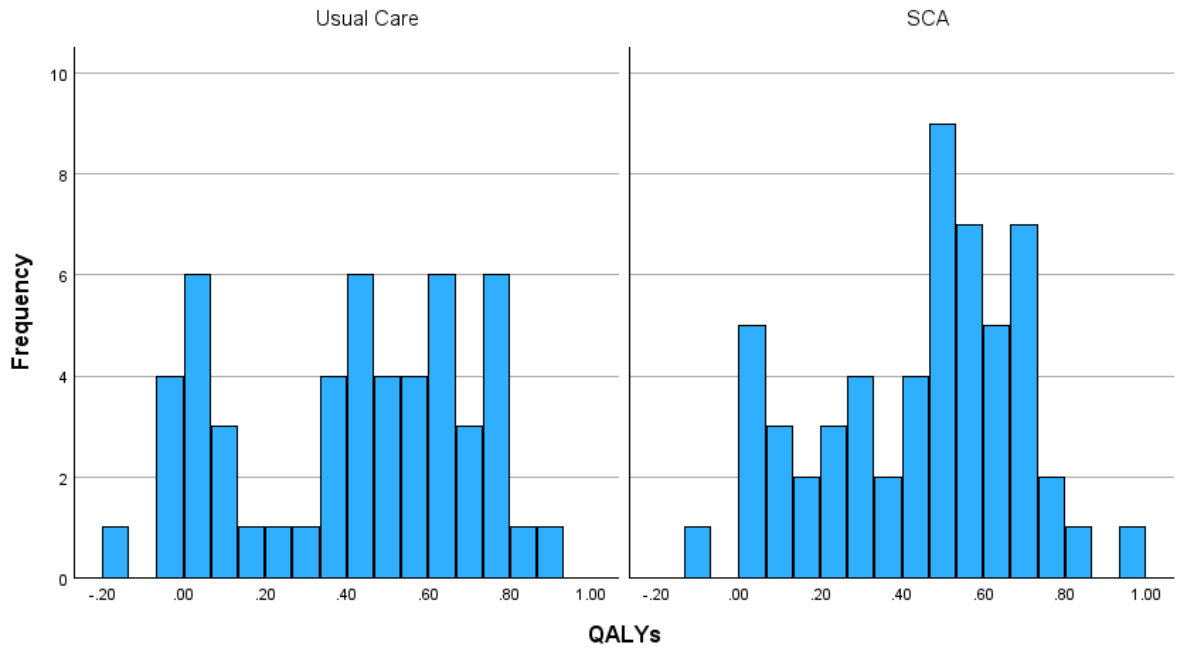


Figure 59: Histograms of QALYs for each arm

The mean value for QALYs in the SCA arm (0.411 [0.29]) was 0.034 higher than in the usual care arm (0.445 [0.25]); this small difference was not significant (95% confidence interval -0.068 to 0.136; p=0.508).

The data for QALYs and costs were used to construct a cost effectiveness plane using a bootstrapping method – this is displayed in Figure 60.

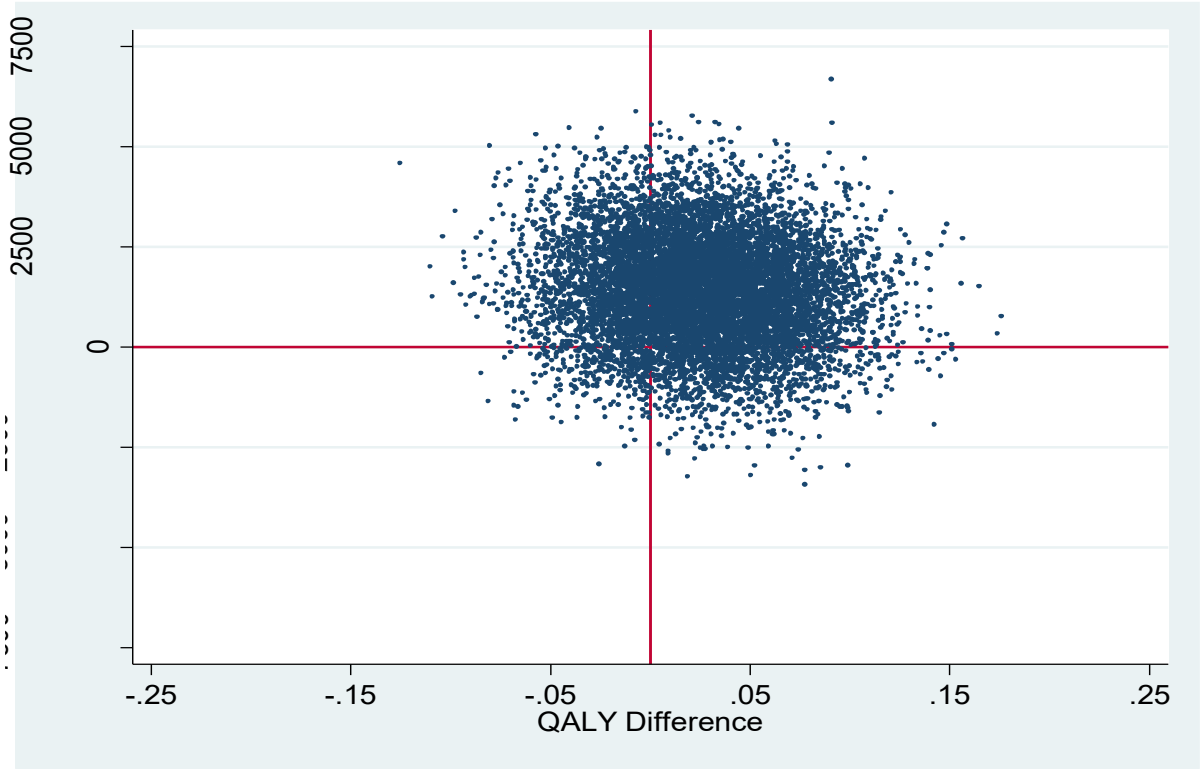


Figure 60: Cost-effectiveness plane generated by bootstrapping (10000 samples with replacement) QALY and cost data

The differences in QALYs and costs are summarised in Table 44. In both cases usual care was the reference case; the observed coefficients therefore estimate the extent to which the values for SCA were greater.

	Observed coefficient	Bootstrap SE	z-value	P value (coefficient > 0)	95% confidence interval
QALY difference	0.023	0.039	0.61	0.545	-0.052 - 0.099
Cost difference (£)	1329.62	1296.33	1.03	0.305	-1211.14 - 3870.38

Table 44: Results of bootstrapping QALY and cost data. SE – standard error.

These bootstrapped results generated an estimated incremental cost effectiveness ratio (synonymous with cost-per-QALY) of £57114.55; the range of values generated for this was very broad (as predicted by the large standard errors for the bootstrapped coefficients, particularly QALY difference); the IQR for ICER was -£18067.17 to £57160.02.

The results of ICER estimation were used to generate a willingness to pay curve; at key cost thresholds the probability that the intervention in the form studied, over one-year follow-up, was cost-effective were: 28.4% at £20000; 32.5% at £25000; 35.9% at £30000. A refinement of the intervention, along with longer follow-up, may produce different cost-effectiveness results due to differences in upfront and subsequent investigation costs between the arms, as well as different quality of life outcomes over a longer period of time.

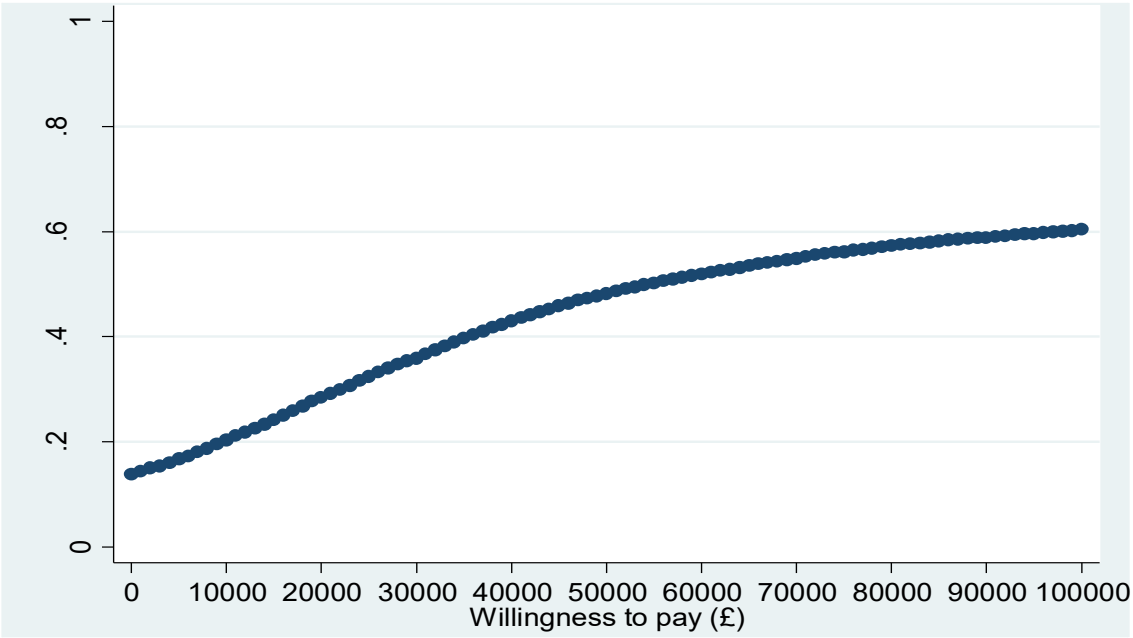


Figure 61: Probability of SCA being cost-effective as willingness to pay threshold increases

6.4.4 Economic analysis summary

The main results of the economic analysis were: 1) quality of life was similar in SCA and usual care arm, with the 95% confidence interval for the estimated between-arm QALY difference including zero; 2) The overall trend was for total costs to be higher in the SCA arm; 3) The estimate for ICER had a very broad confidence interval, with an estimated 28.4% chance of cost-effectiveness at a willingness-to-pay of £20000/QALY and 35.9% at £30000/QALY.

The analysis was performed to fulfil the objective of assessing the feasibility of collecting healthcare resource use data to carry out an economic evaluation of the intervention in a future RCT. 93.8% of participants initially consented were included in the economic analysis, indicating that the methodology employed resulted in a satisfactorily low drop-out rate. However, the breadth of confidence intervals obtained suggest that a significantly larger sample size would be required for a further economic evaluation to have meaningful utility.

6.5 Chapter conclusion

In this chapter, the results of data collected to support the main study objectives have been presented, including the following key findings:

- Regarding the assessment of the effect of the SCA on DAOH, this pilot study did not demonstrate a significant between-arm difference for this measure.
- Regarding other outcome measures of interest, there was a significant increase in diagnosis and appropriate treatment of cardiac disease, and a signal that cardiovascular, or cardiopulmonary, event rate may be the optimal primary outcome measure for future trials of SCA in this population.
- Finally, economic analysis proved feasible but resulted in estimates for cost effectiveness that had broad confidence intervals and were therefore of limited practical value.

Chapter 7: Results – Cardiac investigations

7.1 Introduction

Patients in the intervention arm of the study (n=57) underwent a structured cardiac assessment comprising: cardiac CT scan to provide coronary artery calcium score; transthoracic echocardiogram, repeated 90 days after discharge and when COPD stabilised; 24-hour ECG; blood pressure assessment; blood tests including Hb_{A1C} and cardiac biomarkers.

This chapter contains analyses of the results of these tests and their relationship with clinical parameters and outcomes, in line with the study objective to examine the relationship between changes in cardiac function from baseline to 90 days and severity of COPD, ECOPD and comorbid heart disease. P values are presented as part of assessment of the significance of differences observed, but it is recognised that in an exploratory, unpowered analysis with multiple comparisons that these must be interpreted cautiously.

7.2 Cardiac CT

Cardiac CT was performed on 56 patients: one patient, after giving informed consent to participate in the study, became claustrophobic on arrival at the CT scanner and withdrew consent for this investigation. 53 of the CT scans were performed prior to discharge; 3 patients returned – at 6, 12 and 16 days after discharge – as they were fit for discharge prior to the CT scanner being available and, in line with the study protocol, discharge was not delayed for the purpose of completing the SCA.

Pulmonary artery to aorta ratio (PA:A) was calculated for each patient that had a CT scan (n=56). The mean ratio was 0.91 (SD 0.14). An increased PA:A, defined as greater than 1.0, is regarded as a surrogate marker of right ventricular dysfunction, with increased RV pressures being transmitted to the pulmonary artery and causing its dilatation.[632] In patients with COPD, increased PA:A has been associated with an increased risk of severe exacerbations.[633]

Increased PA:A was a common finding on inpatient cardiac CTs, being identified in 16 (28.6%) patients. The relationship between PA:A ratio and echocardiographic markers is presented in section 7.3.5.

7.2.1 Coronary artery calcium score

5 of 56 patients who had cardiac CT had stent material that precluded accurate CACS calculation. No patients in the intervention arm had previous coronary artery bypass grafting. Figure 62 displays the number of patients whose CACS scores fell within the commonly used classification ranges: 0 (no CAC), 1-99 (mild CAC), 100-399 (moderate CAC), 400-999 (severe CAC) and 1000+ (very severe CAC).[634]

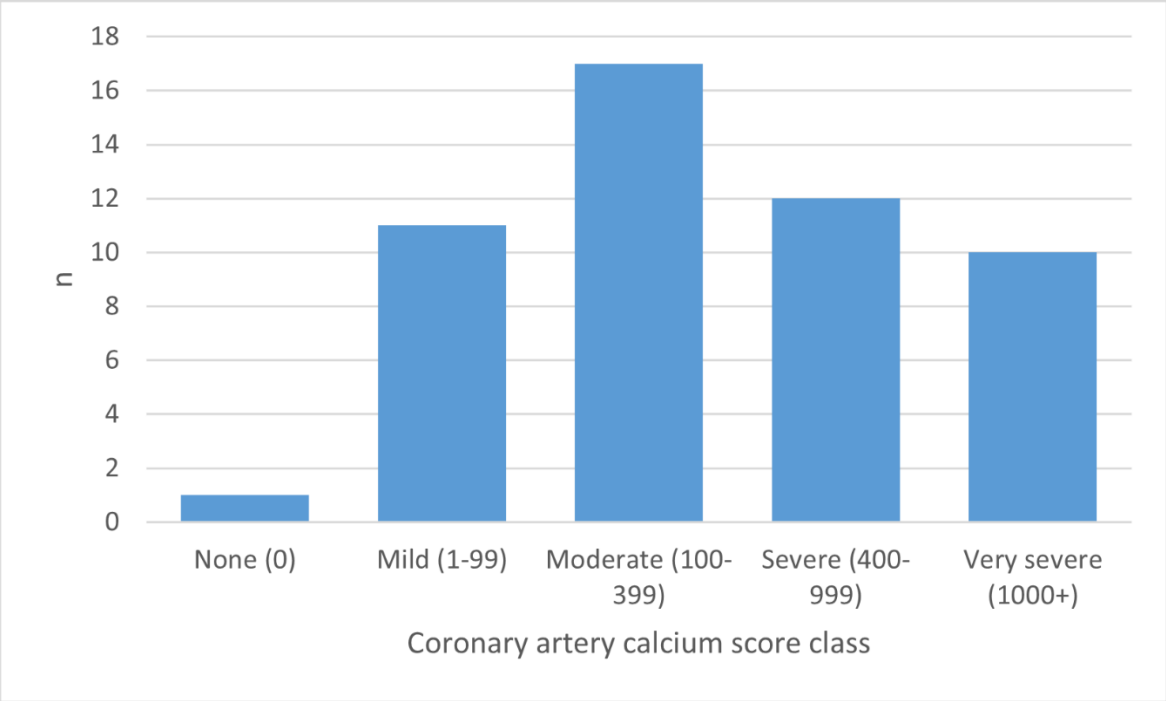


Figure 62: Distribution of coronary artery score by class

Only one patient had no evidence of CAC. 50 (98.0%) had at least mild CAC, 39 (76.5%) had at least moderate CAC and 22 (43.1%) had severe to very severe CAC.

The proportion of patients with a pre-existing diagnosis of CAD increased with higher degrees of CAC. The proportion already taking medication to prevent acute vascular events also increased as CAC increased, although notably the rate of aspirin use was only 50% for those with very severe CAC. The same trends were also observed for a pre-existing diagnosis of vascular disease more generally.

CACS class	Number	Pre-existing diagnosis of CAD, % (n)	Pre-existing diagnosis of ASCVD, % (n)	Pre-existing statin therapy	Pre-existing antiplatelet therapy
None (0)	1	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Mild (1-99)	11	0.0 (0)	27.2 (3)	45.5 (5)	18.1 (2)
Moderate (100-399)	17	17.6 (3)	17.6 (3)	64.7 (11)	17.6 (3)
Severe (400-999)	12	16.7 (2)	58.3 (7)	83.3 (10)	58.3 (7)
Very severe (1000+)	10	40.0 (4)	70.0 (7)	70.0 (7)	50.0 (5)

Table 45: Pre-existing diagnoses and therapy by CACS class. ASCVD – atherosclerotic cardiovascular disease (CAD, cerebrovascular disease and peripheral vascular disease); Total patients included in this analysis = 51

After assessment by cardiac CT, 49.3% of patients had an unmet need for statin therapy, as defined prospectively as any evidence of CAC. 61.5% of patients had an unmet need for antiplatelet therapy (defined as CACS ≥ 100) revealed by cardiac CT.

Patients also had troponin T measured during the first 48 hour of admission. There was no correlation between CACS and troponin level (Pearson correlation coefficient -0.112; p=0.449, Figure 63). In fact, the three highest troponin levels observed were in patients with mild to moderate CAC scores. Each went on to have invasive angiography, and this was negative for obstructive CAD in each case. The significance of these cases is discussed in the following chapter.

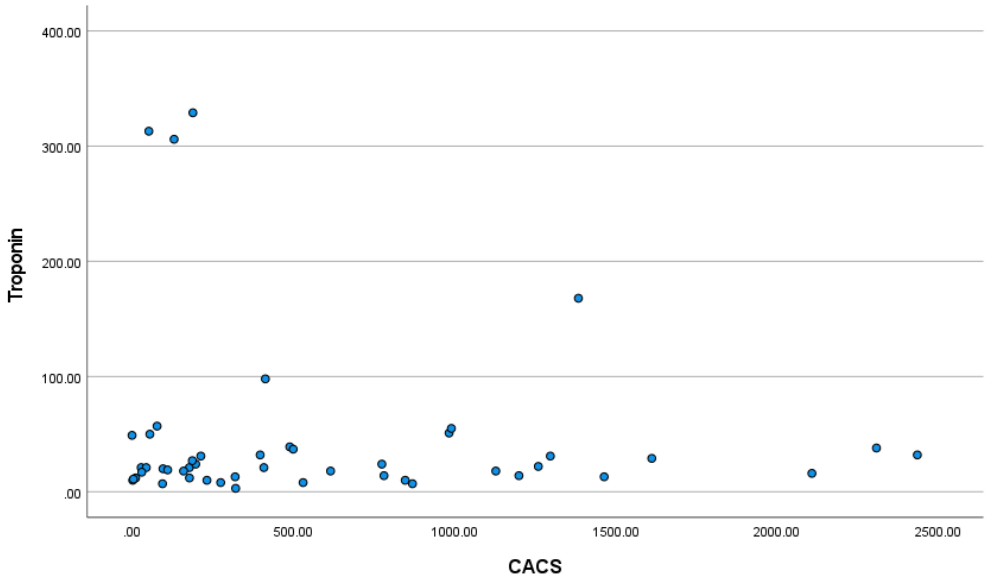


Figure 63: Scatter plot: CACS and Troponin T at baseline

After removal of the three outlying cases with markedly elevated troponin levels without severe CAC, the correlation coefficient became positive, as expected biologically, but remained (0.184; p=0.227, Figure 64). Troponin results are discussed in further detail in section 7.4.3.

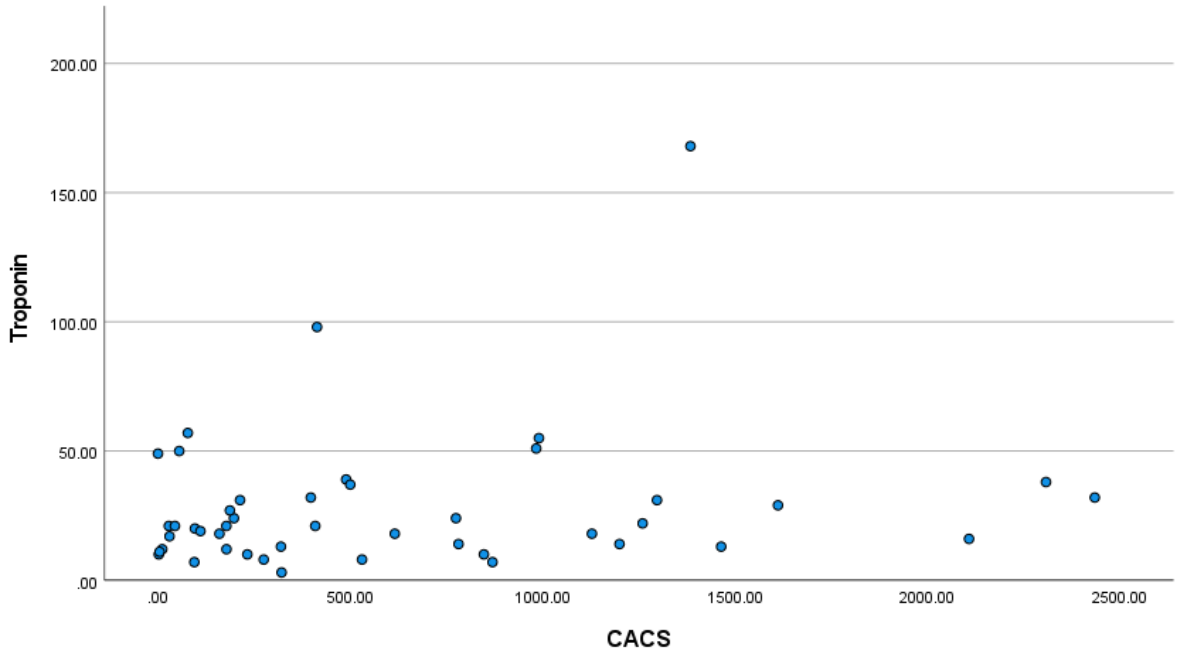


Figure 64: Scatter plot: CACS and Troponin T (outlying troponin results omitted)

The rates of all-cause readmission were similar across difference CACS classes (Table 46). No patients in the intervention arm died without readmission, so enumeration of simple readmission rates does not omit any such cases. There was a trend evident of higher mortality in patients with higher CACS (NB: the one patient who did not have CACS measured died during follow-up, and two patients who died had had previous bypass grafting precluding CACS calculation, hence the total number of within-arm deaths presented here is 11, rather than 14 as per Section 6.3.1).

CACS class	Number	90-day readmission % (n)	1 year readmission % (n)	90-day mortality % (n)	1 year mortality % (n)
None (0)	1	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Mild (1-99)	11	36.3 (4)	81.8 (9)	0.0 (0)	18.2 (2)
Moderate (100-399)	17	35.3 (6)	64.7 (11)	0.0 (0)	11.8 (2)
Severe (400-999)	12	33.3 (4)	83.3 (10)	0.0 (0)	33.3 (4)
Very severe (1000+)	10	40.0 (4)	50.0 (5)	20.0 (2)	30.0 (3)

Table 46: Readmission and mortality rates by CACS class

If the patients with previous bypass grafting were considered to have severe CAD (corresponding to CACS ≥ 400), given their prior need for intervention, there was a signal that a diagnosis of severe (or worse) CAD conferred higher 90 day and 1 year mortality (Table 47).

	Severe CAD		
	Present*, % (n) (n=26)	Not present†, % (n) (n=30)	P value
90-day mortality	11.5 (3)	0.0 (0)	0.09
1 year mortality	34.6 (9)	13.3 (4)	0.11
* CACS ≥ 400 or previous coronary artery stenting † CACS < 400; no previous coronary artery stenting ‡ Fisher's exact test			

Table 47: Mortality according to presence of severe CAD

This finding of increased mortality with higher levels of CAC is in keeping with previous data published in a stable population, the ECLIPSE cohort, that had a lower mortality rate (6.7% over 3 years).[635] The relevance of the ECLIPSE study's findings to the results of this pilot study are discussed further in section 8.2.5.1.

Mortality survival curves for those with and without severe (or worse) CAD separated early and remained so throughout follow-up (log-rank p=0.121).

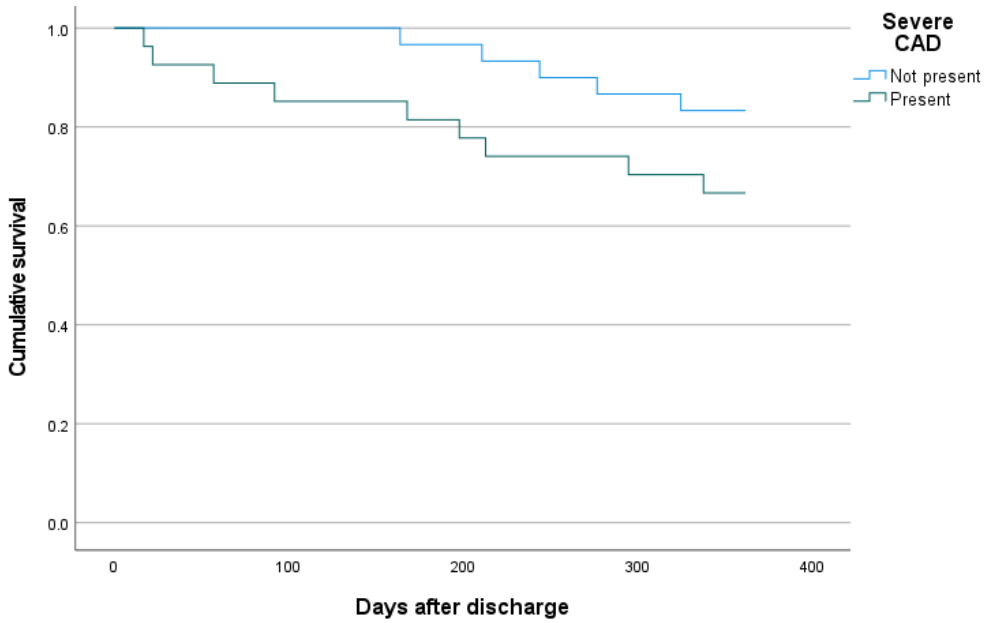


Figure 65: Survival curves according to presence of severe CAD

If higher levels of CAC were connected to mortality because they represent more advanced atherosclerosis and therefore higher probability of acute vascular events, observed rates of ACE during follow-up would be expected to be higher in this subgroup. However, there were only 3 such events in each of the groups, and no evident difference in survival curves log-rank p=0.896).

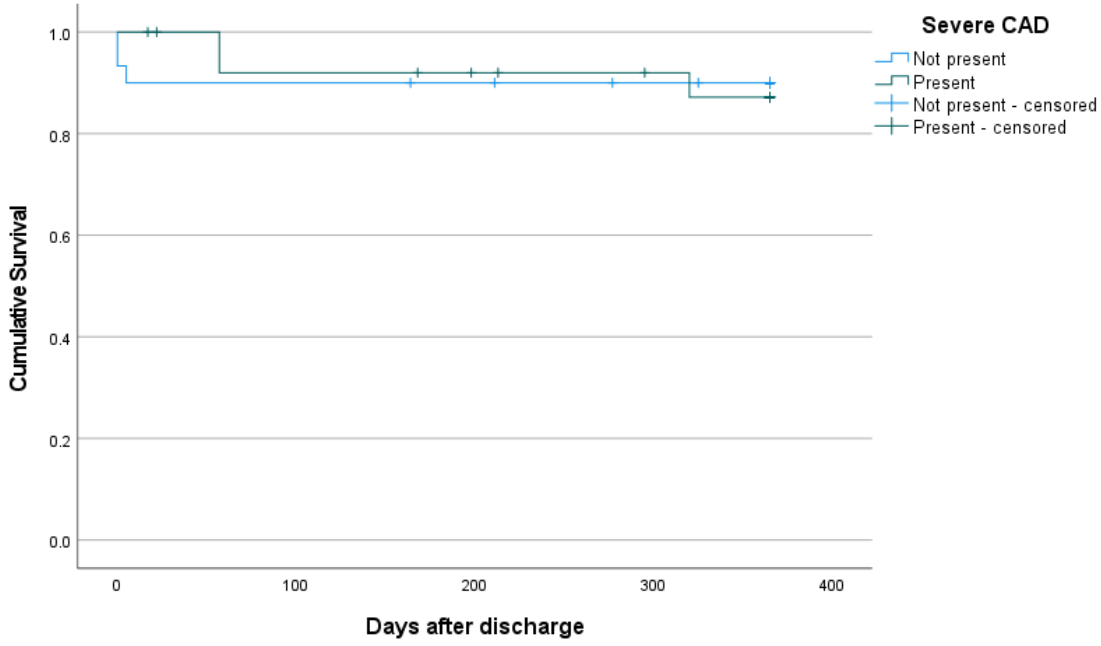


Figure 66: Survival without ACE according to presence of severe CAD

In conclusion, coronary artery calcification was almost ubiquitous, and commonly present to a severe degree; these patients were often on no medication for coronary artery disease. While severe CAD was not associated with an increased rate of adverse cardiovascular events, there was a trend for mortality to be higher for these patients.

7.3 Echocardiography

7.3.1 Summary of echocardiographic findings at baseline

At baseline, echocardiography was performed in 55 patients. Two patients were discharged prior to availability of the sonographer. In 18 patients (32.7%), intravenous contrast was used to improve visibility of the left ventricular endocardial border to facilitate quantitative LVEF assessment. The median interval between admission and echocardiography was 2 days.

The quality of echocardiography, where commented on, was adequate or good in only 38.9% of cases.

Quality	**Frequency, % (n)**
Good	5.6 (3)
Adequate	33.3 (18)
Poor	53.7 (29)
Very poor	7.4 (4)
n = 54; Quality not stated in 1 case	

Table 48: Quality of baseline echocardiography

Data were extracted from reports by the cardiac physiologist, with review of images by an independent cardiologist for completion of any missing data where possible. Despite this process, data were often missing due to inability to acquire the necessary views, or poor image quality from images acquired, as summarised in the following table:

Echocardiographic measure	Missing, % (n)
Biplane LVEF %	12.7 (7)
LVEF %, including range	0 (0)
LVIDd, cm	3.6 (2)
LVEDV mod A4C, ml	12.7 (7)
LA dilatation, presence	0 (0)
E/e' average	29.1 (16)
Diastolic dysfunction, presence*	38.2 (21)
RV dysfunction, presence	0 (0)
TAPSE, cm	9.1 (5)
RV S'	56.4 (31)
RV FAC, %	87.3 (48)
TR velocity, ms^{-1}	29.1 (16)
Estimated PASP, mmHg	29.1 (16)
Pulmonary hypertension probability	0 (0)
RA dilatation, presence	0 (0)

LVIDd: left ventricular internal diameter end diastole; LVEDV mod A4C: left ventricular end-diastolic volume by Simpson method in apical 4-chamber view; LVPWd: left ventricular posterior wall thickness, end diastole; LVOT VTI: left ventricular outflow tract volume-time index; E/e': peak early mitral inflow velocity/early diastolic mitral annular velocity; TAPSE: tricuspid annular plane systolic excursion, RV S': tricuspid peak systolic annular velocity; RV FAC: right ventricular fractional area change
* No comment or unmeasurable

Table 49: Missing echocardiographic data at baseline

Contrastingly, despite image quality often being assessed as poor, and missing data being common, it was possible in most cases for quantitative data to be obtained about LV and RV systolic function. Furthermore, a qualitative judgement about RV function was possible in all cases, as was an estimated range for LV ejection fraction (see Figure 67).

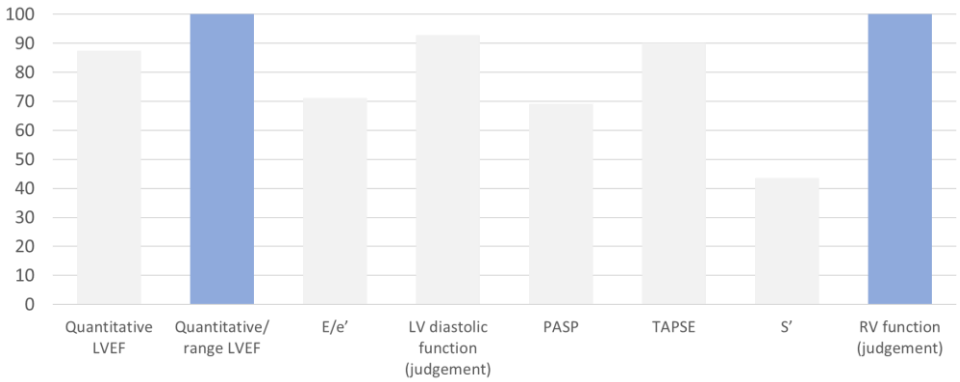


Figure 67: Percentage of cases (n=55) in which quantitative or qualitative ventricular function data were obtained

Summary baseline data for markers with less than 30% missing data are tabulated below. Mean (SD) is given unless stated. The mean LV ejection fraction was at the lower end of the normal range; the most complete objective measurement of RV function, mean TAPSE, was similarly low-normal. A large proportion of patients, almost 3 in 10, had atrial dilatation. Over 40% had a medium to high probability of pulmonary hypertension.

Echocardiographic measure	**Valid cases**	**Summary statistic**
Chamber measurements:		
LVIDd, cm	53	4.49 (0.76)
LVEDV mod A4C, ml	48	87.3 (33.2)
LVPWd, mm	53	9.75 (2.28)
LA dilatation, %	55	27.3
RA dilatation, %	55	28.1
LV function:		
Ejection fraction, %*	55	57.2 (11.8)
Global hypokinesis, %	54	7.4
RWMA, %	54	1.9
E/e' average†	39	8.82 (7.09 – 11.6)
RV function:		
RV impairment, %‡	55	26.3
TAPSE, cm	50	1.89 (0.40)
Pulm. HTN probability, %	55	
Low		58.2
Medium		23.6
High		18.2
Valve disease (%)	55	3.6
*Midpoint of range taken in 7 cases †Median (IQR) ‡Overall impression of sonographer		

Table 50: Summary baseline echocardiographic data

7.3.1.1 Left ventricular function

LV function can be assessed in several ways. In the SCATECOPD study, a simple, pragmatic approach based on LV ejection fraction was taken for diagnosis of significant LV dysfunction, and consequently the recommendation of important therapies.

The distribution of LVEF at baseline echo is presented below, with x-axis markings at 45% and 40%, watersheds in the study management summaries for the recommendation of specific drug treatments.

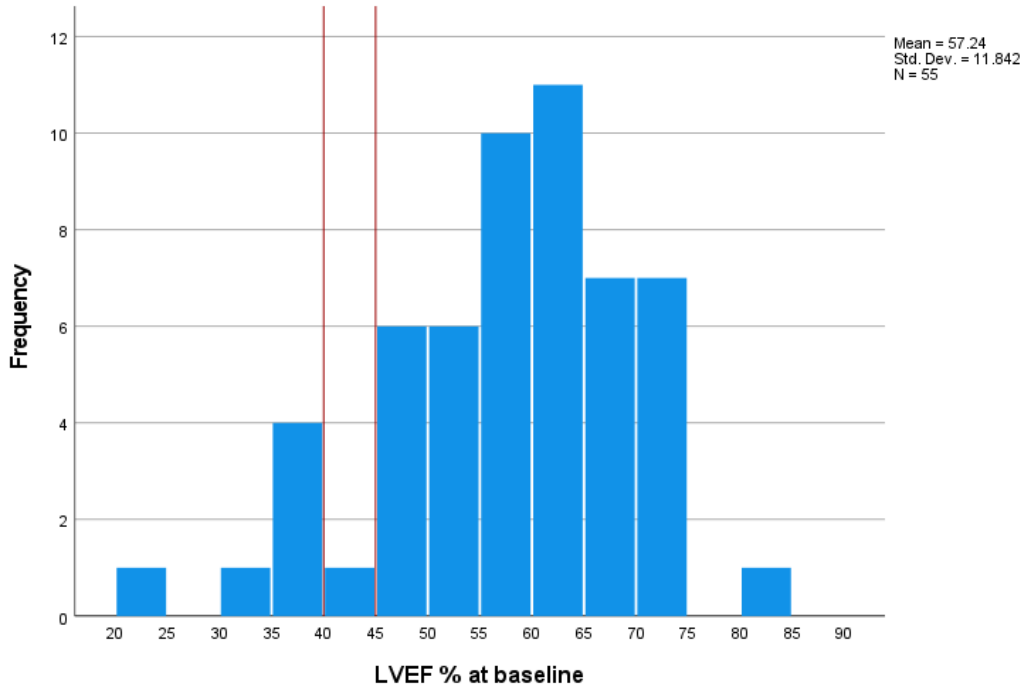


Figure 68: Histogram: LVEF% at baseline

A similar, straightforward approach was taken to the diagnosis of LV dysfunction without significantly reduced LVEF: if patients had diastolic dysfunction, based on the assessment of mitral inflow, recognised by the sonographer, they received a diagnosis of heart failure without moderate/severe LVSD. The below table summarises the frequency of diastolic dysfunction judgements made at baseline:

LV diastolic dysfunction judgement	Frequency, % (n)
None/no comment	50.9 (28)
Mild/Grade 1	18.2 (10)
Moderate/Grade 2	5.5 (3)
Severe/Grade 3	0 (0)
Indeterminate	7.3 (4)
Unmeasurable	7.3 (4)
Not applicable (LVEF < 40%)	10.9 (6)

Table 51: LV diastolic dysfunction at baseline

As discussed previously, however, LV function can be assessed by several additional echocardiographic measures and classification systems. For comparison, the ESC classification

outlined in Chapter 2 (Section 2.2.1) was applied to the echocardiographic data obtained at baseline to classify patients as follows:

ESC Heart failure class	LVEF Criteria	Additional criteria	Frequency, % (n)
HFrEF	LVEF < 40%	Nil	10.9 (6)
HFmrEF	LVEF 40-49%	NTpro-BNP > 300 *and 1 of* LAE, LVH, E/e' ≥ 13	5.5 (3)
HFpEF	LVEF ≥ 50%	NTpro-BNP > 300 *and 1 of* LAE, LVH, E/e' ≥ 13	14.5 (8)
None	LVEF ≥ 40%	Additional criteria for HFmrEF/HFpEF not met	72.7 (40)
LAE: left atrial enlargement and LVH: left ventricular hypertrophy – judgement of sonographer based on measurements of LA size and LV mass			

Table 52: Prevalence of heart failure by ESC criteria

The system based on LVEF and identified diastolic dysfunction diagnosed heart failure more often (41.8% of cases vs. 30.9%); there was agreement between the ESC and SCATECOPD systems in 67.3% of cases. Disagreements between the systems regarding the presence of heart failure were primarily due to: firstly, patients with mild diastolic dysfunction identified at echo did not satisfying the more detailed ESC criteria for HFpEF/HFmrEF; secondly, patients who did meet the ESC criteria for HFpEF having no comment about diastolic dysfunction made by the sonographer.

		ESC classification		
		Present	Absent	*Row Totals*
SCATECOPD classification	Present	11	12	*23*
	Absent	6	26	*32*
	Column Totals	*17*	*38*	

Table 53: Agreement between ESC and SCATECOPD methods for diagnosing heart failure

If only HFrEF, HFmrEF and Moderate/Severe LVSD from the two classification systems were considered, i.e. those diagnoses that attracted specific therapies to improve outcomes, the agreement between the systems improved markedly, to 94.5%.

		ESC classification: HFrEF/HFmrEF		
		Present	Absent	*Row Totals*
SCATECOPD classification: Moderate-Severe LVSD	Present	7	1	*8*
	Absent	2	45	*47*
	Column Totals	*9*	*46*	

Table 54: Agreement between ESC and SCATECOPD methods for diagnosing HFrEF/HFmrEF and LVSD

The baseline characteristics and ECOPD features of those with and without moderate/severe LVSD were compared. As only 7 patients had the diagnosis, statistical power to identify significant differences was limited, and therefore inspection of absolute differences between the groups is most informative. In this exploratory analysis, correction for multiple comparisons was not carried out. To provide a measure of acute hypoxaemia, the ROX index was calculated.[636] This is because not every patient had an ABG, but admission oxygen saturations, respiratory rate (RR in the equation below) and supplemental oxygen were recorded in all. FiO_2 was estimated if necessary by established conventional conversions based on oxygen flow rate and device.[637]

$$ROX\ index = \frac{SpO_2/FiO_2}{RR}$$

The patients with moderate/severe LVSD were older by a mean difference of 5 years, and had a greater degree of airflow obstruction, as well as worse limitation due to breathlessness: all were housebound. Additionally, their reported median exacerbation rate was very high, at 5 per year, compared with 2.5 for patients without moderate/severe LVSD. Almost half had had a previous exacerbation requiring treatment with NIV and their mean CAC score was 803, compared with 500 for patients without moderate/severe LVSD.

	Moderate/Severe LVSD present (n = 7)	Moderate/Severe LVSD absent (n = 48)	P value
Demographics			
Sex (male %)	57.1	39.6	0.435
Age (y)	77.2 (5.6)	71.8 (6.5)	0.092
Background disease severity			
Smoking exposure	41.0 (15.2)	45.2 (15.5)	0.203
FEV1% (historic)	40.4 (17.1)	51.8 (20.9)	0.152
eMRCD*	5b (5a - 5b)	4 (4 – 5a)	0.189
Self-reported exacerbations in past year*	5 (2.5 – 12)	2.5 (1 – 4.75)	0.110
Total admissions in past year*	2 (0 – 4.5)	0 (0 – 1)	0.990
Previous NIV	42.9	16.7	0.134
Known moderate-severe LVSD (%)	28.6	2.1	0.040
CT Coronary artery calcium score	802.9 (875.3)	497.5 (510.8)	0.196
Home oxygen therapy at discharge (%)	14.3	18.8	1.000
Index ECOPD			
ROX index	14.0 (3.1)	13.2 (4.7)	0.949
ABG on admission	*n = 5*	*n = 36*	0.384
No respiratory failure	0	2.7	
Type 1 respiratory failure	0	33.3	
Type 2 respiratory failure	100	63.9	
NIV administered (%)	14.3	22.9	0.687
DECAF score*	3 (2 – 3)	1 (1 – 2)	0.089
C-reactive protein (mg/L)*	16 (8.5 – 66.5)	40 (7.25 – 127.75)	0.834
NT-proBNP (ng/L)*	2409 (535.5 - 10246)	588 (237.25 – 3613.75)	0.193
Troponin T (ng/L)*	32 (18.5 – 109.5)	21 (14.5 – 44.5)	0.068
Chest X-ray diaphragm height (cm)	30.5 (24.2 – 31.0)	37.8 (29.8 – 47.2)	0.130
CXR cardiothoracic ratio	0.56 (0.51 – 0.63)	0.52 (0.46 – 0.59)	0.273

Mean and standard deviation presented unless otherwise indicated
Significance tests are two-sided: independent T-test for continuous parametric data; Fisher's exact test for categorical data.
* Median and IQR presented, MWU test used (non-parametric data)

Table 55: Features of background COPD and index ECOPD severity for patients with and without moderate/severe LVSD

Regarding the index exacerbations of COPD, these had a higher median DECAF score when patients were found to have moderate/severe LVSD (3, compared with 1 in those without), which is accounted for, in part, by the higher eMRCD scores of these patients. Each of the 5 patients with moderate/severe LVSD who had ABG sampling had type 2 respiratory failure and both NT-proBNP and troponin levels were higher in this group. Finally, this group had lower diaphragm height, with a mean difference of 7.3cm, implying greater hyperinflation; there was less of a difference in cardiothoracic ratio, potentially because 51% of chest X-rays were performed with antero-posterior projection that precluded accurate radiographic heart-size measurement. In general, however, inspection of table 55 reveals that there were more overt differences between those with and

without LVSD in terms of background disease severity than there were for index exacerbation severity.

7.3.1.2 Right ventricular function

Several measurements that assess aspects of RV function were collected. These included: TAPSE, S', FAC and pulmonary hypertension probability, derived from TR velocity and other echocardiographic markers according to an internationally adopted algorithm.[504] The overall assessment of RV function as good or impaired was also recorded.

Due to difficulty acquiring the required views and image quality, RV FAC and RV S' were only acquired in a minority of cases, therefore not analysed further.

Definitions of abnormal right ventricular function using the three remaining criteria produced a comparable proportion of positive results, with the overall judgement producing the highest proportion – explained by the inclusion in this measure of a judgement on radial function, which is not assessed by TAPSE, and because TR velocity can be normal in the presence of RV impairment.[582]

Definition of abnormal RV function	Proportion abnormal, % (n/N)
TAPSE < 1.6 cm	16.0 (8/50)
High probability of pulmonary HTN	18.0 (10/55)
Overall sonographer judgement	27.3 (15/55)

Table 56: Proportions with abnormal RV function by the three measures acquired most widely

There was a high level of agreement between the overall judgement of RV impairment and TAPSE, as demonstrated by the mean and 95% confidence interval plots for those with good and impaired RV function.

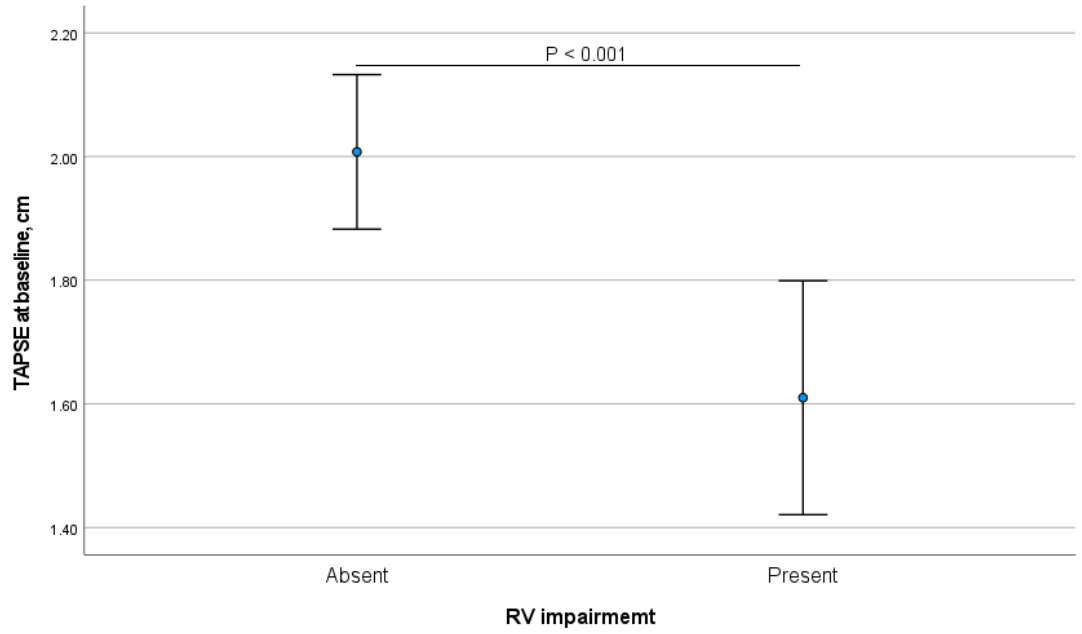


Figure 69: Mean TAPSE, and 95% confidence intervals, for patients with good and impaired overall RV function. P value from independent samples T-test for difference in mean TAPSE between the two groups.

The relationship between classification by RV impairment and pulmonary hypertension probability is shown by the contingency table. Only 2 of 40 (5%) patients with good RV function had a high probability of pulmonary hypertension, although nearly half (7 out of 15) of patients with impaired RV function had only a low or medium probability of pulmonary hypertension.

		Overall RV impairment		
		Present	Not present	*Row Totals*
Pulmonary HTN probability	Low	4	28	*32*
	Medium	3	10	*13*
	High	8	2	*10*
	Column Totals	*15*	*40*	
	χ=3.861; p<0.001 (Fisher's exact test)			

Table 57: Distribution of pulmonary hypertension classes for patients with and without overall RV impairment

In summary, during the index admission with ECOPD, echocardiographic markers of RV impairment were common, and there was generally good agreement between objective markers and the sonographers' overall judgement of RV function.

	RV impairment (n=15)	No RV impairment (n=40)	P value
Demographics			
Sex (male %)	46.7	40.0	0.762
Age (y)	74.5 (5.5)	71.8 (6.9)	0.165
Background disease severity			
Smoking exposure	43 (13)	45 (16)	0.602
FEV1% (historic)	49.5 (17.9)	50.6 (20.7)	0.853
eMRCD*	4 (4 - 5b)	5a (4 - 5a)	0.709
Self-reported exacerbations in past year	3 (1 - 5)	3 (1 - 5)	0.984
Total admissions in past year*	0 (0 - 4)	1 (0 - 2)	0.759
Previous NIV	26.7	17.5	0.468
Known right sided heart failure (%)	13.3	0	0.071
CT Coronary artery calcium score	197 (55 - 1297)	324 (166 - 797)	0.603
Home oxygen therapy at discharge (%)	26.7	15.0	0.434
Index ECOPD			
ROX index	11.7 (4.8)	16.6 (4.7)	**0.005**
ABG on admission	*n=15*	*n=26*	0.360
No respiratory failure	6.7	0.0	
Type 1 respiratory failure	33.3	26.9	
Type 2 respiratory failure	60.0	73.1	
NIV administered (%)	33.3	17.5	0.274
DECAF score*	2 (1-3)	1 (1-2)	0.171
C-reactive protein (mg/L)*	59 (16 - 239)	8 (3 - 98)	0.130
NT-proBNP (ng/L)*	3232 (1082 - 7128)	286 (207 - 1301)	**<0.001**
Troponin T (ng/L)*	31 (24 - 55)	21 (13 - 37)	**0.034**
Chest X-ray diaphragm height (cm)	3.0 (0.75)	3.9 (1.1)	**0.008**
PA:A > 1 (%)	53.3	20.0	**0.022**

Mean and standard deviation presented unless otherwise indicated
Significance tests are two-sided: independent T-test for continuous parametric data; Fisher's exact test for categorical data.
* Median and IQR presented, MWU test used (non-parametric data)

Table 58: Clinical characteristics of patients with and without RV impairment at baseline

To explore which clinical characteristics were associated with RV impairment at baseline, key variables, relating to background disease severity and index ECOPD severity, were compared between those with impaired RV function and those judged to have good RV function (see table 58 above).

There were several statistically significant differences between the groups, as well as an overall trend for markers of ECOPD severity to be more pronounced in the group with RV impairment, while markers of background disease severity did not generally differ. This stands in contrast to the results above for left ventricular function, where background disease severity was more noticeably worse

for those with moderate/severe LVSD. Once again, correction for multiple comparisons was not carried out.

Of note, categorisation of ABG results between the groups did not differ (p=0.360; Fisher's exact test), although 14 of 40 patients without RV impairment did not have an ABG performed – in general patients did not have an ABG if they had satisfactory oxygen saturations, by pulse oximetry, while breathing air. By contrast, all patients with RV impairment had had an ABG performed, therefore the lack of difference could be explained by sampling bias. The ROX index, measurable in *all* patients in both groups, was significantly lower in the group with RV impairment, implying a greater degree of hypoxaemic respiratory failure in this group.

PA:A ratio was more commonly enlarged in the group with RV impairment. This is consistent with the known increase in this parameter during exacerbation, which has been correlated with the severity of acute respiratory failure.[638] However, as nearly half of patients with echocardiographic RV impairment had a normal PA:A, and 20% with enlarged PA:A had *no* RV impairment, it appears that this finding on CT has limited utility in identifying RV dysfunction in the absence of a confirmatory echocardiogram.

Cardiac injury has also been associated with high PA:A ratio during exacerbation.[638] NT-proBNP and troponin T were also significantly higher in the group with RV impairment; the absolute difference being much more marked for NT-proBNP. Additionally, Figure 70 demonstrates that the proportion of patients with RV impairment appeared to be increased for those with the highest DECAF scores (p=0.171; Fisher's exact test).

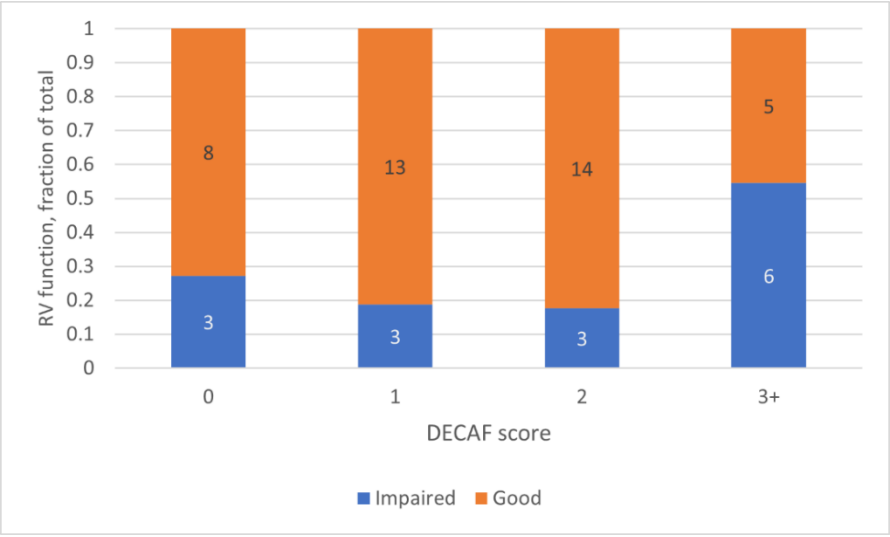


Figure 70: Proportion with and without impaired RV function at baseline, by DECAF score

Finally, chest X-ray diaphragm height was less in the group with RV impairment (estimated difference 0.89 cm [95% CI 0.24 – 1.54 cm]), implying a higher degree of lung hyperinflation in this group, although the extent to which this is acute or chronic is not clear.

By contrast to the many significant differences in measures related the index ECOPD severity, RV impairment did not appear to be as closely associated with markers of background disease severity, although rates were twice as high in the RV impairment group for markers of *previous* very severe ECOPD (previous NIV use) and chronic hypoxaemic respiratory failure (need for home oxygen therapy at discharge).

7.3.2 Summary of echocardiographic findings at follow-up

Echocardiography was performed in 45 patients at the 90-day follow-up point; this included the 2 patients who did not have echocardiography at baseline. 43 paired sets of data were therefore available. The reasons for the 12 missing follow-up scans were: 3 patients died; 5 did not attend hospital follow-up due to feeling too unwell to travel after clinically deteriorating following discharge; 3 changed their consent to home or remote follow-up only; 1 forgot to attend their appointment and died soon after, before this could be rearranged.

The quality of images obtained was broadly similar to that obtained at baseline (see Table 48, section 7.3.1). Once again, image quality was rated adequate or good in a minority of cases.

Quality	**Frequency at follow-up, % (n)**
Good	0.0 (0)
Adequate	43.2 (16)
Poor	51.4 (19)
Very poor	5.4 (2)
	n=37; Quality not stated in 8 cases

Table 59: Quality of echocardiography at follow-up

Missing data was present at follow-up to a similar degree for each echocardiographic measure as at baseline (see Table 49**Error! Reference source not found.**, section 7.3.1):

Echocardiographic measure	Missing at follow-up, % (n)
Biplane LVEF %	20.0 (9)
LVEF %, including range	0.0 (0)
LVIDd, cm	2.2 (1)
LVEDV mod A4C, ml	17.8 (8)
LA dilatation, presence*	0.0 (0)
E/e' average	20.0 (9)
Diastolic dysfunction, presence*	24.4 (11)
RV dysfunction, presence*	0.0 (0)
TAPSE, cm	8.9 (4)
RV S'	48.9 (22)
RV FAC, %	80.0 (36)
TR velocity, ms^{-1}	33.3 (15)
Estimated PASP, mmHg	33.3 (15)
Pulmonary hypertension probability*	0.0 (0)
RA dilatation, presence*	0.0 (0)

Table 60: Missing data at follow-up echocardiography

As a result, the same collection of variables was amenable to analysis. Paired tests for change were conducted and are also presented in Table 61.

Echocardiographic measure	Valid cases, 90d	Summary statistic, 90d	Change from baseline*	Test for change from baseline to 90d*
Chamber measurements:				
LVIDd, cm	44	4.19 (0.71)	-0.115 (-0.306 – 0.076)	0.232
LVEDV mod A4C, ml†	37	68 (52 – 87.5)	-13.0 (-35.8 – 14.4)	**0.027**§
LA dilatation, %	45	15.6	-11.7	0.219¶
RA dilatation, %	45	17.8	-10.3	0.289¶
LV function:				
Ejection fraction, %‖	45	62.2 (8.68)	3.67 (0.357 – 6.982)	**0.031**
Global hypokinesis, %	45	2.2	-5.2	1.000¶
E/e' average	36	9.84 (3.21)	-0.14 (-1.40 – 1.12)	0.820
RV function:				
RV impairment, %‡	45	15.6	-10.7	0.227¶
TAPSE, cm	41	2.01 (0.38)	0.101 (-0.05 – 0.267);	0.173
Pulm. HTN probability, %	45			0.550¶
Low		51.1	-7.1	
Medium		31.1	7.5	
High		17.8	-0.4	
Valve disease (%)	45	2.2	-1.4	1.000¶

* Unless indicated: difference in means (confidence interval); p value (paired Student's t-test); **bold** indicated significant result
‖ Midpoint of range taken in 9 cases †Median (IQR) for change ‡Overall impression of sonographer
§ Wilcoxon signed rank test ¶ McNemar test

Table 61: Change in echocardiographic measures between baseline and follow-up. Summary statistics are mean (SD) unless indicated

The paired variables that showed significant change between baseline and 90-day follow-up were the LV ejection fraction, with a mean increase of 3.67%, and LV end diastolic volume, for which the median value fell by 13ml between baseline and 90-day follow-up.

Mean TAPSE increased by 1mm between baseline and 90-day follow-up, although this difference was not statistically significant. The overall numbers with RV impairment also reduced between baseline and 90-day follow-up. This change is explored in greater detail in the following subsections.

7.3.3 Changes in ventricular function

The persistence of the diagnosis of ventricular dysfunction was assessed between the baseline and follow-up echocardiography studies. For this analysis, ventricular dysfunction was classed as resolved at follow-up if the patient no longer met the criteria for diagnosis (e.g. if LVEF < 45% at baseline but ≥ 45% on follow-up). In contrast, for the purposes of assessing prevalence of diagnosis (as, for example, in Section 6.3.6) patients did not 'lose' a diagnosis of moderate/severe LVSD if this happened.

The diagnoses used in the SCATECOPD study (HF with moderate-severe LVSD, HF without moderate-severe LVSD, RV failure) were used in this section, as these were the criteria used to guide treatment decisions.

Definition	% (n) at baseline (N=55)	New diagnosis, %, (n/N)	Resolved at 90-day follow-up, n/N (%)*
HF with moderate-severe LVSD	12.7 (7)	71.4 (5/7)	75.0 (3/4)
HF without moderate-severe LVSD	27.3 (15)	86.7 (13/15)	33.3 (4/12)
RV impairment†	27.3 (15)	86.7 (13/15)	66.7 (8/12)
* If survived and attended follow-up † Based on overall impression of sonographer			

Table 62: Prevalence, new diagnosis and resolution of heart failure by different definitions

Notably, 3/4 patients with moderate-severe LVSD at baseline that survived to the 90-day follow-up had an improvement of LVEF to above 45%. The individual 90-day LVEF results were 44%, 53%, 68% and 73%. All of these patients had been started on intensive heart failure treatment under the supervision of the heart function team, with initiation of the latest recommended drug therapies including SGLT2-inhibitor and ARNI agents.

Rates of resolution were lower for patients diagnosed with HF without moderate-severe LVSD: 8 of the 12 of these patients who had follow-up echocardiography had ongoing evidence of LV diastolic dysfunction.

RV impairment was observed to resolve in a majority of surviving cases; the relationship between changes in right heart function and other clinical variables in explored in the next subsection.

7.3.4 Relationship between changes in right heart function and (E)COPD severity

This outcome is of interest because, although structural right ventricular abnormalities are common during ECOPD, and have been linked to increased post-discharge mortality,[563] functional echocardiographic data obtained during exacerbation have not been widely acquired. Furthermore, little is known about the frequency with which RV impairment seen during ECOPD reverses at stability, and what factors relate to reversibility. The overall RV function methods of assessing RV function was used for this analysis, as it was acquired most completely, and had good agreement with the other methods (see section 7.3.1.2). Analyses using TAPSE and pulmonary hypertension probability are contained in Appendix G (no statistically significant results were obtained).

12 patients had RV impairment identified at echocardiography and both survived and attended 90-day follow-up. Of these, 8 had overall RV function judged to be good at follow-up; i.e. they had RV impairment that was reversible. 4 had impaired RV function at the 90-day follow-up echo; i.e. persistent RV impairment.

Although the numbers involved were extremely small, the measures of baseline disease severity and index ECOPD severity, as well as the echocardiographic findings at baseline and 90-day follow-up, were compared between those with reversible and persistent RV impairment.

Clinical variable	RV impairment		
	Reversible (n=8)	Persistent (n=4)	P value
Demographics			
Sex, male %	37.5	50	1.000
Age, y	75.3 (6.6)	75.0 (2.0)	0.944
Background disease history			
Smoking PYH	46.3 (13.0)	43.8 (10.3)	0.746
FEV1% (historic)	49.2 (18.6)	54.8 (9.1)	0.591
eMRCD*	4 (4 - 5b)	4 (4 - 5a)	1.000
Self-reported exacerbations in past year*	1.5 (1 – 4)	5 (1 - 9)	0.214
Total admissions in past year*	0 (0-1)	0 (0-4)	0.933
Previous NIV, %	25.0	25.0	1.000
Known right sided heart failure. %	12.5	0.0	1.000
CT Coronary artery calcium score*	126 (4 - 846)	200 (105 – 1262)	0.461
Home oxygen therapy at discharge, %	12.5	50	0.236
Index ECOPD			
Oedema on examination, %	25	100	0.061
ROX index	10.5 (5.1)	14.9 (3.7)	0.164
NIV administered, %	37.5	25	1.000
DECAF score*	2 (0 - 3)	2 (0 - 3)	1.000
CRP, mg/L*	55 (9 - 197)	63 (13 - 132)	0.808
NT-proBNP, ng/L*	3324 (645 - 6114)	2821 (1414 – 6154)	1.000
Troponin T, ng/L*	40 (15 - 54)	30 (28 - 51)	1.000
Chest X-ray diaphragm height, cm	29.0 (8.2)	29.1 (7.1)	1.000
PA:A > 1, %	0.75	0.25	0.222
Baseline echocardiogram			
TAPSE (cm)*	1.75 (1.43 - 2.10)	1.45 (1.39 - 1.76)	0.461
Pulmonary HTN probability			1.000
High	62.5	75.0	
Medium	25.0	0.0	
Low	12.5	25.0	
LVEF, %	58.3 (9.2)	46.4 (8.6)	0.056
RA Area, cm^2*	15.7 (13.0 – 26.4)	24.5 (18.2 – 31.7)	0.073
Follow-up echocardiogram			
TAPSE change, cm	0.5 (0.4)	0.2 (0.3)	0.296
LVEF change, %	8.0 (9.1)	2.4 (7.4)	0.282
RA Area change, cm^2*	-3.0 (-4.8 – 3.4)	2.5 (-3.3 – 6.0)	0.368
Mean and standard deviation presented unless otherwise indicated. * Median and IQR presented, MWU test used (non-parametric data)			

Table 63: Clinical characteristics of patients with reversible and persistent RV impairment

The very small numbers substantially limited statistical power. Nevertheless, some signals emerge of difference between the groups that had reversible and persistent RV impairment. Those patients

whose RV impairment was persistent universally had oedema present at presentation; this was only seen in 2 of 8 with reversible RV impairment. A higher degree of acute hypoxaemic respiratory failure in patients with reversible RV impairment was suggested by a lower ROX index in this group.

There were also signs of cardiac structural differences between the groups. Firstly, LV function appears to have been superior in those with reversible RV impairment: mean LVEF was higher at baseline and improvement from baseline to follow-up was also greater. Additionally, right atrial dilatation was seen to a greater degree in those with persistent RV impairment. Finally, a higher proportion of patients with reversible RV impairment had dilatation of the pulmonary artery on CT scan.

In conclusion, it was difficult to derive from this data a clear answer to the question: how are background COPD severity and exacerbation severity related to changes in right heart function? Two key factors in this were the small numbers of patients involved, and the high rate of attrition between baseline and follow-up, which meant that for over 20% of patients the trajectory of right heart function was unknown. Nevertheless, it was noteworthy that, when RV function was assessed as impaired during exacerbation, it normalised in the majority of survivors. Furthermore, there was a consistent trend that *reversible* RV impairment appeared to be associated with markers of more severe acute exacerbation, as signified by higher DECAF score, lower ROX index and increased PA:A ratio. Conversely, *persistent* RV impairment seemed to be associated with wider cardiac structural and functional abnormalities, such as right atrial dilatation and impaired left ventricular function.

7.3.5 Relationship between changes in right heart function and comorbid heart disease

Evidently, the right ventricle does not operate in isolation: its function is strongly affected by the presence of other cardiac pathologies, for example impaired myocardial perfusion due to coronary artery disease or impaired ventricular filling in the context of atrial fibrillation. Evidence of this has already been provided by the association between LV impairment and persistent RV impairment presented in section 7.3.4.

Accordingly, the prevalence of known and, at admission, undiagnosed comorbid heart disease was compared for those with and without RV impairment at baseline. As in the previous subsection overall assessment of RV function was used, Appendix G contains additional analysis using TAPSE and pulmonary hypertension probability (no statistically significant results were obtained).

	RV function at baseline		
Heart disease comorbidities and risk factors: known at admission	Impaired, % (n) *n=15*	Good, % (n) *n=40*	P value
Moderate-severe LVSD	6.7 (1)	5.0 (2)	1.000
HF without moderate-severe LVSD	6.7 (1)	7.5 (3)	1.000
Myocardial infarction	13.3 (2)	15.0 (6)	1.000
Atrial fibrillation	20.0 (3)	2.5 (1)	0.057
Angina	6.7 (1)	22.5 (9)	0.255
Hypertension	53.5 (8)	50.0 (20	1.000
High cholesterol	6.7 (1)	10.0 (4)	1.000
Diabetes	33.3 (5)	32.5 (13)	1.000
Heart disease comorbidities: undiagnosed at admission			
Moderate-severe LVSD	20.0 (3)	5.0 (2)	0.119
HF without moderate-severe LVSD	40.0 (6)	17.5 (7)	0.151
Atrial fibrillation	6.7 (1)	0.0 (0)	0.273
Moderate-severe coronary artery disease*	53.3 (8)	62.5 (25)	0.553
* CACS >100, without pre-admission diagnosis of MI			

Table 64: Prevalence of heart disease comorbidities (known and undiagnosed) according to presence of impaired RV function

Table 64 reveals that known comorbidity rates were comparable for most conditions, excepting atrial fibrillation, which was more common amongst patients with RV impairment. There was a noticeably higher proportion of undiagnosed heart failure with the group that also had RV impairment. Since LV dysfunction is known to adversely impact the right ventricle, this is biologically plausible, and suggests a role for left heart disease in the genesis of right ventricular impairment in COPD, alongside the development of pulmonary hypertension through processes related to COPD itself (see Section 2.3.4).

The relationship between comorbid heart disease and changes in right heart function was then examined. Once patients had undergone the SCA which identified RV impairment, they were regarded as having had, to the greatest degree practically possible, all cardiac comorbidities identified and treated. Hence diagnosed heart disease prevalence at the point of completion of the SCA was compared for patients with reversible and persistent RV impairment.

	RV impairment trajectory		
Heart disease comorbidities and risk factors: following SCA	Reversible, % (n) *n=8*	Persistent, % (n) *n=4*	P value‡
Moderate-severe LVSD	12.5 (1)	25.0 (1)	1.000
HF without moderate-severe LVSD	37.5 (3)	50.0 (2)	1.000
Myocardial infarction	0.0 (0)	0.0 (0)	-
Atrial fibrillation	0.0 (0)	50.0 (2)	0.091
Moderate-severe coronary artery disease*	50.0 (4)	75.0 (3)	0.576
Hypertension	50.0 (4)	50.0 (2)	1.000
High cholesterol	12.5 (1)	50.0 (2)	0.236
Diabetes	12.5 (1)	25.0 (1)	1.000
Any major treatable heart disease†	67.5 (5)	75.0 (3)	1.000
* CACS >100 or PCI, without diagnosis of MI † At least one of moderate-severe LVSD, MI, moderate-severe CAD ‡ Fisher's exact test			

Table 65: Heart disease comorbidity prevalence in patients with reversible and persistent RV impairment

Small numbers of patients within each group limited this analysis as in section 7.3.4. In this case, the small numbers almost completely preclude any conclusions from the comparisons made, beyond the observation that the prevalence of every comorbidity was higher in the group with persistent RV impairment.

There were three patients whose RV function was judged to be good at baseline but impaired at 90-day follow-up. Given the very small number of patients, detailed analysis of their comorbidity burden was not performed. 2 of these 3 patients died before the end of study follow-up (67% mortality, vs 25% for the overall cohort).

7.3.6 Relationship between ventricular function and outcome

Heart failure is demonstrated to increase the rates of adverse outcomes in patients with COPD, largely by studies of stable populations with heart failure diagnoses based on clinical records rather than inpatient echocardiographic data.[639,640] The data collected in the SCATECOPD study allowed comparison of clinical outcomes for patients with and without heart failure as defined by inpatient echocardiographic assessment.

Mortality, survival and time to readmission was compared for patients with and without moderate-severe LVSD at baseline echocardiography (n=7 and n=48 respectively).

1 year mortality was higher for those with moderate-severe LVSD: 57.1% vs 20.8% (p=0.061; Fisher's exact test).

Survival curves shown in Figure 71 demonstrate the poorer survival for the cohort with moderate-severe LVSD (p=0.013, log-rank test)

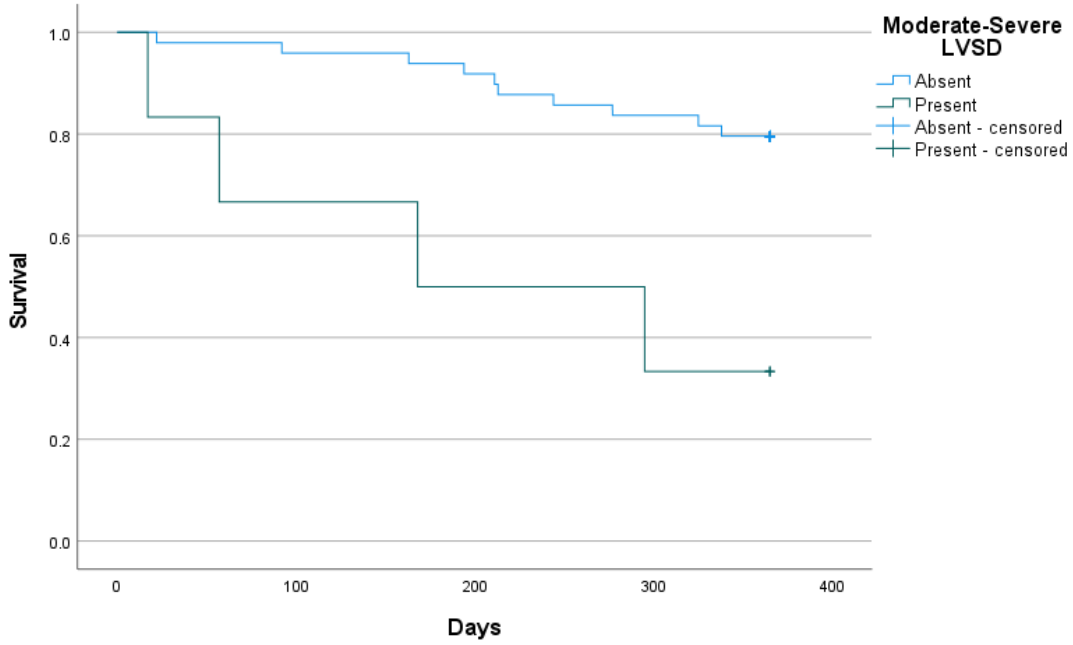


Figure 71: Survival according to presence of moderate-severe LVSD

All-cause readmission (or death without readmission) in the 12 months of follow-up was equally common for those with or without moderate severe LVSD (71.4% and 72.9% respectively), with no difference in survival without readmission (p=0.937, log-rank test; see Figure 72).

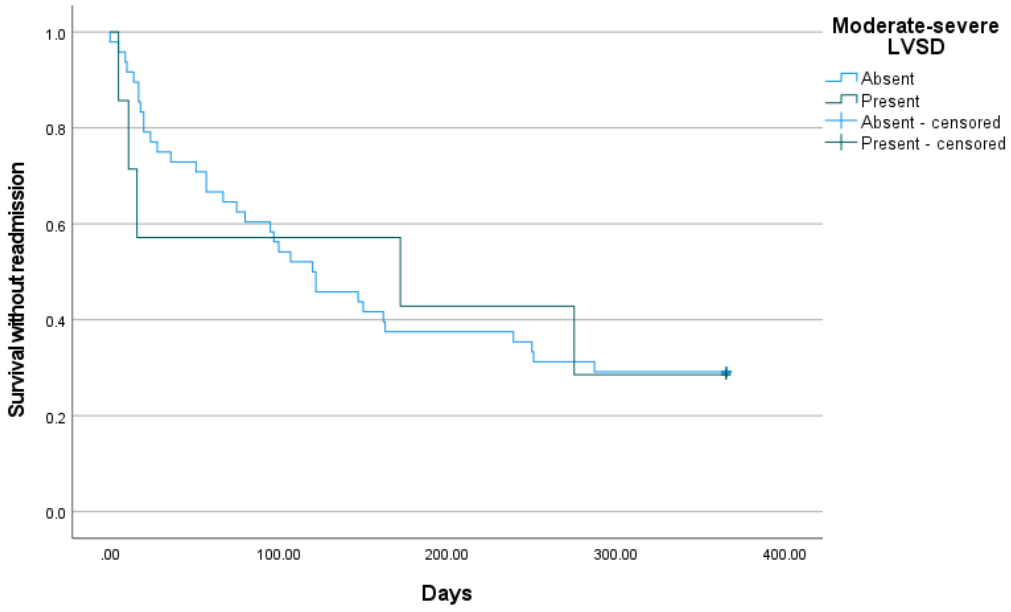


Figure 72: Survival without readmission according to presence of moderate-severe LVSD

Considering the right ventricle, 12-month mortality was 33.3% (5/15) for patients with overall RV impairment at baseline and 22.5% (9/40) for those with good RV function (p=0.493, Fisher's exact test).

There was no evident difference in time to death during follow-up between those with and without overall RV impairment identified at baseline (p=0.420, Fisher's exact test; see Figure 73).

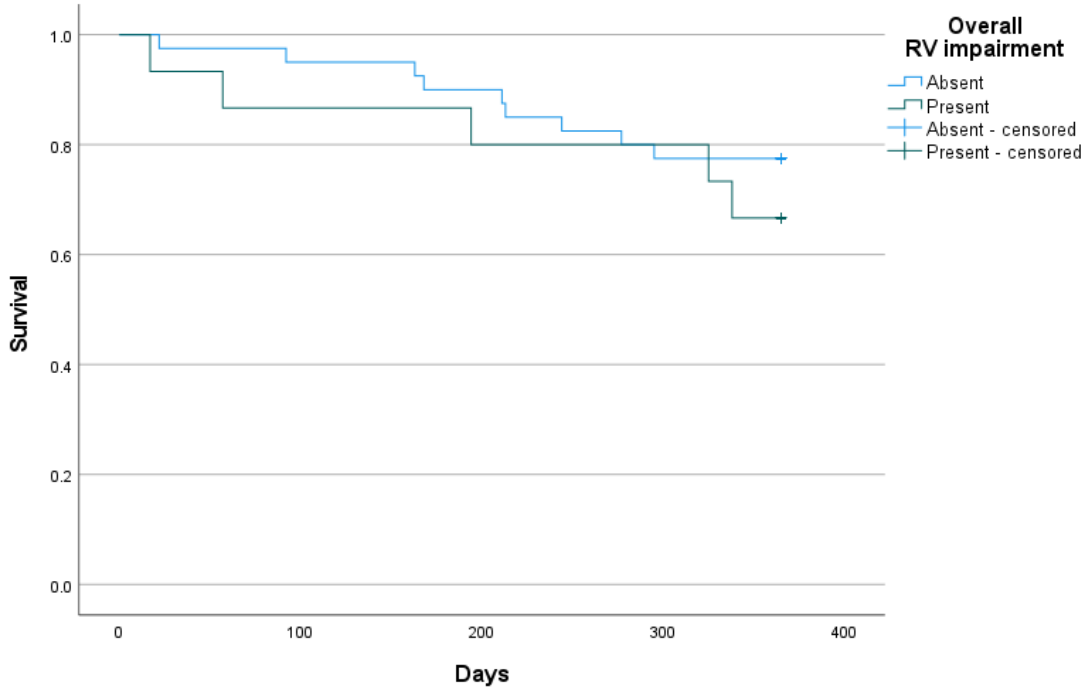


Figure 73: Survival according to overall RV function

Unexpectedly, the proportion of patients admitted for any cause was lower for patients *with* overall RV impairment than without: 53.3% vs 80.0% for those without (see Figure 74; p=0.086, Fisher's exact test). This results of analysis of time to readmission (or death without readmission) were congruent: survival curves separated demonstrably, log-rank test p=0.062.

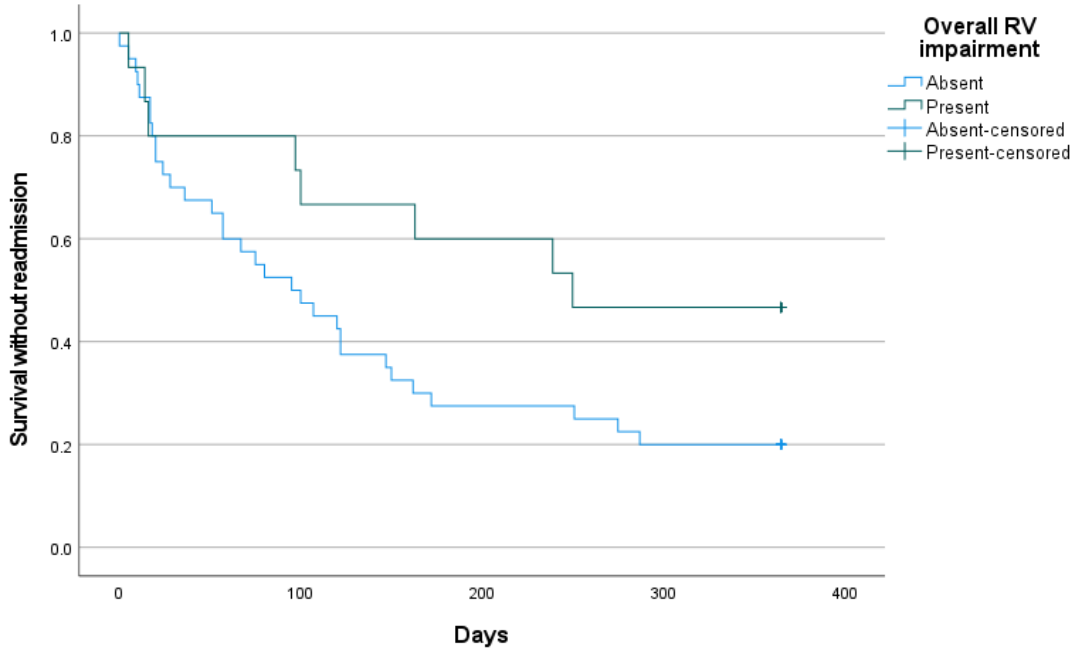


Figure 74: Survival without readmission according to presence of overall RV impairment at baseline

7.3.7 Summary: Prevalence, persistence and outcomes of LV and RV dysfunction

This section summarises the baseline echocardiographic findings regarding ventricular function, the changes seen at follow-up, and the relationship between ventricular dysfunction and outcomes. This summary was presented at the BTS winter meeting in 2023 (see Appendix A for details). The key rates of prevalence, new diagnosis, resolution and 90-day mortality for three major definitions of heart failure are contained in Table 66**Error! Reference source not found.**. Ejection fraction cutoffs of 50% and 40% were used here as they are widely recognised and the main focus was prevalence of left ventricular dysfunction (rather than diagnosis and treatment rates using local guideline recommendations, as in the main SCATECOPD study analysis). For each of the definitions, there was a high rate of new diagnosis and also of resolution in survivors. Mortality was increased significantly when LVEF was under 40%.

Finding	Present	New finding	Resolved at 90 days*	90-day mortality	p value, Fisher†
LVEF < 40%	6/55 (11%)	4/6 (67%)	3/3 (100%)	2/6 (33%)	0.029
LVEF < 50%	13/55 (24%)	10/13 (77%)	5/9 (56%)	2/13 (15%)	0.136
RV dysfunction‡	15/55 (27%)	13/15 (87%)	8/12 (67%)	2/15 (13%)	0.177
* If survived and attended review † vs. those without finding ‡ Global impression by sonographer					

Table 66: Rates of ventricular dysfunction and 90-day outcomes

Outcomes over one year are summarised in Table 67. Once again, the significant mortality increased conferred by the presence of significant LV systolic dysfunction is demonstrated, as is the initially counterintuitive finding that patients with known RV dysfunction had reduced time to readmission (or death without readmission). Reasons for the occurrence of this finding are discussed in Chapter 8.

Definition	365-day mortality	p value, Fisher	Time to readmission or death*	p value, log-rank	$DAOH_{365}$ *	p value, MWU
LVEF < 40%	4/6 (67%)	0.031	94 (264)	0.448	213 (347)	0.092
LVEF > 40%	10/49 (20%)		122 (333)		356 (30)	
LVEF < 50%	4/13 (31%)	0.719	239 (347)	0.456	361 (153)	0.749
LVEF > 50%	10/42 (24%)		114 (331)		353 (52)	
RV dysfunction	5/15 (33%)	0.493	250 (268)	0.062	364 (83)	0.215
No RV dysfunction	9/40 (23%)		98 (241)		350 (59)	
MWU = Mann-Whitney U Test * Median (IQR)						

Table 67: Outcomes according to presence of ventricular dysfunction

To sum up the key findings from the echocardiographic studies conducted:

- Echocardiography during ECOPD yielded usable information for the diagnosis of ventricular dysfunction;
- Ventricular dysfunction was common and usually unknown – 24% had LVEF less than 50% (3 standard deviations below the mean), and this was a new diagnosis in 77% of cases;
- Severe LVSD was associated with high early mortality, but also high resolution rates in treated survivors;
- Right ventricular dysfunction is often dynamic, with inpatient RV dysfunction resolving in 67% of survivors at 90 days;
- There is a signal of an association between higher degrees of acute physiological stress and reversible RV dysfunction that merits further exploration.

7.4 Other cardiac investigations

7.4.1 24-hour ECG

All 57 patients had an ambulatory ECG recorded. The intention was for this to be 24 hours in duration; the mean duration of analysable recording proved to be 22 hours. 4 recordings were less than 12 hours in duration, due to patients removing the recorder overnight and not being aware of this; 1 recording was completely uninterpretable due to extremely poor recording quality.

ECG quality was generally adequate for interpretation (Figure 75); it was poor to very poor in 14 (24.6%) of cases.

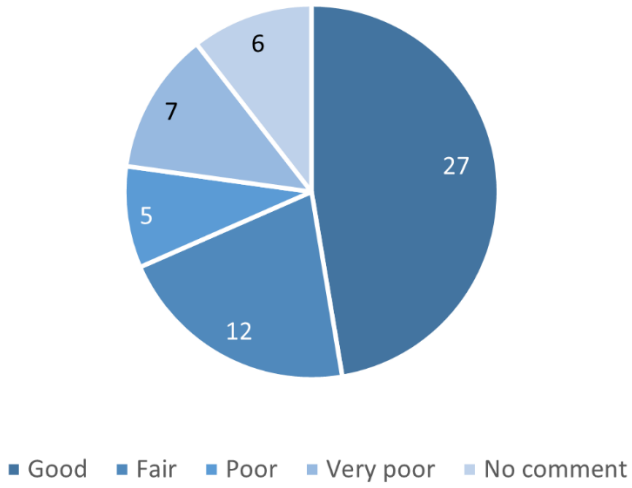


Figure 75: 24-hour ECG recording quality

In the vast majority (94.6%) of cases the predominant rhythm was sinus rhythm. In 3 cases (5.4%) the predominant rhythm was atrial fibrillation. In all 3 cases atrial fibrillation had been identified on the admission 12-lead ECG, i.e. prolonged ECG recording did not contribute any additional diagnostic yield for the identification of patients with atrial fibrillation as a predominant rhythm.

In terms of transient events, there were no episodes of sinus pause or heart block. All patients had some evidence of either supraventricular or ventricular ectopy (Table 68); this was rated as occasional or frequent in 23 (41.1%) of patients.

Event Frequency*	Supraventricular beats (n=53), % (n)	Ventricular beats (n=56), % (n)
None	3.8 (2)	1.8 (1)
Very rare	60.4 (32)	55.4 (31)
Rare	11.3 (6)	19.6 (11)
Occasional	18.9 (10)	17.9 (10)
Frequent	5.7 (3)	5.4 (3)
*As reported by physiologist		

Table 68: Frequency of ectopic beats, where stated in 24-hour ECG report

A single patient had a prolonged (>30 seconds) episode of supraventricular tachycardia (SVT). 16 patients (28.6%) had a shorter recorded run of SVT; these lasted between 4 and 22 beats. 6 patients had runs of broad complex tachycardia of 3 to 8 beats.

The rate of ectopy could be dichotomised into high and low rates of supraventricular and ventricular ectopic beats (Table 69). A high rate of supraventricular ectopic beats did not appear to be associated with markedly higher long-term adverse outcome There was an impression of a higher mortality rate in the patients with high rates of ventricular ectopic beats: 5/13 (38.5%) of patients in this group at one year vs 7/43 (16.3%) of patients with at most rare ventricular ectopic beats. Furthermore, 90-day readmission rates appeared higher in those with a high burden of ectopic beats (53.8% vs 37.5% for high vs low supraventricular ectopic rates; 61.5% vs 34.9% for high vs. low ventricular ectopic beats).

Ectopy	Number	90-day readmission % (n)	1 year readmission % (n)	90-day mortality % (n)	1 year mortality % (n)
High* SVE rate	13	53.8 (7)	76.9 (10)	7.7 (1)	23.1 (3)
Low† SVE rate	40	37.5 (15)	72.5 (29)	2.5 (1)	20.0 (8)
High* VE rate	13	61.5 (8)	84.6 (11)	15.4 (2)	38.5 (5)
Low† VE rate	43	34.9 (15)	67.4 (29)	2.3 (1)	16.3 (7)
SVE = supraventricular ectopic beats VE = ventricular ectopic beats Patients in atrial fibrillation excluded from SVE analysis * Occasional/frequent as reported by physiologist † Rare/very rare/none as reported by physiologist					

Table 69: Readmissions and mortality according to frequency of ectopic beats, where stated in 24-hour ECG report

7.4.2 Blood pressure assessment

Blood pressure in the final 24 hours of admission was examined, with two observations of either systolic blood pressure above 140mmHg or diastolic blood pressure above 90mmHg required to define hypertension.

18 patients (31.6%) met this threshold for hypertension. Of these, 13 were already known to have hypertension and had intensification of their antihypertensive medication recommended. This represented 44.8% of the 29 patients in the SCA arm with known hypertension.

Therefore, BP assessment identified 5 patients with potential undiagnosed hypertension (8.8% of the 57 assessed; 17.9% of the 28 without known hypertension). 3 of these patients had ABPM assessments following discharge – all 3 were negative for hypertension. 1 patient declined ABPM assessment; 1 was swiftly re-admitted due to orthostatic hypotension, contra-indicating antihypertensive treatment.

In conclusion, inpatient blood pressure assessment did not identify new hypertension: where high blood pressure was identified in a patient without known hypertension, further investigation outside of the acute episode revealed that blood pressure had normalised. However, for patients with known hypertension, an opportunity to improve blood pressure control was commonly identified when a structured approach to cardiovascular disease assessment was taken.

7.4.3 Blood tests

7.4.3.1 NT-proBNP

NT-proBNP was measured in 56 patients at baseline. Levels were raised above 300 pg/ml - the ESC recommended cut-off for ruling out heart failure in acutely unwell patients[641] – in 36 patients (64.3%).

As expected, NT-proBNP was negatively associated with LV ejection fraction (Pearson's correlation coefficient -0.363, p=0.007; Figure 76). The scatter plot reveals, however, a substantial variability in LV ejection fraction for lower values of NT-proBNP, in line with the low accuracy of this test for diagnosing LVSD demonstrated later in this subsection.

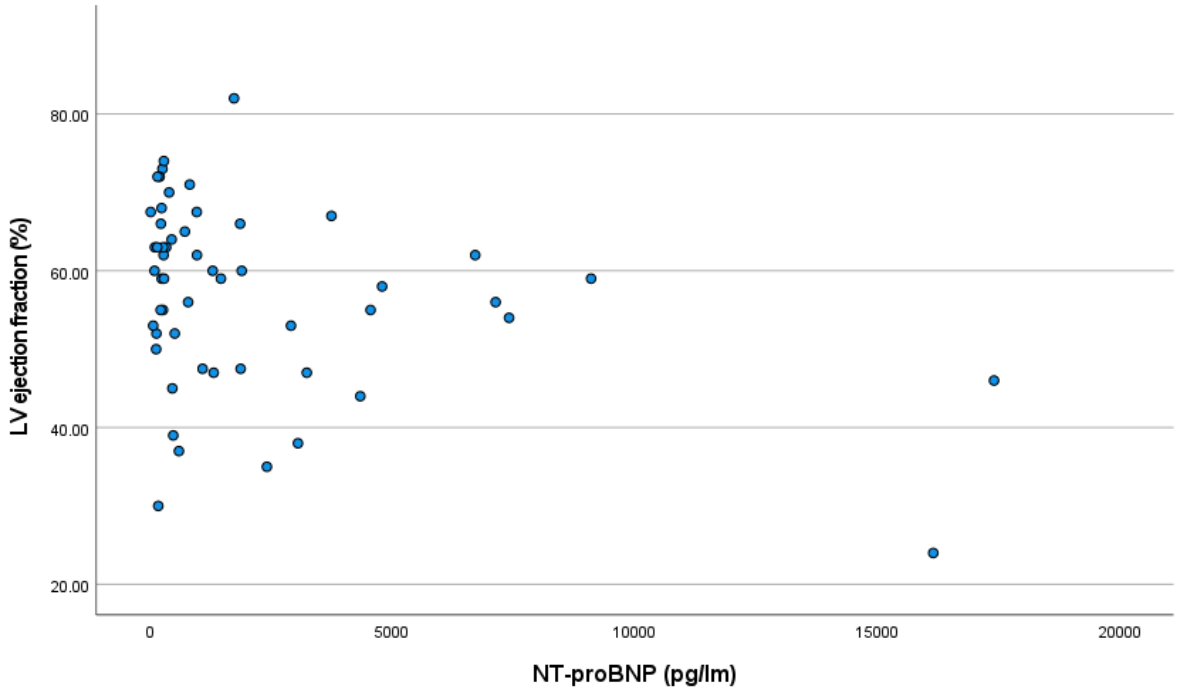


Figure 76: Scatter plot: NT-proBNP vs. LV ejection fraction

Using a cut-off of 300pg/ml, NT-proBNP had a high sensitivity and negative predictive diagnosing LVSD and RV failure, but low positive predictive values, particularly for LVSD (Table 71). Likelihood ratios imply that a positive test result increases the absolute probability of ventricular dysfunction by less than 10%, while a negative result reduces that probability by around 25%.[642]

	Moderate-severe LVSD	**No** Moderate-severe LVSD	RV failure	**No** RV failure
NT-proBNP +ve	7	27	14	20
NT-proBNP -ve	1	19	2	18

Table 70: Contingency table – ventricular failure and NT-proBNP

	Moderate-severe LVSD	RV failure
Sensitivity (%)	87.5	87.5
Specificity (%)	41.3	47.4
PPV (%)	20.6	41.2
NPV (%)	95.0	90.0
LR(+)	1.49	1.66
LR(-)	0.30	0.26
Accuracy (%)	48.1	59.3
PPV – positive predictive value; NPV – negative predictive value; LR – likelihood ratio		

Table 71: Performance of NT-proBNP > 300 pg/ml as a diagnostic test for ventricular failure

Given the modest performance of NT-proBNP at the ESC recommended threshold of 300 pg/ml, particularly in the context of a raised NT-proBNP, the diagnostic performance of other thresholds was explored through receiver-operator curve analysis.

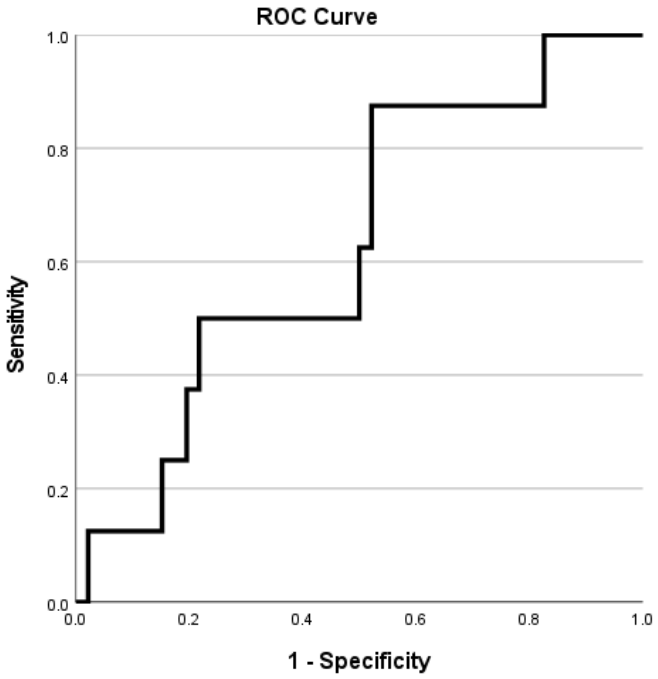


Figure 77: ROC curve: diagnosis of moderate-severe LVSD using NT-proBNP (AUC 0.630)

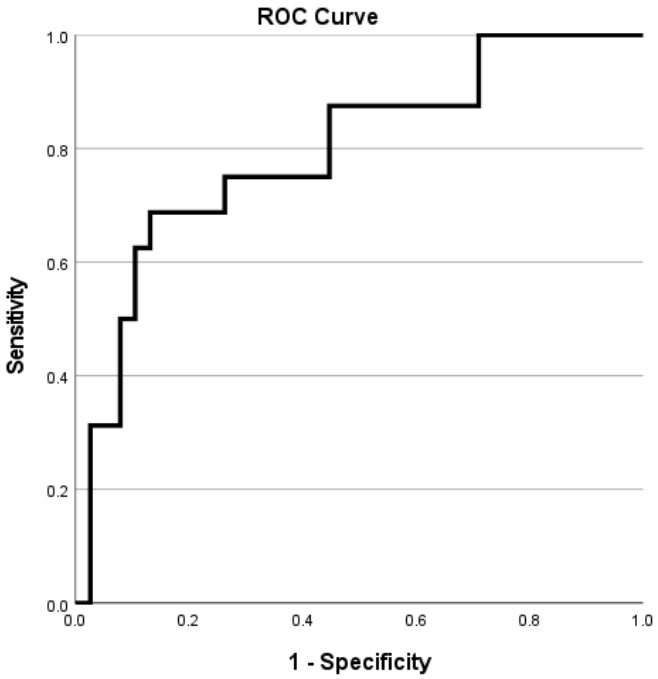


Figure 78: ROC curve: diagnosis of RV failure using NT-proBNP (AUC 0.794)

Examining the coordinates of the ROC curves revealed that an NT-proBNP threshold of 468 pg/ml would slightly improve the specificity of this test for diagnosis of moderate-severe LVSD to 52.1%,

while preserving sensitivity at 83.3%. If this threshold, rather than 300 pg/ml, was used to select patients for echocardiography, the proportion of inpatients that would require further testing would be reduced, albeit only slightly, from 64.3% (with a cut-off of 300 pg/ml) to 57.1%; in both cases, 1 in 6 cases of moderate-severe LVSD would not have this diagnosis identified.

An NT-proBNP threshold of 935 pg/ml, as recommended by a systematic review of previous inpatient studies[643], provided a sensitivity of only 50% for the diagnosis of moderate-severe LVSD, with specificity increasing from 41.3 to 58.3%.

For diagnosis of right ventricular dysfunction, the AUROC was substantially more favourable at 0.794, indicating better diagnostic performance of NT-proBNP in this context. The optimal NT-proBNP threshold for diagnosis of RV function based on this data was 450 pg/ml: this provided a sensitivity of 87.5% and specificity of 55.3%.

NT-proBNP levels were repeated at 90-day review in survivors who remained in face-to face follow-up. This yielded 46 paired NT-proBNP results. Median (IQR) NT-proBNP had fallen to 225 (90 – 553) from 612 (233 – 2533) ($p<0.001$; Wilcoxon signed rank test).

In 35 (76.1%) of cases NT-proBNP had fallen at follow-up. The changes for lower values of NT-proBNP are better visualised on a logarithmic axis, with lines drawn at and 300ng/ml to highlight important thresholds for diagnosis of acute and chronic heart failure. This plot shows that most patients at follow-up had NT-proBNP measured above 125 ng/ml, the level recommended to support a diagnosis of heart failure in stable patients.[641]

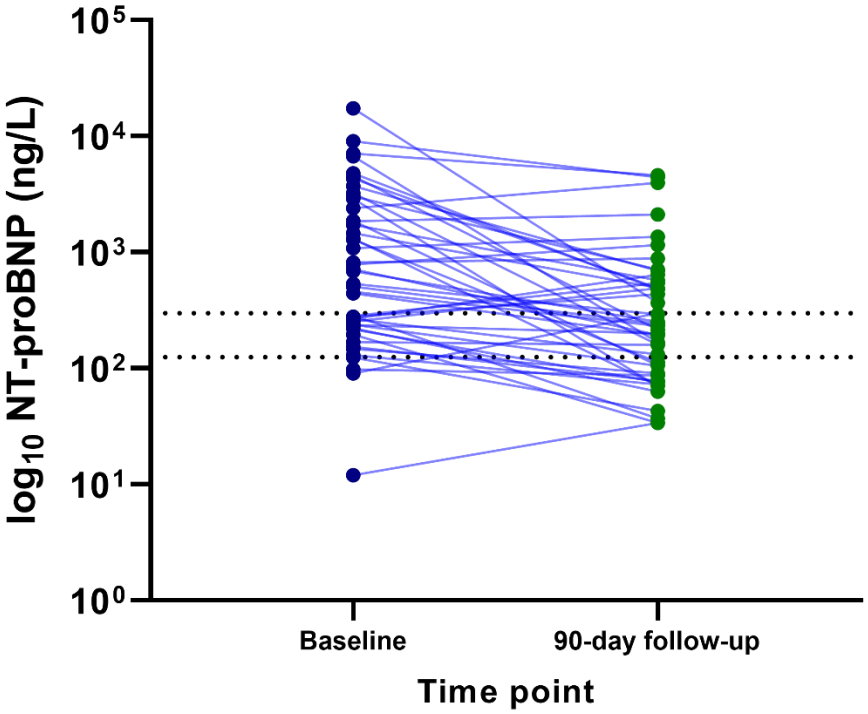


Figure 79: Before-after plot: log10 NT-proBNP at baseline and 90-day follow-up. The lower dotted line is at 125 ng/ml and the upper dotted line is at 300 ng/ml - ESC-recommended threshold for diagnosis of heart failure in outpatients and inpatients respectively

Elevated levels of NT-proBNP (≥ 300 ng/L) at the 90-day follow-up point were more closely associated with mortality than elevated levels at baseline, when patients were mid-exacerbation (see table 72). Of the 7 patients who died with raised stable-state NT-proBNP levels, 6 had repeat echocardiography, none had moderate-severe LVSD at this point (the lowest-recorded LVEF was 49%), 3 (50%) had impaired RV function.

		n	Mortality, % (n)	p-value‡
Admission n=56	NT-proBNP ≥ 300 ng/L	20	30.6 (11)*	0.334
	NT-proBNP < 300 ng/L	36	15.0 (3)*	
90-day follow-up n=46	NT-proBNP ≥ 300 ng/L	19	36.8 (7)†	0.006
	NT-proBNP < 300 ng/L	27	3.8 (1)†	
* To 365 days † 90-day follow-up to 365 days ‡ Fisher's exact test				

Table 72: Mortality according to presence of raised NT-proBNP at baseline and 90-day follow-up

7.4.3.2 Troponin T

Troponin T levels were measured in 54 patients. The median level was 21.5 (IQR 13 – 38). In 39 patients (72.2%) the level was greater than 14 ng/L, the 99th percentile for the assay used. Table 73 shows the proportion of those with raised and normal troponin levels who had diagnoses of coronary artery disease pre-admission and by cardiac CT.

	Troponin T > 14 ng/L *(n=39)*	Troponin T ≤ 14 ng/L *(n=15)*	P value*
Inpatient diagnosis MI	5.1 (2)	0.0 (0)	1.000
Previous diagnosis CAD†	28.2 (11)	13.3 (2)	0.311
CACS ≥ 100‡	65.8 (25)	73.3 (11)	0.748
CACS ≥ 400‡	42.1 (16)	40.0 (6)	1.000
* Fisher's exact test † Previous MI, angina or PCI for CAD ‡ NB one patient with raised Troponin T did not have CACS measured			

Table 73: MI/CAD diagnoses according to presence of raised troponin T

The proportion with a prior diagnosis of CAD was twice as high amongst patients with raised troponin, although, as also demonstrated in section 7.2.1, there was no relationship between raised inpatient troponin and raised CACS.

Troponin was measured a second time in 47 patients at 90-day follow-up. Levels were raised in a comparable proportion as at baseline: 29 patients, or 61.7%, with a comparable median (IQR) of 18.5 (12-29).

There were 44 paired troponin measurements. The before-after plot, using a logarithmic scale for clarity (Figure 80), reveals that the highest troponin levels, unsurprisingly, fell at disease stability, but that it was not uncommon for lower troponin levels to rise between admission and 90-day follow-up. Despite this, follow-up measurements were significantly lower than those taken at baseline (p=0.035, Wilcoxon rank-sum test).

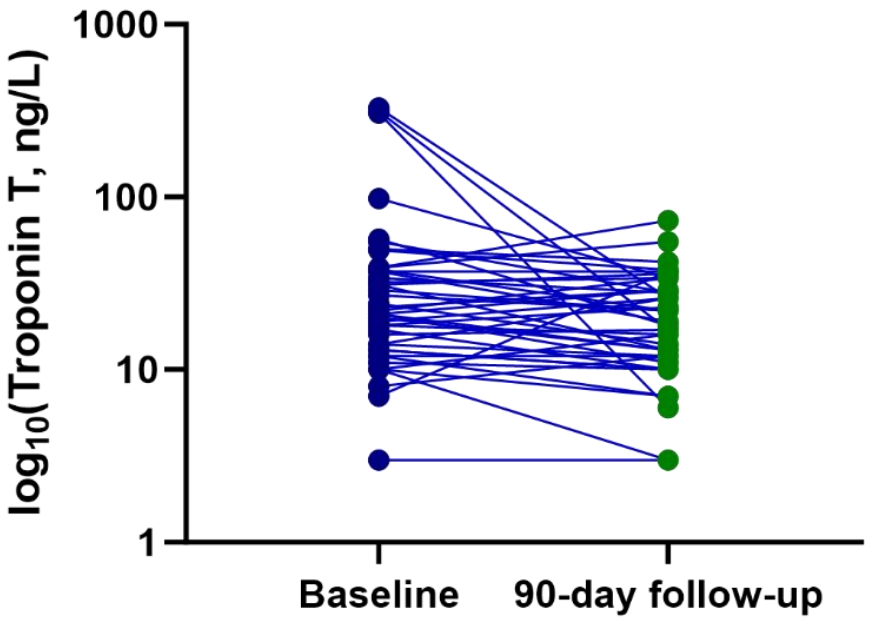


Figure 80: Before-after plot: log10 troponin T at baseline and 90-day follow-up

Mortality was compared for those with raised or normal troponin at each time point. As was the case for NT-proBNP, the same trend for mortality to be more closely associated with raised troponin at stability, rather than mid-exacerbation, was demonstrated.

		n	Mortality, % (n)	p-value‡
Admission n=54	Troponin T > 14 ng/L	39	28.2 (11)*	0.311
	Troponin T ≤ 14 ng/L	15	13.3 (2)*	
90-day follow-up n=47	Troponin T > 14 ng/L	29	24.1 (7)†	0.130
	Troponin T ≤ 14 ng/L	18	5.6 (1)†	
* To 365 days † 90-day follow-up to 365 days ‡ Fisher's exact test NB: one patient who died at 164 days had no baseline troponin measured, hence total deaths in this analysis = 13 (total for arm = 14, see section 6.3.1)				

Table 74: Mortality according to presence of raised troponin T at baseline and 90-day follow-up

7.4.3.3 Lipid profile

Lipid profiles were obtained from 55 patients during hospital admission; the breakdown of results is displayed in Table 75**Error! Reference source not found.**:

Lipid parameter	Summary statistic* n=55
Total cholesterol, mmol/L	4.13 (1.13)
Triglycerides†, mmol/L	1.3 (0.8 - 1.7)
HDL cholesterol†, mmol/L	1.4 (1.2 - 1.7)
Non-HDL cholesterol, mmol/L	2.64 (0.92)
Total:HDL cholesterol ratio†	2.63 (2.29 – 3.42)
* Mean (SD) unless stated † Median (IQR); distribution non-normal	

Table 75: Summary of lipid profiles measured at baseline

The results obtained for each individual were compared with the target reference values published by the NHS: total cholesterol < 5mmol/L; triglycerides < 1.7 mmol/L; HDL cholesterol ≥ 1.2 mmol/L in women, ≥ 1.0 mmol/L in men; Non-HDL cholesterol < 4 mmol/L; Total/HDL cholesterol ratio < 6.[644] In most cases, values obtained were within the recommended ranges, with the most commonly abnormal measures being total cholesterol (raised in 27.3%) and triglycerides (raised in 25.5%).

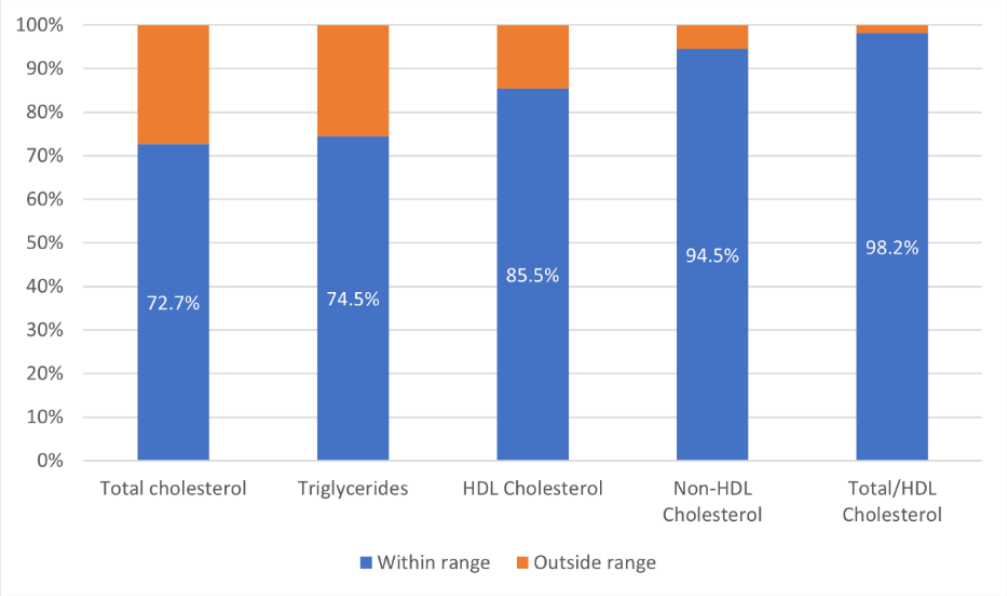


Figure 81: Proportion of within-range results for components of lipid profile at baseline

The results of the lipid profile screen were incorporated into QRISK3 scoring (see Section 7.4.4). Reasons for the low frequency of abnormal lipid levels, despite the high frequency of adverse cardiovascular events in the population, are discussed in section 8.2.5.6.

Non-HDL cholesterol is the primary driver of atherosclerosis[645] yet higher levels were not correlated with a higher degree of coronary artery calcium (Pearson correlation -0.014; p=0.924). It should be noted that that patients with coronary artery stenting were excluding from CAC scoring and that non-HDL cholesterol-lowering treatment (predominantly statins) was commonly used in those with diagnosed ASCVD.

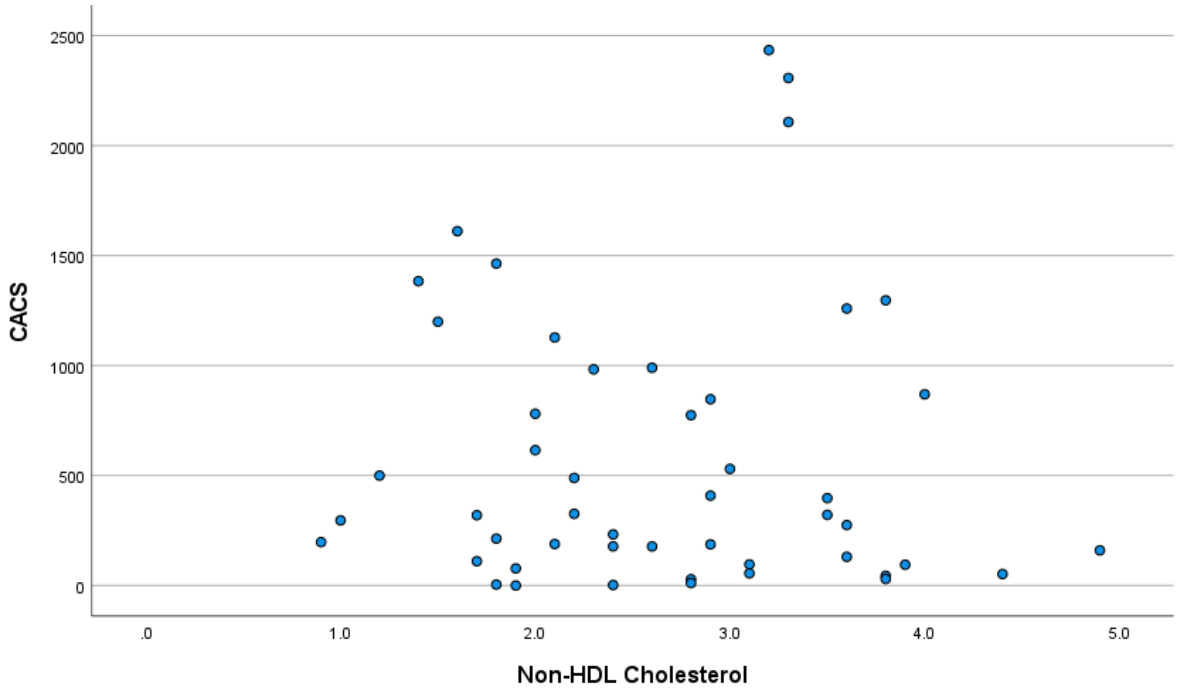


Figure 82: Scatter plot: Non-HDL cholesterol vs CACS

Equally, and also subject to confounding due to treatment, there was no difference in the mean non-HDL cholesterol level between patients who had a prior history of ASCVD and those with no known ASCVD at admission (2.50 and 2.76 mmol/L respectively; t = -1.031, p=0.307).

Recently, the management of dyslipidaemia has expanded to include the PCSK9 inhibitors, which increase the concentration of LDL receptors on hepatic cell membranes. This leads to reduced non-HDL cholesterol levels. NICE guidelines indicate these drugs if patients have had a previous event such as MI, stroke, or peripheral arterial disease and have levels above 4 mmol/L despite maximum tolerated lipid lowering therapy, or if they have multiple events and have levels above 3.5 mmol/L despite therapy.[646] According to the lipid profiles obtained, only 1 patient would have had an indication for PCSK9 inhibitor therapy (a patients with stroke, peripheral arterial disease and non-

HDL cholesterol level of 4.0 despite statin therapy). However, as noted about, assessing lipid profile at stability may have identified many more patients, as would integrating CACS into the risk profiles currently recommended by NICE.

7.4.3.4 HbA_{1c}

Hb_{A1c} levels were measured in 54 patients during admission. The distribution is presented below, for patients with and without an existing diagnosis of diabetes, along with reference lines indicating Hb_{A1c} levels of 58 and 48 mmol/mol, thresholds for action in patients with and without diabetes respectively.

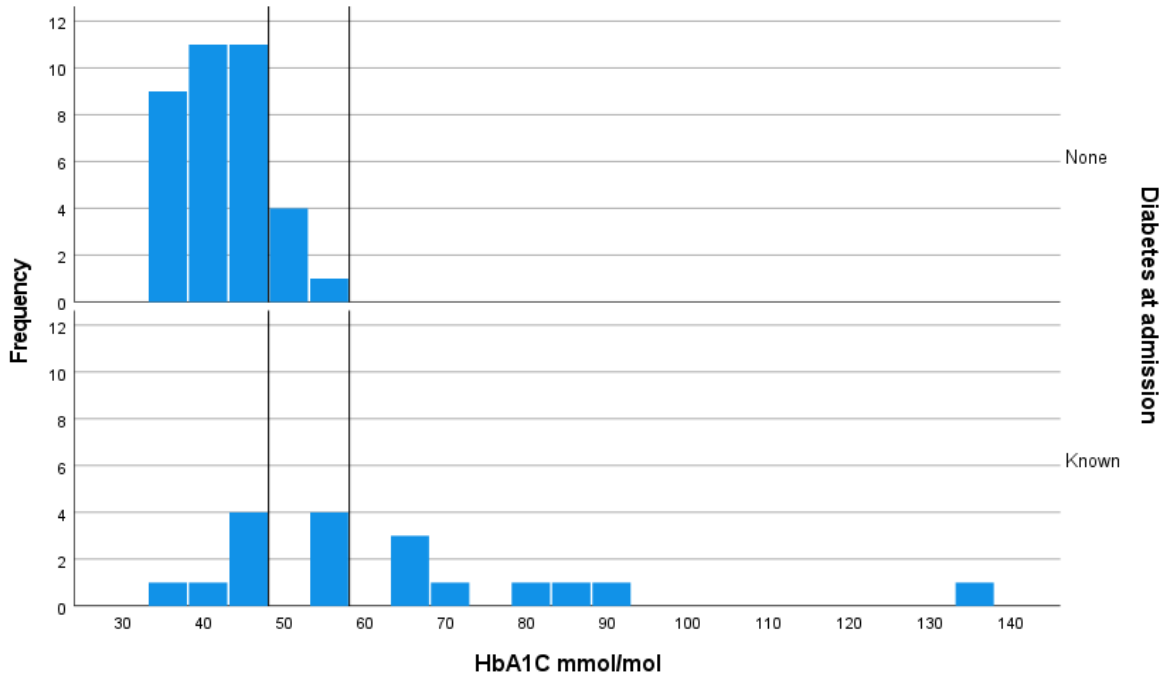


Figure 83: Distribution of HbA1c according to presence of known diabetes. Vertical lines indicate levels of 48 mmol/mol and 58 mmol/mol.

Raised Hb_{A1c} levels were uncommon in the 39 patients without known diabetes, exceeding 48 mmol/mol on 5 occasions (12.8%). Of these patients: one received an eventual diagnosis of diabetes; one deteriorated and died shortly after discharge before diagnosis could be confirmed; one had a normal Hb_{A1c} on repeat; two did not have repeat testing as recommended and also died before the end of study follow-up.

By contrast, evidence of poor diabetes control was common where the diagnosis was known pre-admission: of 18 patients, 8 (44.4%) had an Hb_{A1c} level above 58 mmol/mol. Also of note, a substantial proportion (35.9%) of patients without a diabetes diagnosis had levels in the range regarded as at risk of progression to diabetes (42-47 mmol/mol).

7.4.3.5 Fibrinogen

Fibrinogen levels were tested in 50 patients during admission. They were tested in 46 of the surviving patients who remained in face-to-face follow-up at 90 days; this yielded 40 paired samples.

Distributions were skewed positively. Median fibrinogen was 4.1 g/L at 90-day follow up, compared with 4.7 g/L during exacerbation (p=0.137, Wilcoxon signed rank test).

Fibrinogen has been identified as marker of COPD severity, exacerbation frequency and mortality.[647] Importantly, elevated circulating fibrinogen is also an independent risk factor for the occurrence of acute coronary syndromes.[648]

Fibrinogen levels were compared in patients who did and did not experience an adverse cardiovascular event during follow-up:

		n	Fibrinogen, g/L Median (IQR)	P value*
Admission	ACE to 365 days	6	4.7 (3.9 – 5.4)	0.716
	No ACE to 365 days	44	4.7 (3.6 – 6.2)	
90-day follow-up	ACE 90-day follow-up to 365 days	4	4.8 (4.4 – 5.3)	0.057
	No ACE 90-day follow-up to 365 days	42	4.0 (3.6 – 4.5)	
* Wilcoxon signed rank test				

Table 76: Fibrinogen levels according to occurrence of adverse cardiovascular events during follow-up

Although the number of events was small, a signal emerges that is in keeping with that seen for NT-proBNP and troponin T: higher levels of stable-state fibrinogen were seen in those who had adverse cardiovascular events; but there was no difference in acute-phase fibrinogen between these two groups. Once again, the stable state biomarker levels appear to have more clinical significance than those measured during admission.

7.4.4. QRISK3 assessment

QRISK3 was calculated in all patients aged up to 84 (the age limit of the validated tool); this excluded one patient. The best available information was used; for example, if an up-to-date lipid profile had not been obtained during admission, the most recent available lipid profile was used.

QRISK3 scores for the whole cohort was generally very high, with 92.6% (52/56) of patients exceeding the 10% threshold that prompts intervention under NICE guidelines.

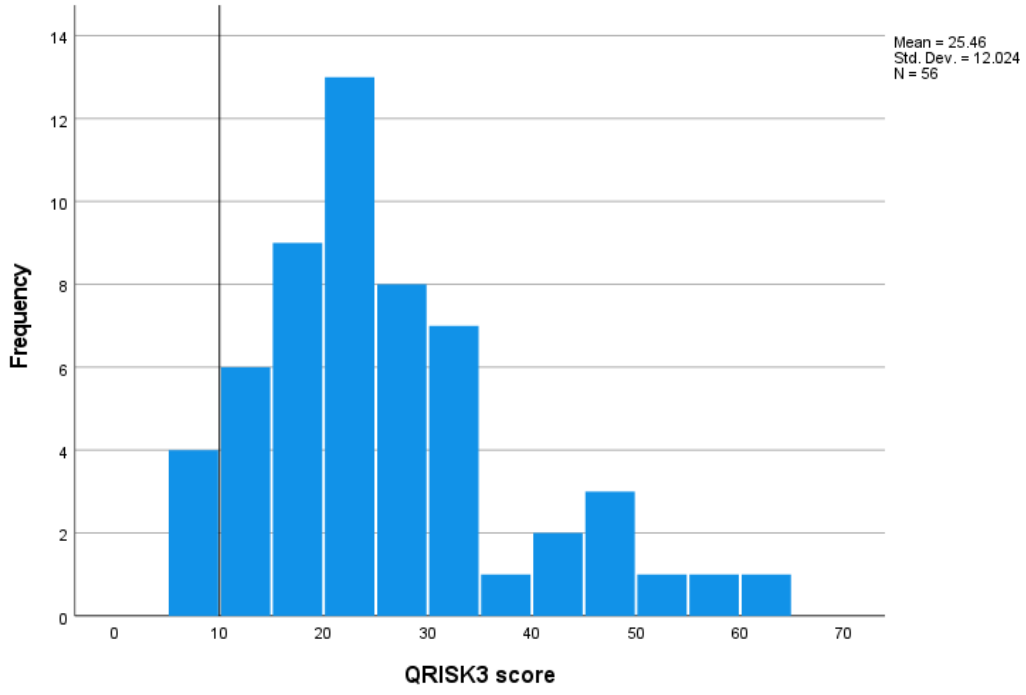


Figure 84: Distribution of QRISK scores based on baseline assessment (x-axis marker indicates 10% threshold)

The distribution of scores for the 31 patients with no previous ASCVD (to whom the QRISK3 strictly applies) were not appreciably different, with 96.8% (30/31) above the 10% 10-year risk level. 2 of these 31 patients (6.5%) had a first myocardial infarction during the one year of study. There was no correlation between QRISK3 score and CACS (Pearson correlation coefficient –0.126, p=0.383).

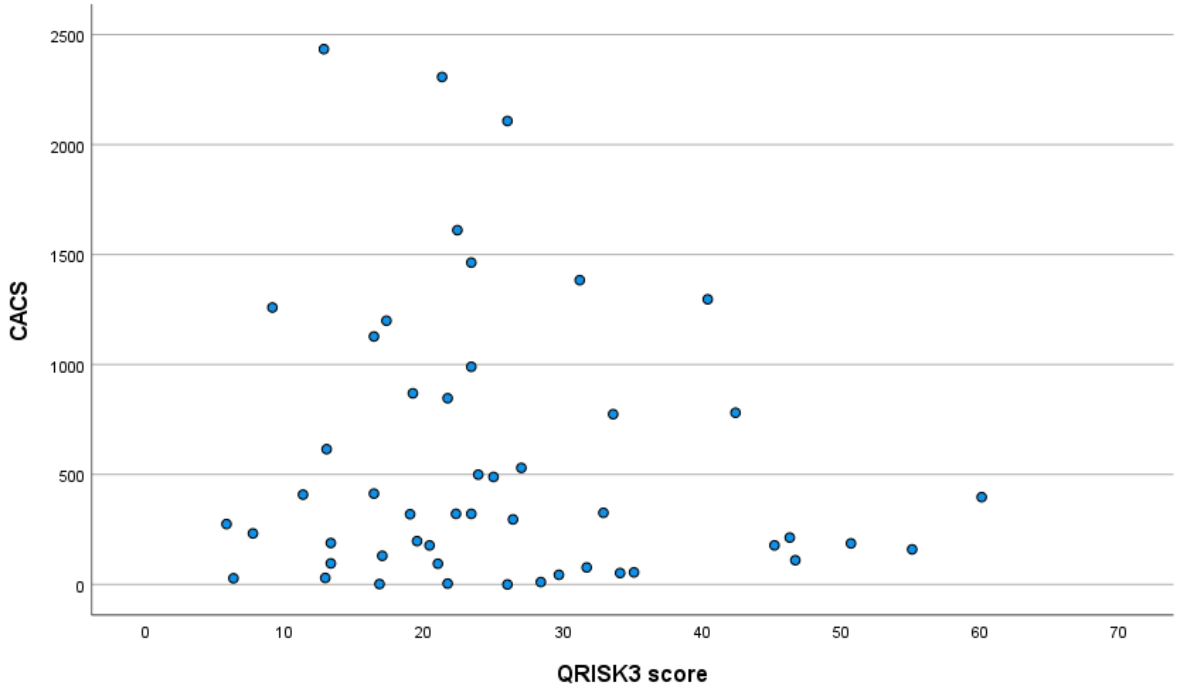


Figure 85: Scatter plot: QRISK3 score vs. CACS

In conclusion, QRISK3 scores, predictive of 10-year MI/stroke risk, are very high – in keeping with the observed rate of incident MI/stroke being over 10% in a single year of follow-up. This supports the rate of adverse cardiovascular events being a promising primary outcome measure for future studies of structured cardiovascular assessment in this population. The newly devised QRISK4 score is discussed in section 8.2.5.6.

7.5 Chapter conclusion

In this chapter the results of tests conducted on patients who were part of the SCA arm of the SCATECOPD study have been presented. The headline findings from analysis of these test results were:

- CT coronary artery calcium was found in 98% of patients in the cohort, with severe levels in 43%;
- Ventricular dysfunction was common and often unknown, with severe LVSD associated with increased mortality;
- In this cohort, raised cardiac biomarkers during admission were not significantly associated with adverse outcomes, although there a trend emerged that raised levels at follow-up had a link to mortality and adverse cardiovascular events.

Chapter 8: Discussion and conclusions

8.1 Chapter introduction

This chapter contains a discussion of the results from the pilot randomised controlled trial presented in Chapters 5 to 7. This discussion includes an assessment of the way in which the results contribute to the achievement of the objectives stated in the study protocol and detailed in Chapter 4, as well as their contextualisation within the wider body of research into cardiovascular disease in patients with COPD. The strengths and weaknesses of the study are critically assessed, and, finally, directions for future research implied by the results of this study are discussed.

8.2 Discussion of results

8.2.1 Summary of results according to study objectives

A concise overview of the results according to study objectives is contained at the end of this subsection in Table 77.

8.2.1.1 Assessment of the effect of SCA on important clinical outcomes

DAOH

A key objective of the study was to assess the effect of SCA on DAOH to allow powering of a multi-centre randomised controlled trial. As presented in section 6.2.1, the absolute mean difference between DAOH was 13.2 days, with a higher value seen in the intervention arm. Because the standard deviation of DAOH in the whole population was very large (111.4), the resulting calculated sample size for a trial powered on this difference, using conventional values for type 1 and 2 error rates (0.05 and 0.2 respectively) and 1:1 randomisation, is 2238 patients.[649] This is larger than most previous COPD trials outside of studies of inhalers, which involved a relatively simple intervention compared with the structured cardiac assessment. Notably, however, a primary care-based trial, underpinned by a rationale that is comparable to that of the SCATECOPD study, (TargetCOPD) investigated a cohort of 74818 patients with a history of smoking via GP practice records to be randomised to a COPD case-finding intervention.[650] This demonstrates that large-scale trials can be carried out in similar populations.

More problematically, the extreme skewness of the distributions (see Figure 35, section 6.2.1) observed for DAOH necessitates caution with the use of t-test-based sample size calculation, since

the assumption of normality is violated. The difficult statistical properties of DAOH have been recognised by statisticians, with simple, normality-reliant models such as linear regression performing poorly in comparison with the negative binomial distribution and machine-learning methods.[651] However, with large sample sizes such as that suggested by the sample size calculation in this case, the t-test may be an appropriate method with which to test the null hypothesis of no between arm difference, since it has been shown to have satisfactory performance even with highly-skewed distributions with study arm sizes of the order of 1000.[652] Therefore, it may be concluded that a feasible, statistically robust, definitive trial could be designed based on the findings of this pilot study.

Other important outcome measures

Mortality, readmissions, adverse cardiovascular events and COPD exacerbation rates were evaluated for suitability as potential outcome measures in a definitive RCT. While there was no discernible difference in mortality and COPD exacerbation rates between study arms, there may have been improved early (within 90 days) survival without readmission (or death without readmission) in the intervention arm. Additionally, there was a separation of the survival curves for adverse cardiovascular events, with approximately half the rate of events in the intervention arm. This is a plausible effect of the higher intensity of cardiovascular disease treatment in this arm, and suggests that future trials of similar interventions should use cardiovascular disease-related outcomes, such as adverse cardiovascular events rate, as the primary outcome measure. The results pertaining to this objective are discussed further in section 8.2.3.

8.2.1.2 Rates of heart disease underdiagnosis and undertreatment

The first of the secondary objectives was to report rates of cardiovascular disease, including undiagnosed and undertreated cardiovascular disease. In this respect, the study produced some highly salient results, chief among them the number of new diagnoses of cardiovascular disease made in the intervention arm. Amongst these, 18.2% of patients had newly identified left ventricular failure with an ejection fraction below 50%. This rate of underdiagnosis is consistent with that derived from the meta-analysis of published studies presented in Chapter 3, which yielded an estimate of 9.2% - 21.0%. Furthermore, 53.6% had undiagnosed coronary artery disease on the basis of a CAC score in at least the moderate range. Known disease was undertreated in a large proportion: in the whole cohort, at study entry, less than half (47.6%) of the 21 patients with known

heart disease were on appropriate guideline-directed treatment. Furthermore, where new diagnoses were made, patients were not already on treatment for other reasons – for example, 61.5% of patients who had an indication for antiplatelet therapy identified by cardiac CT were not already on this treatment; this proportion was 49.3% for statin therapy.

These results validate the premises underlying the design of the study: that there would be a large amount of undiagnosed cardiovascular disease to be revealed by structured cardiac assessment, and that there would be a significant amount of additional therapy given to patients who underwent the SCA. They also indicate that the current model for addressing cardiac comorbidities in patients COPD – that is, investigating for these if traditionally recognised symptoms or signs are present – is failing to adequately identify these conditions, and needs to be supplanted by active case finding based instead on individual cardiac disease risk.

8.2.1.3 Cardiac function changes

A further secondary objective was to examine the relationship between changes in cardiac function from baseline to 90 days and the severity of background COPD, the index ECOPD and comorbid heart disease, in the patients who had echocardiograms as part of the structured cardiac assessment. The broad conclusions from comparison of patients with and without left and right ventricular dysfunction at baseline were that patients with left ventricular dysfunction had more markers of severe baseline COPD, but less evidence of severe index exacerbation, whereas patients with right ventricular dysfunction differed less in terms of baseline disease severity but had significantly higher markers of hypoxaemic respiratory failure and lung hyperinflation. Furthermore, there was a trend for those in whom right ventricular impairment had improved at 90 days to have worse baseline hypoxaemic respiratory failure and to have other echocardiographic abnormalities such as LV systolic dysfunction and right atrial dilatation.

8.2.1.4 Healthcare resource use data collection, costs and QALYs

Costs were found to be higher in the SCA arm, with a median increased cost per patient of £1555.39 over one year. QALYs were not significantly different between arms, and therefore the probability of the intervention being cost-effective at accepted willingness-to-pay thresholds was low: this was 35.9% at £30000 per QALY. However, the estimations of both costs and QALYs were imprecise, due to wide within-group variation and outlying high-cost cases. Complete healthcare resource use data could be collected for 93.8% of participants. However, this was laborious, requiring 5 contacts during

the 365-day study period, with repeated efforts often required to make contact with patients, and frequent rescheduling of appointments due to intercurrent illnesses. This would have significant resource implications if upscaling a study with the same design to a multicentre RCT.

Study objective	**Summary of relevant results**
To assess the effect of SCA on important outcome measures to allow powering of a multi-centre randomised controlled trial.	Utility of DAOH over one year limited by skewness and ceiling effect. DAOH associated strongly with mortality, more weakly with readmissions, and not significantly correlated with quality of life. Summary of key outcomes at 1 year (SCA vs UC): • Mean DAOH: 305 vs 292, p=0.526 • Mortality: 24.5% vs 25.8%, p=1.000 • Mean days to readmission: 164 vs 176, p=0.814 • Mean days to ACE: 334 vs 314, p=0.286 • Mean days to CP event: 236 vs 192, p=0.229
Report rates of cardiovascular disease, including undiagnosed and undertreated heart disease in patients admitted with ECOPD.	Undiagnosed heart disease was highly prevalent: 18.2% were found to have LVSD and 53.6% moderate CAD according to CACS. Approximately half of patients with known heart disease were not receiving guideline treatment. Most patients who had at least moderate CAD were not already on antiplatelets.
In the intervention group, examine the relationship between changes in cardiac function from baseline to 90 days and severity of COPD, ECOPD and comorbid heart disease.	LV dysfunction during ECOPD more associated with background COPD severity and often reversible with treatment. RV dysfunction also commonly resolved at stability, and was more associated with acute illness severity during ECOPD.
Collect healthcare resource use data to report differences in health costs and quality adjusted life years (QALYs) between the study arms.	Costs higher in SCA arm and QALYs not significantly different between arms; low probability that intervention effective at standard willingness-to-pay thresholds.
Assess the feasibility of collecting healthcare resource use data to carry out an economic evaluation of the intervention in a future RCT.	Healthcare resource use collection feasible although ensuring accuracy was laborious. Broad confidence intervals for costs due to outliers limited precision of estimation of QALYs and cost-effectiveness.

Table 77: Concise summary of results of the SCATECOPD study, according to prespecified objectives

8.2.2 The population recruited

In critically appraising the results of an interventional study, the nature of the population recruited must be carefully considered, as this has important implications regarding the relationship of the intervention to the outcomes observed, and how the findings can be applied to other patients.

8.2.2.1 Background demographics and COPD severity

As detailed in section 5.2, the population recruited was notable for a significant limitation of physical function and independent daily living: the median eMRCD score was 4, indicating most patients could not walk 100 yards without stopping, and 43% were unable to leave the house due to breathlessness. Patients also scored highly on the clinical frailty scale, with 95% having some degree of frailty and this being moderate to severe in 37%. It was also apparent that the population recruited was characterised by a high rate of COPD exacerbation, with a median of 3 self-reported exacerbations in the previous year; 72% had been admitted previously due to COPD and 23% had required NIV during an admission for exacerbation. A substantial majority (76%) had been treated in secondary care and a similar proportion (82%) were prescribed triple inhaled therapy. 13% had respiratory failure to the extent they required LTOT. These points are made specifically here because, although many of the characteristics of the study population, such as age, sex distribution and smoking status, were consistent with inpatients with COPD included in recent national audit data[615], this was clearly a subset of the wider COPD population with extremely impactful disease. To illustrate the contrast with the overall COPD population: the overwhelming majority of patients with COPD are cared for exclusively in primary care,[653] only a third are prescribed triple inhaled therapy,[654] and the Department of Health and Social Care estimates that only around 50000 patients with COPD in England use LTOT; this represents only 4% of the total COPD population.[53,655] Furthermore, observation of primary care records reveals that, in one year, the majority of patients with COPD (53%) will experience *no* COPD exacerbations, with only 23% experiencing two or more.[656] Similarly, the degree of limitation by breathlessness recorded in the same national cohort is far less: only 3.2% were housebound due to breathlessness.[657] A final important point to note about the recruited population was that it was ethnically 100% white. Other cohorts have reported much higher racial diversity and reported differences in cardiovascular disease mortality. For example, this was significantly higher in black women than white women in a 2148-member US cohort of which 34% were black individuals.[658] This has implications for the generalisability of the study findings both to more ethnically diverse parts of the UK and internationally.

8.2.2.2 Characteristics of exacerbations leading to recruitment

It is also important to contextualise the nature of the COPD exacerbations that led to hospitalisation of the recruited patients. The derivation and validation studies of the DECAF score provide a natural comparator, as these involved consecutive recruitment of patients at UK centres with broad inclusion and exclusion criteria that closely match those in the SCATECOPD study.[175,500] In the derivation study of 920 patients, 22.0% had a DECAF score of 3 or more, denoting high risk for mortality; in the validation study of 1725 patients this proportion was higher, at 26.3%. In SCATECOPD, the proportion with a DECAF score of 3 or more was lower, at 18.2%. In keeping with this, lower proportions of patients in the SCATECOPD study had attributes affording them points in the DECAF score: for example, 22.6% had radiographic consolidation in comparison with 32.5% in the DECAF derivation cohort and 28.3% in the validation cohort. Furthermore, inpatient mortality was 10.4% in the DECAF derivation study and 7.7% in the validation study, but was much lower in SCATECOPD at 1.7%, even accounting for the lower DECAF scores. Taken together, these comparisons imply that the recruited population in the SCATECOPD study had, overall, less severe exacerbations in terms of mortality risk, than in other similar inpatient COPD studies.

8.2.2.3 Factors influencing the characteristics of the population recruited

Why was a highly frail and functionally limited patient group, with more mild COPD exacerbations than seen in comparable studies, recruited in this case? Two factors are readily apparent to explain this. Firstly, as shown in Figure 86, recruitment took place during successive waves of the COVID-19 pandemic, including the periods when hospital occupancy levels were at their highest, as well as the third national lockdown. During this period, shielding was advised for clinically extremely vulnerable patients, which included patients with serious respiratory disease such as severe COPD. Published data collected at the study site shows that periods of lockdown, and of shielding without lockdown, significantly reduced COPD admissions, although mortality rates did not differ when compared with the same period in the pre-pandemic year.[659] There was also a trend towards the admission of patients with a higher comorbidity burden during lockdown periods. This suggests that lockdowns and shielding advice reduced the overall incidence of COPD exacerbations in the community during the study recruitment period, but that those with the poorest baseline health still required admission. This provides an explanation for the recruitment of an especially frail cohort recruited to this study.

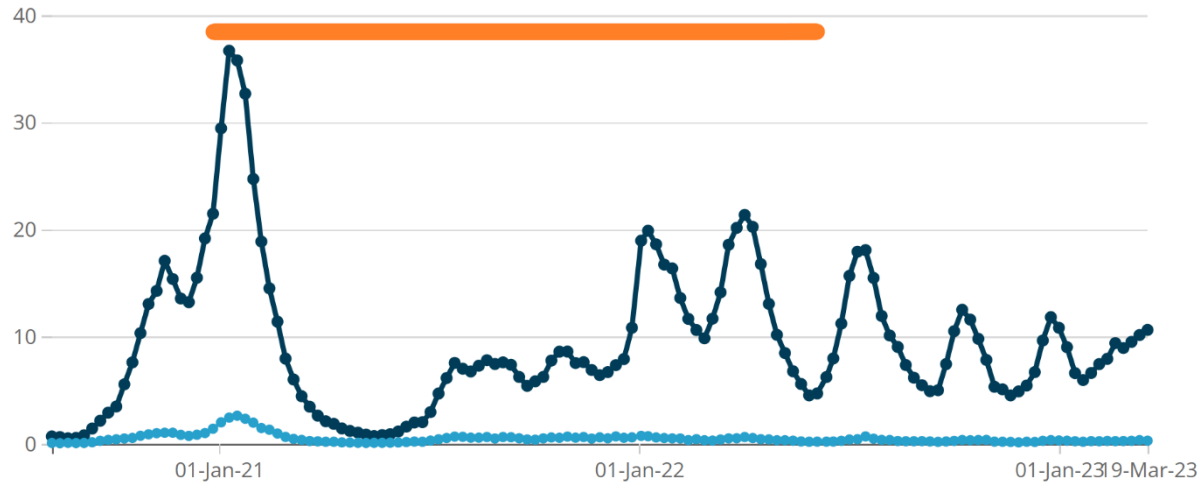


Figure 86: Weekly overall COVID-19 positive hospital admission rates (dark blue) and ICU/HDU admission rates per 100,000 people (light blue). The period of recruitment is indicated by the orange bar extending from December 2020 to May 2022. Source: Severe Acute Respiratory Infection Watch surveillance system from the UK Health Security Agency

The second factor relates to the inclusion and exclusion criteria used in the SCATECOPD study. In the comparator studies, observational data was collected from all admitted patients, whereas in the SCATECOPD study patients had to be able to consent to participation. This requirement will have excluded patients who were exceptionally sick or had significant cognitive impairment – even if the latter was transient. In some cases, these patients would also have been excluded from the DECAF derivation and validation studies, because life expectancy under 1 year was also an exclusion criterion in those studies. Nevertheless, this aspect of the study design introduced an element of selection bias, which was unavoidable given the ethical requirement for patients to be able to decide if they would be agreeable to the additional investigation and treatment burden should they be randomised to receive the intervention. This bias may explain why, overall, exacerbations were somewhat less severe than those described in cohorts recruited for the comparable observational studies.

8.2.2.4 Implications of the attributes of the population recruited

This subsection examining the population recruited concludes by considering the effect of the attributes of this population on the interpretation of the results presented in Chapters 5-7. Two major implications can be discerned:

1) Firstly, it is plausible that the high degree of frailty and baseline COPD severity in the studied population limited the ability of increased diagnosis and treatment of heart to disease to positively impact many of the outcome measures assessed as part of the pilot study. COPD accounted for the cause of death of 18 patients within the study: 15.6% of the total cohort and 62.0% of the total deaths. Furthermore, nearly half of patients had an admission with ECOPD during the year of follow-up, and this was the most common reason for readmission. Added to this, outside of readmissions, the COPD exacerbation rate was high, with over half of patients experiencing three or more. Hence, the overwhelmingly determining factor for outcomes such as mortality and admissions, and consequently DAOH, was likely to have been the background COPD. Alterations of the risk of adverse cardiovascular events and improved treatment of heart failure in the intervention group may therefore have been unable to markedly alter the rate with which these patients experienced all-cause outcomes such as death and readmission. Additionally, the frequent exacerbations experienced by the majority of the population are likely to have been a major determinant of health-related quality of life, given their impact on symptoms, function and socialisation (particularly during the COVID-19 pandemic, when those with acute respiratory symptoms were instructed to isolate). Similarly, therefore, any signal of benefit from the improvement in treatment of cardiovascular disease may have been obscured by poor overall quality of life. As health-related quality of life determines QALYs, this would also have impacted assessments of cost-effectiveness. These effects may explain why it was only for adverse cardiovascular events, an outcome measure more independent of the impact of underlying COPD, that a signal of difference between the study arms was seen.
2) An alternative way to view the recruited population is as a highly heterogeneous group composed of patients representing several different COPD subtypes. It has been recognised for decades that patients with COPD can be subcategorised into those with hyperexpanded lungs and minimal sputum, and those with copious sputum and smaller total lung capacity who showed a greater tendency to hypercapnoea and cor pulmonale; initially called type-A and type-B patients, these had become known as the emphysema and chronic bronchitis subtypes by the 1960s.[660] Many further subtypes have been described subsequently; these have become known as ‘phenotypes’, with this term having deviated from its original genetic meaning.[661] Some are based on observations of the clinical manifestations of the disease, such as the ‘frequent exacerbator’ phenotype,[662] others on the underlying pathophysiology driving airway dysfunction, such as the eosinophilic phenotype.[238] In reality, elements of genetic predisposition and environmentally-influenced specific

pathophysiology likely underly each of the described subgroups – the 'muscle-loss phenotype' being a third representative example.[663] Their importance in this context is that individual COPD phenotypes have been identified as specific populations in which to investigate therapeutic interventions. For example, patients with spirometric abnormalities that are consistent with severe emphysema benefit from lung volume reduction surgery,[664] while those with a chronic bronchitis phenotype and frequent exacerbations were found to have fewer exacerbations with the use of roflumilast, an antiinflammatory phosphodiesterase type 4 inhibitor.[665] Exacerbations have also been subtyped,[666] with emerging evidence suggesting that eosinophilic exacerbations can be more successfully treated with the addition of benralizumab, a monoclonal antibody that blocks the interleukin 5 receptor.[667] The population recruited to the SCATECOPD pilot study comprised representatives of many different baseline COPD and exacerbation phenotypes: for example, while the majority of patients conformed to the 'frequent exacerbator' phenotype, 25% had had one or no exacerbations in the preceding year. Given that patients experiencing the most frequent exacerbations have the highest incidence of myocardial infarction[668], it is plausible that identifying and treating heart disease is a high yield intervention in these patients, but is less beneficial in more stable patients, and that in this pilot study this effect was mitigated by the heterogenous population recruited. In summary, differential effects of the intervention in the various COPD subgroups comprising the recruited population may have affected overall conclusions about the efficacy of the intervention.

8.2.3 Evaluation of outcome measures

One of the key objectives of this pilot study was to evaluate the various outcome measures employed to assess the intervention, to determine which might be most suitable for use as primary outcome measures in future multicentre trials. A summary of outcomes by study arm is found in Table 29, section 6.3. Of the clinical outcome measures assessed, those most likely to be considered for future study are discussed in this subsection.

8.2.3.1 Days alive outside hospital

Days alive outside hospital had, as discussed above, several shortcomings that suggest modifications to the study design would be required if it were to be used as a definitive primary outcome. Firstly, the DAOH values recorded were difficult to analyse statistically due to their distribution, with over a

third of patients recording the maximum value of 365 days. This ceiling effect could be mitigated by studying patients over a longer time period, so that a higher proportion recorded some time in hospital or experienced mortality.

Additionally, alternative methods of handling DAOH data could be considered in future trial designs. For example, the CHARM program, one of the first studies to publish DAOH data, enrolled into several sub-studies at different rates, producing a range of follow-up times but allowing a large number of patients' outcomes to be pooled.[515] To account for the different follow-up times, %DAOH was reported (ranging from 0- 100%). In close correspondence with the SCATECOPD pilot study, approximately 30% of individuals recorded values of 100% for %DAOH (see Figure 87). However, the large sample size afforded by pooling studies allowed for comparison of the arithmetic means by t-test, based upon demonstrations that parametric tests are robust for sufficiently large sample sizes.[669] Besides enlarging the sample size, other researchers have compared days alive outside hospital before and after the delivery of an intervention, for example ventricular assist device implantation.[522] Although not done in this study or others, there is the potential to study the absolute difference, or ratio, between DAOH during set time periods before and after structured cardiac assessment. This would offer a benefit analogous to the 'self case control' methodology employed by certain observational studies, whereby an individual's pre and post exposure risk can be compared,[155] and potentially allow greater power to discern any changes in DAOH.

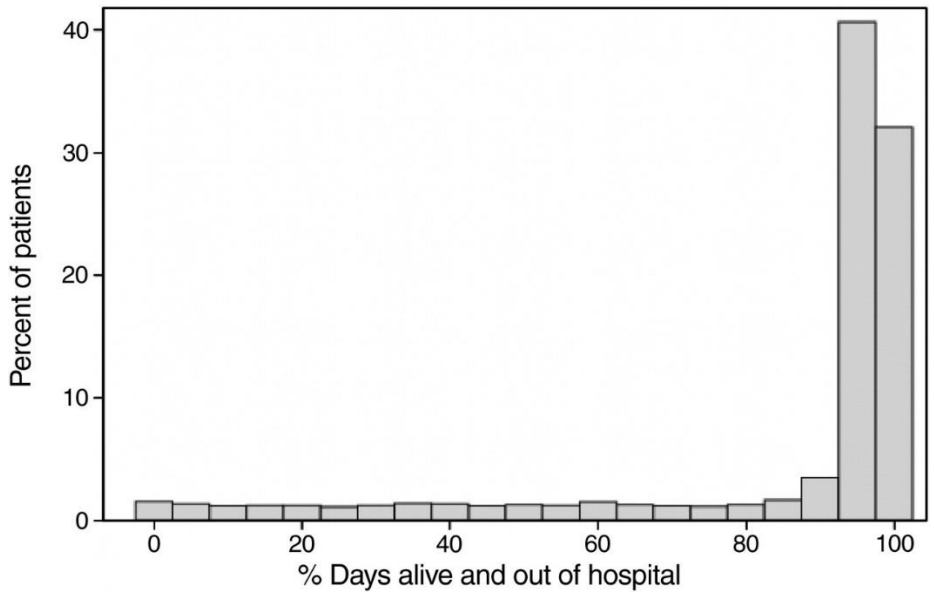


Figure 87: Distribution of %DAOH for patients included in the CHARM study of candesartan vs placebo in patients with symptomatic heart failure, showing similar proportion recording the maximum value for DAOH, and similar degree of left skew as in the SCATECOPD study (see Figure 35, section 6.2.1). Reproduced with permission from Ariti, et al[515] Copyright © 2011 Mosby, Inc

8.2.3.2 Mortality and readmissions

Regarding the secondary outcome measures, mortality rates were similar between arms, although survival curves remained separated (see Figure 39, section 6.3.1). Even after extending follow-up to two years, a very large sample size would be required to adequately power a study based on mortality – the observed hazard ratio of 0.903 implies that 7754 patients would be required.[649]

Overall readmission rates were similar between arms, although the survival curves for time to readmission (or death without readmission) showed a separation in the first 3 months of follow-up before subsequently crossing and ultimately terminating at a similar level at 12 months. Survival curve crossing may have been an incidental finding arising from the stochastic nature of readmissions in each arm, or it may have been due to effects at the individual patient level: for example, if treatments given following the SCA were initially beneficial but after some time exhibited reduced benefits or even harm, perhaps due to side effects. Alternatively, it may be that an unrecorded patient characteristic existed, if present, was associated with higher early risk in the usual care arm, but that patients without this characteristic had a lower risk if they received usual care. A notable real-world example of this phenomenon occurred in an early trial of gefitinib vs conventional chemotherapy for lung adenocarcinoma, where survival curves crossed. This was explained by better survival in the gefitinib arm if an EGFR mutation (the molecular target of gefitinib) was present, and worse survival in the gefitinib arm if EGFR was not mutated, because the drug was ineffective and these patients therefore got no beneficial anticancer therapy.[670] In the present study it is possible that a characteristic, such as severe frailty, if present, meant that intensified treatment did more harm than good, producing a graph like panel B (with the SCA arm in grey and usual care in black), and if absent, meant that it was beneficial, producing a graph like panel C. However, this seems unlikely to be the case, as no serious adverse events were recorded associated with drugs prescribed based on SCA, which was an intervention that generally led to increased understanding of the indications for treatments, all of which were based on established evidence for efficacy and safety. Therefore, this phenomenon seems unlikely to explain the crossing of survival curves for readmission in this study.

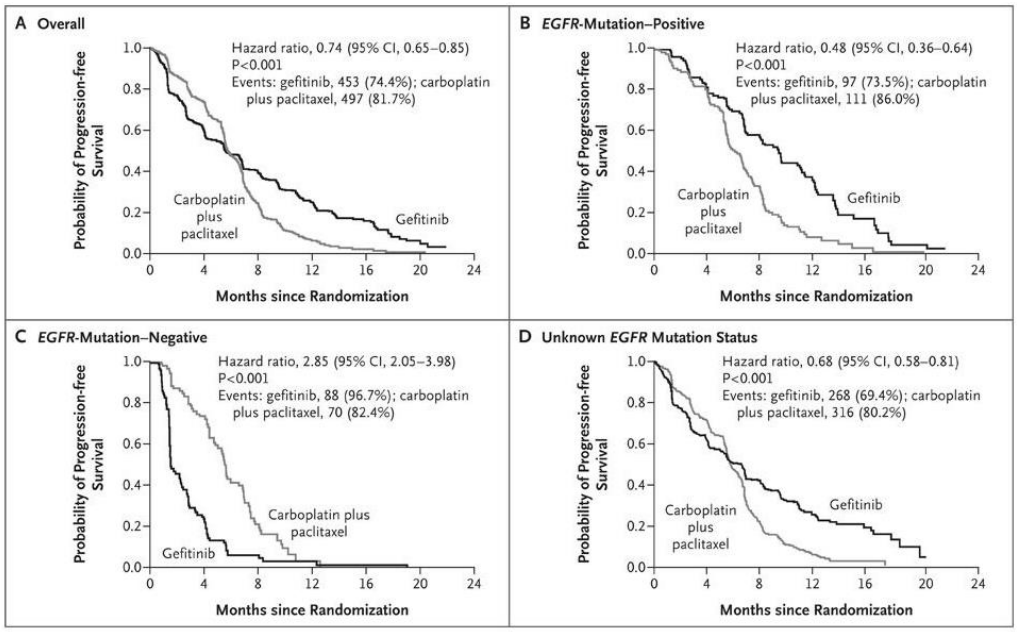


Figure 88: Survival curves from the IPASS study illustrating crossing of survival curves (panel A), due to improved survival with gefitinib in the EGFR-mutation-positive group and worse early survival with gefitinib in the EGFR-mutation negative group.

Regarding time to readmission, it should be emphasised that, since of course all survival curves will eventually meet, prevention of early readmissions remains an outcome worth pursuing for patients with COPD. This is particularly true given the deleterious effect of rapid readmission on recovery of musculoskeletal conditioning and functional performance. In a 64-month observational study, mortality over several years beyond an index early readmission after ECOPD, underscoring the lasting impact of such events.[622] At 90 days, the hazard ratio for readmission (or death without readmission) in the SCA group was 0.747 (0.430 – 1.297); a 1:1 study powered to detect a difference of this magnitude would require a total sample size of 1019; significantly more feasible for a study of this nature than the sample size calculation based on mortality.

8.2.3.3 Heart disease diagnosis and treatment

Of all the outcome measures assessed, the greatest differences between the arms were seen in terms of diagnosis of heart disease, where 42/57 (73.7%) in the SCA arm, received a new cardiac diagnosis, compared with 11/58 (19.0%; p<0.001) in usual care, and rates of undertreated heart disease, where 32/57 (56.1%) in the SCA arm received new cardiac treatment, compared with 5/58 (8.6%; p<0.001) in usual care.

These results support the hypothesis that conducting a structured cardiac assessment on patients during COPD exacerbation would identify significantly more heart disease than usual practice. They refute the counter-hypothesis, which is that the current practice of opportunistic testing based on clinical suspicion identifies a similar quantity of undiagnosed heart disease. The results also counter concerns that it would be difficult to obtain timely, sufficiently high quality echocardiographic or CT images during acute exacerbation.

The reduction in rates of undertreated heart disease supports the related hypothesis that the conditions identified by SCA would include those with specific indicated treatments, and that these would be implementable around the time of exacerbation. This result also arose because treatment of existing heart disease was optimised through the process of SCA.

The significant reduction in undertreatment represents a notable success of the SCA, since the increase, through better diagnosis, in the denominator of this metric (i.e., the number of conditions to be optimally treated) meant that the numerator (the number of optimally treated conditions) had to increase markedly to produce a significant reduction in overall underdiagnosis. Furthermore, the patients in usual care would have been exposed to the 'inclusion benefit' of being in the control arm of a randomised controlled trial,[671] therefore were liable to have experienced higher rates of heart disease testing, diagnosis and review of existing treatment. The fact that the rates of diagnosis and optimal treatment of heart disease observed in the intervention arm were, nevertheless, significantly higher implies that the benefit could be even higher in the real world.

However, rates of diagnosis and optimal treatment, in a population such as the one studied, are not ideal primary outcome measures for future definitive trials: these should aim to demonstrate meaningful benefit to patients in the form of hard clinical outcomes, in order to conclusively refute the hypothesis that any benefit to increased heart disease testing and treatment in patients with COPD would be negligible, or potentially outweighed by the potential negative consequences of increased polypharmacy.

8.2.3.4 Adverse cardiovascular events

In section 6.3.5 it was shown that adverse cardiovascular events occurred approximately twice as often in the usual care arm of the pilot study. It is biologically plausible that this could be an effect of the SCA, since the most commonly made new diagnosis was of coronary artery disease above the calcium score threshold to trigger recommendation of antiplatelet therapy. Antiplatelets were also the most commonly newly-prescribed drugs. As described in the introductory chapters, the

increased risk for myocardial infarction and stroke in the post-exacerbation period provides the motivation for targeting optimal prophylaxis against acute coronary syndromes (and acute events in other vascular territories). However, It was uncertain, prior to the running of the pilot study, whether any signals of benefit to this strategy would be seen in outcomes such as all-cause admissions, mortality or their composites, or whether the effects would appear to be limited to cardiovascular disease outcomes. The latter appears to be the case, and therefore the adverse cardiovascular event rate emerges as the measure best suited to be the primary outcome for a future definitive RCT of SCA delivered following hospitalisation with ECOPD. From the hazard ratio observed (0.582) and the rates of censoring due to drop-out from non-ACE causes, the total sample size required to adequately power a study using the primary outcome of time to ACE, with two years of follow-up, would be 528.

Three points should be highlighted regarding ACE as an outcome measure in this context. Firstly, the second most common diagnosis made after coronary artery disease was heart failure, and it has become increasing common practice for randomised trials within cardiology to include heart failure hospitalisations within the definition of ACE.[672] Given that the SCA considerably influenced diagnosis and treatment of heart failure as well as coronary artery disease, it would be rational to expand the definition of ACE to include hospitalisation due to heart failure. This component of the composite outcome measure would need to be accurately defined: rigorous guidelines for this exist from the US Heart Failure Academic Research Consortium.[673] Secondly, the number of patients that had already experienced an adverse event such as MI or stroke was over 20%. Therefore, numerous opportunities for the SCA to provide benefit regarding this outcome had already been missed by the time of its implementation; this supports a strategy that would identify patients that require adequate coronary artery disease treatment prior to their exposure to multiple exacerbations (see section 8.5.1.3 below). Thirdly, it was noted during assessment of ACE rate that the *cardiopulmonary event* has recently become more widely recognised as an important outcome to target in COPD risk reduction. If the results from the SCATECOPD study regarding time to first CP event were used to power a study to detect a difference in this primary outcome, the total sample size required for a study with 2 year follow-up would be similar, at 541 patients.

8.2.4 Economic evaluation

The overall results of the economic evaluation were summarised in section 8.2.1 with reference to the objectives relating to this aspect of the study. There are several discussion points arising from the economic evaluation that will be addressed in this subsection:

1. Firstly, a principal motivation for conducting an economic analysis as part of this pilot study was to evaluate the feasibility of this process. Conclusions about this are mixed. It was certainly possible to collect detailed information on healthcare costs for the overwhelming majority of patients recruited. However, this required multiple contacts, which were challenging to schedule in many cases, as patients were often feeling too unwell due to intercurrent illness for review at the planned time points. This was possible with a dedicated researcher, but a similar strategy, conducted outside of a coordinating centre by research staff working on multiple trials simultaneously, would be liable to result in unacceptably high rates of missing data. A potential solution to this would be to simplify cost collection by using only data from hospital admissions, as these are the most resource-intensive periods that occur during follow-up. However, inspection of the table of subcategorised costs in section 6.4.2 reveals that costs accrued by primary care and other community services were significant – in both arms the median cost in this domain was almost equivalent to that for post-discharge admissions. Therefore, an alternative strategy would be to run a future economic analysis as a sub-study on a limited sample of patients, aiming nevertheless to increase the sample size over the current pilot study without excessively burdening recruiting sites with laborious data collection.
2. The results suggest a need for a larger sample size in order to accomplish an informative economic analysis, proceeding from the fact that there was extreme variation in spend between individuals, as signified by the large interquartile ranges displayed in Table 43. This was problematic as it resulted in very broad confidence intervals for derived metrics such as incremental cost effectiveness (or cost-per-QALY), which was estimated to have an interquartile range between -£18067.17 and £57160.02. Improved precision in these estimates could be achieved by a larger sample size. Another potential measure to reduce variance would be to consider excluding outlying patients from the analysis. Outliers were present in both arms of the trial, with one patient in usual care accounting for approximately 7.7% of the total healthcare costs in that arm, and two in the SCA arm accounting for approximately 6.7% and 8.3% respectively. Removing outlying patients is not uncontroversial, not least because the existence of healthcare experiences such as these are noteworthy and should not simply be discounted, as they likely involve a very poor patient experience. However, authors have noted that healthcare use of such magnitude does not represent a typical experience and is often influenced by non-modifiable factors such as psychiatric comorbidities and difficult social circumstances.[674] Multiple methods exist for identifying outliers, and statisticians have compared the effects of using different methods

on the same cohort.[675,676] One study concluded that the optimum method for reducing the confidence interval widths for bivariate data (such as healthcare costs and QALYs), while minimising the change in overall estimate for the cohort, was the DFBETA method that removes results that excessively alter the regression line through, in this case, the cost effectiveness plane (see Figure 89).[675] Ultimately, the optimum way to identify outliers in future assessment of cost-effectiveness would need to be carefully planned with a statistician in order to minimise the negative effects of excluding outliers, which include an increase in type 1 error rate.[677]

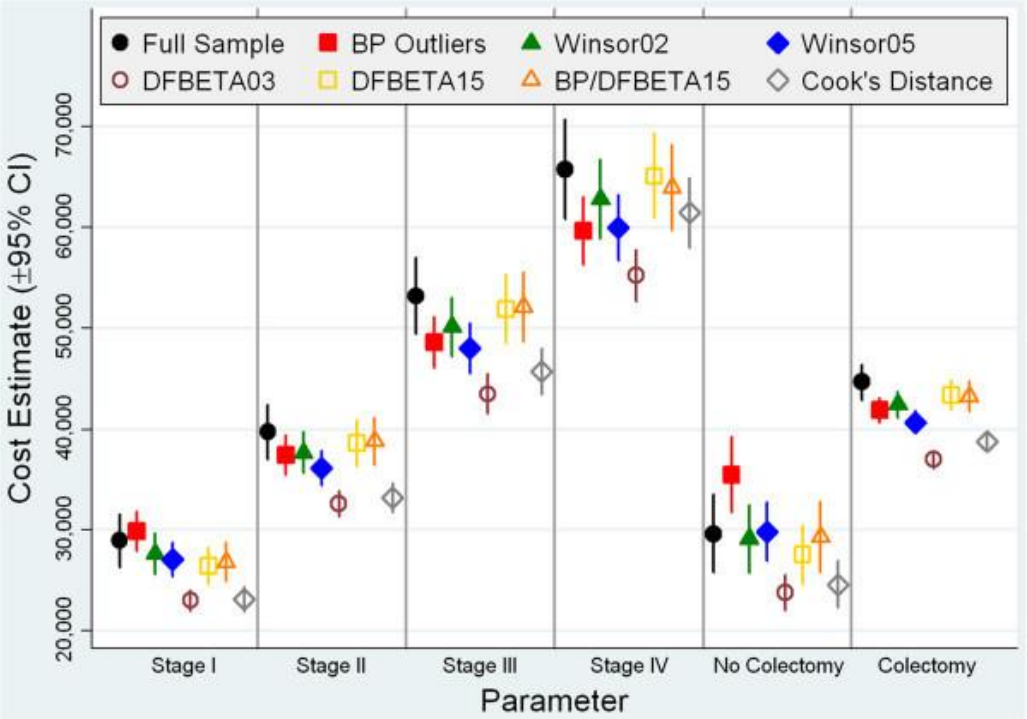


Figure 89: Illustration of the change in cost estimate for 12 months of care for colon cancer of different stages and with and without colectomy, when different methods of handling outliers are applied. The DFBETA method with a threshold of 0.15 (yellow squares) produces cost estimates with narrower confidence intervals while minimally altering the mean cost, compared with the full sample (black circles). Reproduced from Weichle et al(673) © 2013 BioMed Central Ltd.

3. The breakdown of the healthcare cost analysis presented in Table 43 in section 6.4.2 merits discussion. Notwithstanding the lack of statistically significant differences between arms for most of the categories of healthcare resource use, the trends to difference between the arms suggest how the intervention may have affected resource use in comparison to usual care.

   Firstly, costs associated with index admission were higher for patients randomised to SCA,

and this difference exceeded the additional costs incurred by the investigations that comprised the SCA. This extra cost may have been accounted for by a prolonged length of stay for patients having more inpatient tests and more initiation and alteration of medications, which necessitates additional time to organise medication prescriptions. While the design of the study was such that patients were not required to wait in hospital longer to receive their investigations, it is possible that the results of investigations led to patients being kept in hospital longer, for example if their treating clinicians wanted to assess the effects of newly started treatments prior to discharge, or if they had heightened concerns about early discharge due to the increased number of comorbidities revealed after SCA. Secondly, the patients in usual care incurred a higher spend on post-discharge outpatient investigations than those in the SCA arm. This may have been because many of these patients continued to have undiagnosed heart disease contributing to their daily symptoms and episodes of deterioration, and therefore clinicians were investigating for non-COPD causes of this. However, it does not appear that these post-discharge investigations effectively identified undiagnosed heart disease at a later stage – as noted in section 6.3.6 the number of diagnoses made in the usual care arm post-discharge was small. Therefore, this costs day indicates that post-discharge investigations were applied in the usual care arm with low diagnostic efficiency.

Thirdly, it is notable that median hospital costs were higher post-discharge in the intervention arm. There are several reasons why this may have occurred, beyond random variation in the health outcomes of the studied patients. It may be that patients in the SCA arm, because they had new or intensified medications prescribed on the basis of new diagnoses or treatment optimisation, experienced more complex admissions due to polypharmacy and side effects. Alternatively, as for the discharge process, the increased comorbidity profile of the patient group who had been through the SCA may have led clinicians to manage them more cautiously and intensively; patients themselves may also have had altered health-seeking behaviour, perhaps due to feeling less confident managing episodes of deterioration at home while living with a greater number of medical conditions and an increased in prescribed medications. Lastly, the influence of outlying patients appeared to be stronger in this group, as discussed in the previous point in this subsection and demonstrated in the histograms in Figure 58 (section 6.4.2). Evidently, the explanation for increased hospital admission costs in the year post-SCA is complex. Future studies could include qualitative data collection to test some of the hypotheses put forward here about

how patients and their caregivers respond to the increased diagnostic and therapeutic burden conferred by the SCA.

4. A key aspect of the economic evaluation was the assessment of quality of life change over the year of follow-up, as this determined the QALY estimate that was the denominator for the incremental cost-effectiveness of the intervention. Accordingly, it is necessary to consider how effectively the methods implemented to assess quality of life in this pilot study accurately captured the patients' lived experiences during the year of follow-up. One notable feature of the scores recorded at each time frame was that several were below zero when converted to a UK-specific utility index. In total, 5.1% of EQ5D5L responses collected had this trait. A score below zero is considered to represent a state of living that is 'worse than death', although at no point on completion the EQ5D5L instrument are patients asked to make judgements of this nature about their quality of life. Indeed, one third of the value states within the UK value set applied to EQ5D5L instrument are negative.[678] However, patients who actually live in these states are often not dissatisfied with life: 46% state their life is quite satisfactory, satisfactory or very satisfactory, and 45% describe themselves as happy or even very happy (see Figure 90).[678] The finding that most patients who receive NIV are glad they did, would choose to do so again, and are happy with their quality of life also highlights a discordance between externally applied quality of life judgments and patients' lived experience.[679] In this study, patients who died during follow-up from a health state with a negative utility index appeared to have improved quality of life, regardless of whether they themselves would have agreed with this conclusion. Given time to death was longer (albeit not significantly; see Figure 39, section 6.3.1) in the SCA arm, this may have biased again quality of life improvement being detected in this arm relative to the usual care arm, since patients had a higher chance of spending longer in a health state with a negative utility index.

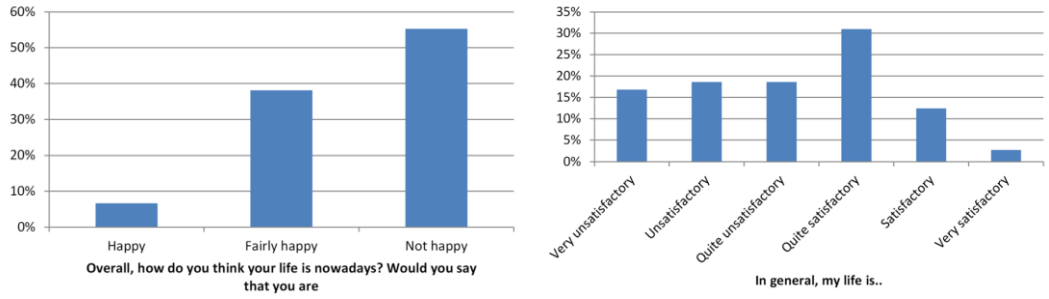


Figure 90: Responses of patients in health states worse than death, according to the UK EQ-5D-5L value set, to questions about their happiness and life satisfaction. Reproduced from Bernfort et al,[678] ©2018 Springer Nature

8.2.5 Cardiac investigations

This subsection pertains to the results of the investigations carried out in the SCA arm and reported in Chapter 7, and contains a discussion of the potential mechanisms explaining significant results or notable trends within the data.

8.2.5.1 Cardiac CT

A key finding from investigation with cardiac CT was the high proportion of patients with significant coronary artery calcification: 76.5% had an Agatston score of at least 100. This threshold has been identified, using data from 6470 patients in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, as the level above which aspirin use is likely to have benefit by lowering adverse cardiovascular event in excess of the harm it causes through excess bleeding events.[680] 43.1% had a score of over 400, for which the risk/benefit ratio is estimated to be even further in favour of antiplatelet treatment.[680]

The proportion with significant coronary artery calcium is higher than that reported in other studies. For example, in the ECLIPSE cohort, 52% and 29% of subjects had Agatston scores above 100 and 400 respectively.[635] Patients in this study were younger (mean age 63.2 [SD 7.0] in ECLIPSE, 72.0 [SD 6.4] in SCATECOPD). This is likely a major explanatory factor for the difference because CAC scores are known to increase with age.[681] Regarding other factors linked to CAC levels, there was a similar degree of smoking exposure (mean PYH 47 in ECLIPSE, vs 45 in SCATECOPD). Proportions with diagnosed CV disease are difficult to compare given the definition used in ECLIPSE ('heart trouble', angina or 'heart attack') but proportions with hypertension were similar (41% in ECLIPSE, 47% in SCATECOPD). Patients in the ECLIPSE cohort also had to be exacerbation-free for at least 3 weeks at the time of enrolment.

It has been found that the coronary artery calcium score does not correlate exactly with the degree of stenosis of the coronary arteries. Even among patients with symptoms highly suggestive of coronary artery disease, 21% of those with a CAC score over 100 had no significant (that is, >75%) vessel stenosis on invasive angiography.[682] Equally, amongst patients in the MESA cohort who underwent invasive angiography during follow-up, 16% of coronary arteries with over 75% stenosis had no detectable calcification.[683] However, despite these shortcomings, in patients with COPD a higher CAC score is associated with increased all-cause mortality,[635] and in this population CAC has been shown to be a better predictor of a broad composite of adverse cardiovascular events (including MI, stroke, angina/IHD event, PAD requiring surgery) than the Framingham score.[684]

Therefore, there is a strong rationale behind proactively addressing CT-detected coronary artery calcification. Amongst treated patients in SCATECOPD, mortality was higher in those with CAC scores in the severe range (34.6% if CACS ≥ 400 vs 13.3% if CACS < 400), but the incidence of adverse cardiovascular events was not higher (3/26 with severe CACS had events vs 3/30 without). This implies that mortality may be related to both micro- and macrovascular disease in diverse vascular territories, for which severely elevated CAC is a marker, and that treatment with medications that achieve general prevention of atherosclerosis-related events – i.e. antiplatelets and statins – is justified in efforts to reduce all-cause mortality. Alternatively, the high rates of myocardial infarction seen in the year post-exacerbation could motivate a strategy of incorporating more detailed non-invasive imaging than the gated non-contrast CT used to calculate CACS, such as CT coronary angiography (CTCA). This could better characterise the nature of CAD and direct intervention where coronary artery obstruction is most critical. A recent and highly relevant study of patients with stable COPD investigated by CTCA demonstrated a very high rate of obstructive coronary artery disease, with 28% having ≥75% stenosis in at least one vessel (see Figure 91); this was asymptomatic in 76.2%. CACS once again proved the most accurate screening method for detecting obstructive CAD (AUC 0.89, vs 0.64 for QRISK3 score and 0.73 for troponin I level).[685] Thus, an algorithmic approach to screening for CAD using CACS, investigating severe scores with CTCA and potentially treating severely stenosed vessels with percutaneously inserted stents could be considered, although resource implications and the potential complications of invasive angiography in this patient group are important concerns.

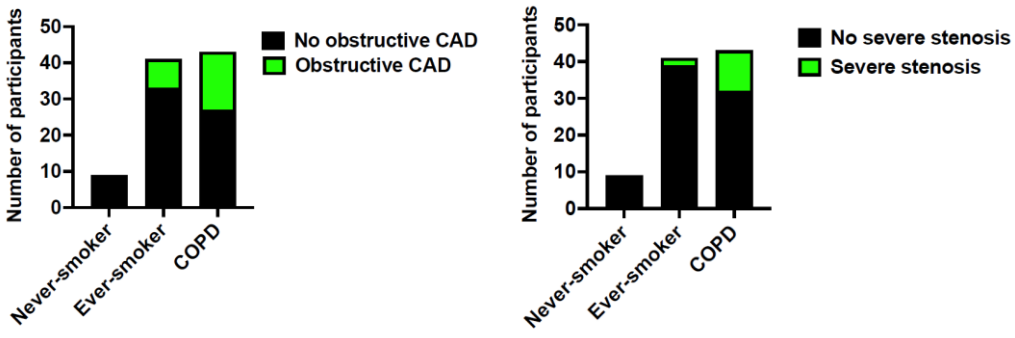


Figure 91: Proportion of COPD patients, never-smoking controls and ever-smoking controls with obstructive (≥50% stenosis of any vessel) CAD and severe coronary artery stenosis (≥70% stenosis). Proportions in COPD: 42% and 28% respectively. Reproduced with permission from MacLeod et al.,[685] Copyright © 2024 by the American Thoracic Society.

Regarding troponin levels and their relationship to CACS, there was no evident correlation between these two variables, implying that troponin levels, particularly those taken during exacerbation, are not a useful method of identifying those likely to have significant CAD on objective testing. Further evidence to support this statement is provided by the fact that the three highest troponin levels observed on index admission were in patients with only mild to moderate CAC scores. Each of these patients underwent angiography, with none having haemodynamically significant coronary artery disease. This indicates that alternative mechanisms of troponin release besides myocardial infarction due to acute coronary occlusion by thrombus, such as stress cardiomyopathy,[686] were responsible for very high troponin levels (>200 ng/L) seen during COPD exacerbation.

8.2.5.2 Echocardiography

An important conclusion from the echocardiographic data collected as part of the structured cardiovascular assessment was that it was possible to obtain a judgement about both left and right ventricular function in all cases. Prior studies in patients with severe COPD have found high rates of inadequate image quality due to emphysema for specific measurements such as tricuspid regurgitation velocity: 70% in a group with mean PaO2 < 8 kPa.[367] However, the use of a global assessment of RV function, and of intravenous contrast where needed to aid left ventricular systolic function assessment, appeared able to mitigate the difficulties associated with echocardiography in this patient group.

Regarding the clinical characteristics associated with moderate-severe LVSD at echocardiography during ECOPD, inspection of Table 55 (section 7.3.1.1) reveals that, although no significant differences were seen between the groups with and without this finding, those with moderate-severe LVSD tended to be older, to have lower historic FEV1 and to have higher eMRCD scores. They also had numerically more previous exacerbations, including those requiring NIV, as well as higher levels of CAC. In terms of the index ECOPD, DECAF scores tended to be higher amongst those with moderate-severe LVSD, although this may be accounted for in part by the increased age and eMRCD scores noted above, and CXR hyperinflation was greater, although the extent to which this is acute or chronic is not known. Therefore, it may be concluded that background disease factors are more of an influence on LVSD seen during ECOPD that the index exacerbation severity. Perhaps the key finding from the assessment of LV function during ECOPD was the poor prognosis conferred by severe systolic dysfunction: of these patients, 1/3 had died by 90 days, and 2/3 by 365 days. This suggests that the identification of severe LVSD during ECOPD should be a moment where long-term decision making takes place amongst clinicians and patients: while in some patients this represents a

moment where initiation of aggressive targeted treatment is required to aid LV functional recovery, in others it indicates a need for advance planning and appropriate palliative care during the final stages of life.

Regarding right ventricular dysfunction, inspection of the differences between those with and without this finding at exacerbation (presented in Table 58, section 7.3.1.2) reveals that, compared with the findings for LVSD discussed above, a greater number of differences were seen in markers related to the acute exacerbation itself. For example, ROX index was significantly lower, and NTpro-BNP and troponin levels significantly higher. Median CRP was also higher, at 59 vs. 8 mg/L, although this difference was not significant; the same was true for the proportion of patients requiring NIV: 33.3% for those with RV impairment and 17.5% for those without. By contrast, the background attributes of patients were similar for those with and without RV impairment, with the exception that those with RV impairment tended to be older, to have had previous NIV and, unsurprisingly, to have known right sided heart failure. A greater proportion of those with RV dysfunction had home oxygen therapy at discharge, although this not necessarily mean they had worse resting hypoxaemia, because for those with RV dysfunction a lower threshold would be set for the prescription of oxygen (i.e. PaO2 8kPa vs 7.3 kPa).

As RV dysfunction was not treated with agents targeted at its pathogenesis, as was the case for LVSD, the extent to which it reversed spontaneously could be evaluated. Unfortunately, this analysis was limited by small numbers to begin with. These reduced further because of patients who did not survive to 90-day review, or were too unwell at this time point to attend hospital for repeat echocardiography, but it was still evident that in a significant proportion (67% of survivors), RV dysfunction was no longer present at 90 days. Furthermore, differences could be appreciated between those with reversible and persistent RV dysfunction, which suggested that RV dysfunction identified during ECOPD is more likely to be persistent if patients have peripheral oedema, are frequently exacerbating, have impaired LV systolic function or right atrial dilatation, and had an index ECOPD involving a lesser degree of hypoxaemic respiratory failure than those with RV dysfunction that subsequently reversed. These findings require confirmation in a larger sample size before conclusions about their implications can be drawn.

There was also, notably, a difference in outcome between patients with and without right ventricular dysfunction. While mortality over 365 days was similar, time to readmission (or death without readmission) was *longer* for those with RV dysfunction. This difference was not statistically significant (see Table 67, section 7.3.7), but survival curves separated widely (see Figure 74, section 7.3.6). This mirrors the finding of reduced readmission rates for those with increased PA:A described

in section 8.2.5.1, and is once again surprising because RV dysfunction associated with COPD has been consistently linked to poorer outcomes – for example, raised pulmonary pressures measures by right heart catheter led to double the risk of readmission (see Figure 92).[687]

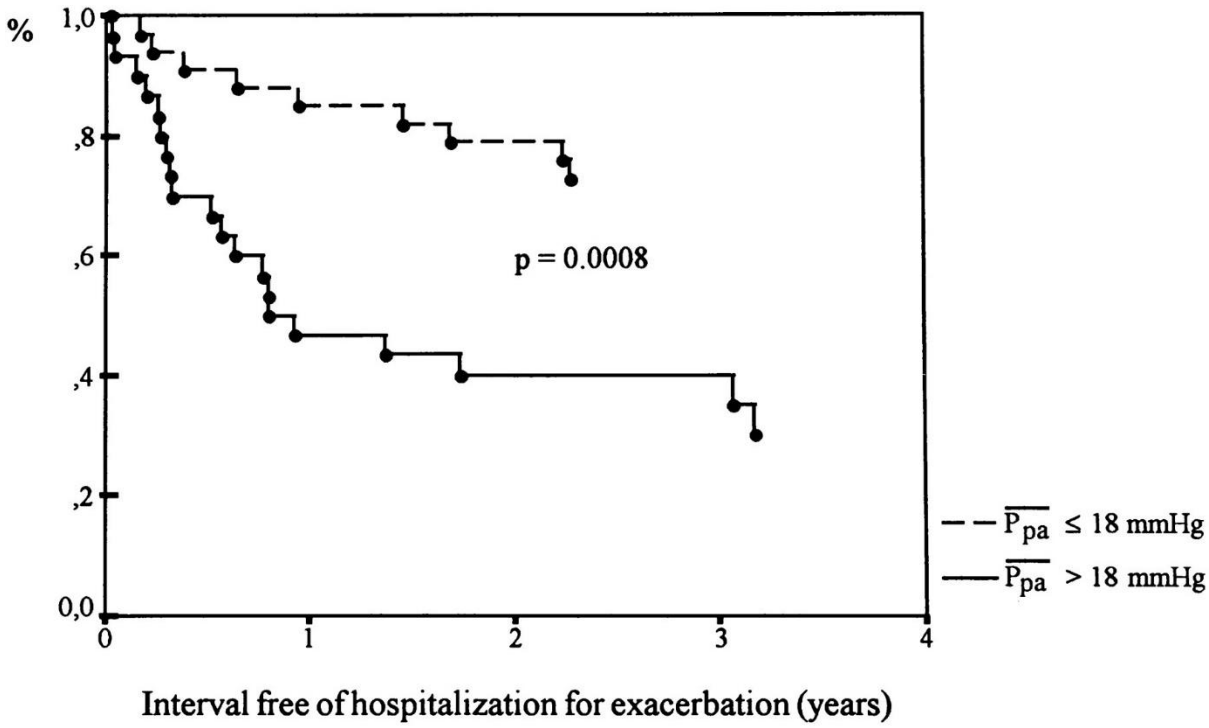


Figure 92; Survival without readmission due to ECOPD for patients with raised (solid line) and normal (dashed line) pulmonary artery pressure on right heart catheterisation. Reproduced with permission from Kessler et al.[687] Copyright © 1999 by the American Thoracic Society.

It is not clear why, in the present study, patients with RV dysfunction appeared to have better outcomes in terms of readmissions. One possibility includes a form of survivorship bias, which was discussed above in relation to outcomes in those with raised PA:A (see section 8.2.5.1). Those with RV dysfunction tended to have markers of more severe exacerbation, and perhaps a different exacerbation phenotype: CRP, for example, was higher in those with RV dysfunction, but the median level was barely above the normal range in those without RV dysfunction. Therefore, those that were recruited may have possessed features of resilience to acute illness that meant that they were less likely to be readmitted in the future. Another possibility relates to the finding that a higher proportion of patients with RV dysfunction had undiagnosed left sided heart failure identified during their admission (20%, vs 5% without RV dysfunction, had undiagnosed moderate-severe LVSD; 40% vs 17.% had undiagnosed HF without moderate-severe LVSD). This group of patients may therefore

have received a greater degree of attention from heart failure (and other) services, including medication changes and other follow-up, which led to reduced admissions.

Ultimately, this reasoning remains speculative, but the finding that RV dysfunction seen during ECOPD commonly reverses at follow-up, and was not linked to worse outcomes, implies that clinicians should be cautious about diagnosing cor pulmonale in patients with COPD on the sole basis of an echocardiogram performed during exacerbation.

8.2.5.3 24-hour ECG recording

Regarding 24-hour ECG recording, the most notable finding was of a low proportion of patients with atrial fibrillation. This was seen in 5.4% of cases, all of which were patients with known AF. This is lower than the 12.5% prevalence seen in a cohort of 920 patients at the same study site, where AF was identified by medical history and 12-lead ECG.[175] A 24h ECG recording would be expected to identify a higher rate of AF than this methodology. Indeed, a recently published observational study of 197 patients admitted with ECOPD, also conducted during the COVID-19 pandemic and excluding those with known permanent AF, reported paroxysmal AF in 15.2%, although no mention was made of the durations of AF observed.[688] One possible reason for the absent pick-up of undiagnosed AF is poor recording quality, although this was rated at least adequate for analysis in 75% of cases. Additionally, it is notable that in the observational study by Nguyen referenced above, over half of patients received either NIV or invasive ventilation, substantially more than in the SCATECOPD cohort, where NIV was used in 21.7%. Finally, it is worth noting that in the study by Nguyen, repeated 24-hour ECG recordings were taken if symptoms that could represent arrhythmia were reported later in admission, which would be expected to increase the diagnosis rate; it is not stated, however, how many recordings were done per patient.

An exploratory tabulation of adverse outcome rates based on the frequency of supraventricular and ventricular ectopic beats did suggest that patients with high burdens of ectopy had higher rates of early readmission and, for ventricular ectopy, mortality. Excessive supraventricular ectopic activity (ESVEA) does not have a consistent definition, but has been associated with increased risk of later AF, as well stroke, all-cause mortality and cardiovascular mortality.[689] In COPD specifically, supraventricular ectopic beats are associated with a significantly higher BODE index, a predictor of mortality.[690] Meanwhile, excessive ventricular ectopy has been found to predict mortality and incident heart failure,[691] and to be associated with more severe COPD.[692] Ventricular ectopic rates increase during ECOPD, and are significantly higher in those with raised troponin levels.[476] Therefore, while 24-hour ECG recording had a low yield in terms of identification of undiagnosed

arrhythmia during ECOPD, it may have a role in identifying patients at high risk of future adverse cardiovascular events, including sudden cardiac death.

8.2.5.4 NT-proBNP

At admission, 2 out of 3 patients had an NT-proBNP level above 300 pg/ml, the ESC-recommended cut-off to 'rule out' heart failure. 21/56 (37.5%) of patients had levels above the age-adjusted values for which further investigation is recommended for patients presenting acutely to the emergency department (see Figure 93).[693] This serves to highlight the substantial degree of myocardial stress incurred by COPD, and intensified during exacerbation. Additionally, it indicates that while NT-proBNP would be extremely useful for stratifying inpatients for further investigation by echocardiography, this test would still be indicated for a large proportion of patients by most established cutoff values. The latest edition of the GOLD guidelines for COPD care contains the following statement: "*It may be advisable to measure routinely during ECOPD markers of CVD, such as troponin and brain-natriuretic peptides… if any of these markers are abnormal during the episode of ECOPD, appropriate further investigations and treatment are required.*"[694] This represents an encouraging advance on previous advice to base investigations for heart disease on symptoms on signs, which has shown to be inaccurate. However, as a diagnostic biomarker, NT-proBNP demonstrated low precision in the population investigated in this pilot study, with an AUC for diagnosis of moderate-severe LVSD of 0.630 (see Figure 77).

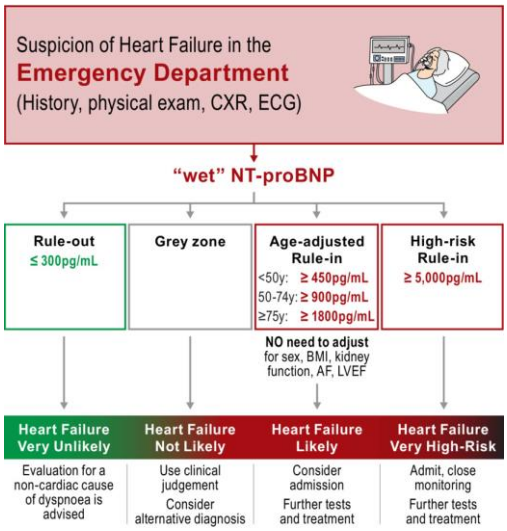


Figure 93: NT-proBNP values suggested to rule-out and rule-in heart failure for patients presenting acutely to the emergency department. Reproduced with permission from Bayes-Genis et al,[693] © John Wiley and Sons.

Regarding clinical outcomes, it was notable that the difference in mortality between those with normal and raised (> 300 pg/ml) values was more marked for measurements taken at stability 90-days post-discharge, than during ECOPD. 7 of 19 patients (36/8%) that had raised values at 90 days died by 12 months, compared with 1 out of 27 whose NT-proBNP was < 300 pg/ml at follow-up (3.8%). All but one of the deceased patients in the group with raised-NT-proBNP had a diagnosis of heart failure by the 90-day time point, although only one had moderate-severe LVSD. This is congruent with the finding that raised levels of NT-proBNP at stability are associated with higher rates of COPD exacerbation.[695] The risk increases seen in this study by Labaki were relatively modest: the incidence rate ratio was 1.13 (95% CI 1.06 – 1.19) for all patients, but 1.22 (1.01 – 1.47) for patients with known cardiovascular disease, and 1.10 (1.02 – 1.20), although the NTpro-BNP cutoff used was higher, at 900 pg/ml. Together with the data from patients who underwent structured cardiac assessment, this suggests that NT-proBNP measurement at stability might be a useful method for risk stratification of patients with COPD and comorbid heart failure.

8.2.5.5 Troponin

Troponin measurement was also less informative during exacerbation, with poor correlation between troponin levels and levels of coronary artery disease identified by coronary artery calcium scoring. This likely reflects the multiple different mechanisms by which troponin release is triggered during ECOPD, including hypoxia, tachycardia, systemic inflammation and dynamic hyperinflation (see Section 2.3.6). Previous studies have shown that troponin elevation during ECOPD predicts future mortality,[696] and there was an impression that this was the case in the SCA cohort from the results displayed in Table 73, section 7.4.3.2. However, it is the results of Campo, et al, that are most intriguing in relation to the present study of an intervention to address cardiac disease in COPD. As shown in Figure 94, amongst patients with known coronary artery disease, the proportion of patients with adverse cardiovascular events was not higher if troponin was raised during ECOPD. However, in those with no known CAD, those with raised troponin had three times the rate of adverse cardiovascular events during follow-up (15% vs 5%, p = 0.0005). Given that those with raised troponin did not seem to have more severe ECOPD, by markers of inflammation and respiratory failure, it is likely, given the underdiagnosis of heart disease in this population evidenced in Chapter 3, that many of these patients with no known CAD and raised troponin actually had unknown and therefore untreated disease. This indicates that a critical factor in determining outcome after ECOPD associated with increased troponin is identification of treatable CAD in order to provide risk-reducing therapy.

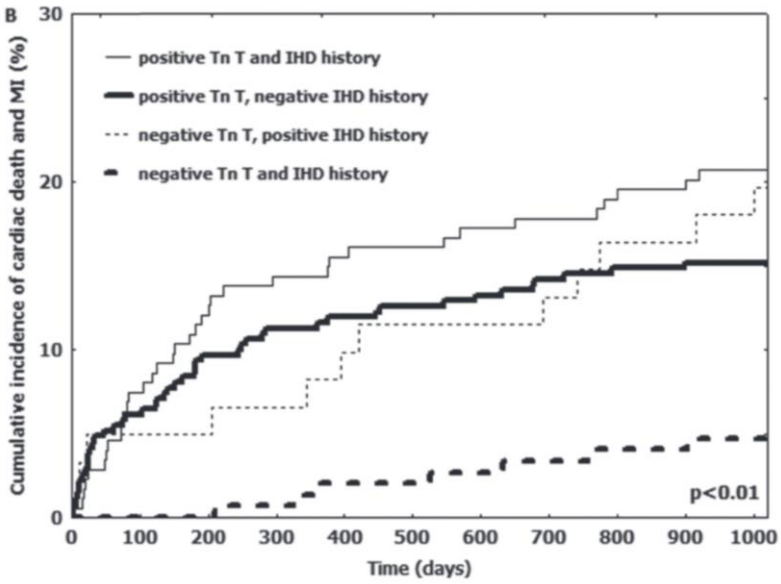


Figure 94: Cumulative incidence of cardiac death and nonfatal MI stratified according to Tn T elevation and ischaemic heart disease (IHD) history. Solid line: positive Tn T. Dotted line: negative Tn T. Thinner lines: patients with positive IHD history. Thicker lines: patients with negative IHD history. Reproduced with permission from Campo et al, 2015(698) © Taylor & Francis

The three patients that had very high troponin levels and no obstructive coronary artery disease by invasive angiography are noteworthy. None of these patients experienced an adverse cardiovascular event or died during follow-up. There is no published research on the implications of extremely high troponin levels during ECOPD without coronary artery disease, besides the recognition that obstructive airways disease increases the risk of a diagnosis of MI with non-obstructive coronary arteries (MINOCA),[(697)] and that stress cardiomyopathy has been widely reported in associated with ECOPD (this is usually associated with lower troponin levels, however).[(698)] Nevertheless, data from the SCA group suggests this scenario is not rare, as it was observed in 5.3% of cases.

8.2.5.6 Other cardiac investigations

The QRISK3 score was calculated during the process of structured cardiac assessment, with the headline finding from this process being that 96.1% of eligible patients had scores consistent with at least a 10% 10-year risk of stroke, TIA, MI or angina. This finding is in line with recently published data that updates the QRISK score to version 4 by including seven additional risk factors for men and nine for women, including COPD for both sexes (a publicly-accessible calculator is not yet available for QRISK4).[(699)] Interestingly, while COPD carried an adjusted hazard ratio for cardiovascular events of 1.37 (95% CI 1.32 - 1.41) for men, and 1.85 (1.50 – 2.29), an increased risk comparable to that seen with the other chronic conditions included in the score, 79% of patients with COPD included in

the validation cohort had a high QRISK4 score, defined as a 10% risk of the same cardiovascular diseases listed for QRISK3. This was the highest percentage for any non-cardiac condition, highlighting the extent to which cardiovascular risk in COPD relates to the co-occurrence of multiple factors besides the disease itself, including age, socioeconomic deprivation, smoking and physical and psychiatric comorbidities. Also notable was the fact that 32.9% of patients with COPD who have a low QRISK3 score were reclassified by QRISK4 as high risk; this is congruent with previous evidence that QRISK 3 underestimated the real-world risk of cardiovascular disease in patients with COPD.[700]

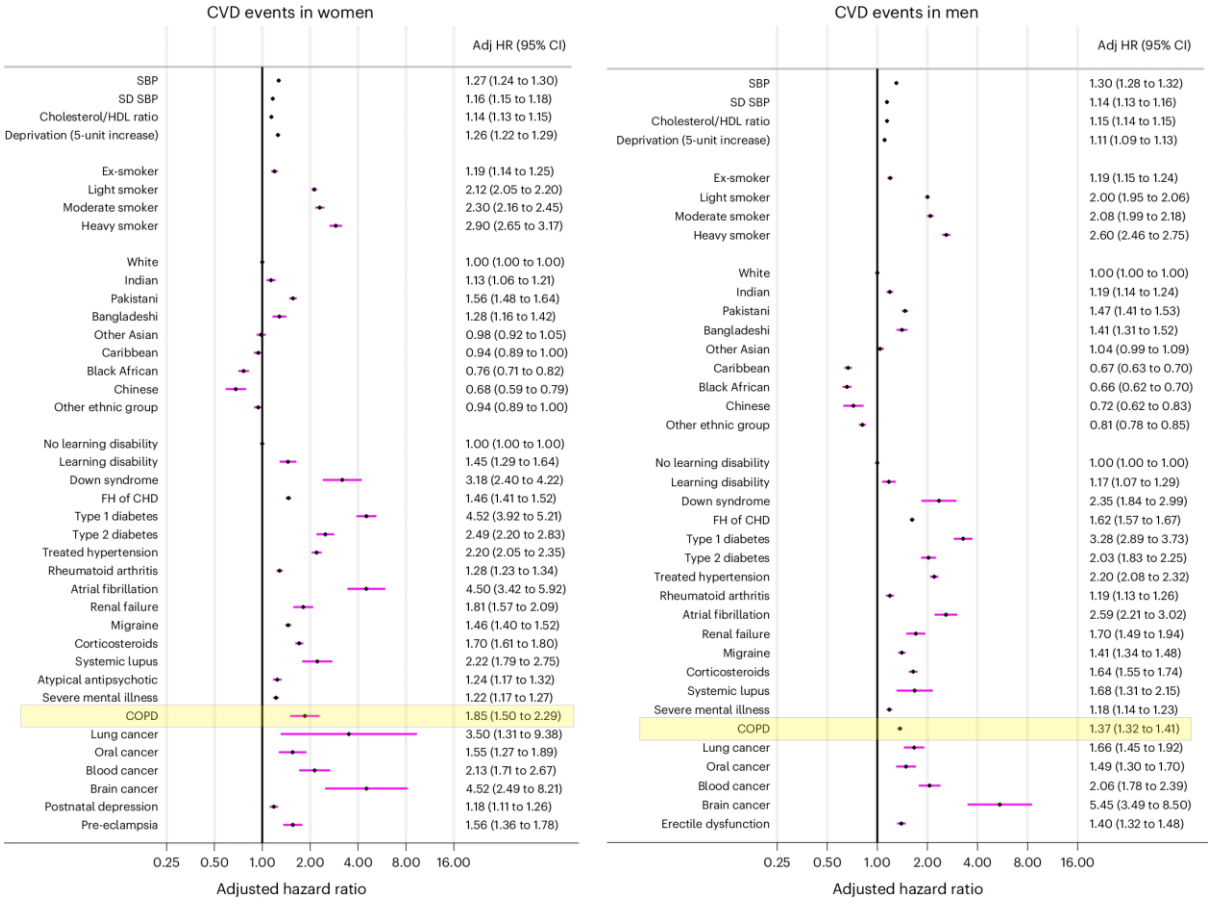


Figure 95: Adjusted hazard ratios for 10-year incidence of cardiovascular disease in 5,155,595 women and 4,820,711 men, presented at the mean age of 39 years for variables with age interactions. COPD is highlighted in both cases. Reproduced with permission from Hippisley-Cox et al.,[699] © 2024 Springer Nature Limited.

The high QRISK scores seen for the vast majority of patients with COPD imply that default prescription of statins to all with COPD would be beneficial. However, as noted in section 2.5.3, a prominent randomised controlled trial of simvastatin versus placebo was negative for its primary outcome of reducing exacerbation rates.[400] The STATCOPE study, however, excluded – in the words of the authors – patients who should have been receiving statins. In doing so, the STATCOPE

investigators accomplished a worthwhile goal: they demonstrated that statin therapy itself does not appear to have a direct effect on the pulmonary manifestations of COPD; what is clear from the SCA group, along with the QRISK4 validation cohort, is that 'the patients who should be receiving statins' are the overwhelming majority of those admitted with ECOPD. Statin therapy in COPD cannot be, based on RCT evidence, expected to preserve lung function or postpose exacerbations, but it can attenuate the excessive cardiovascular risk conferred by the nexus of risk factors described above. Improved recognition of this risk is key, and is currently lacking – a succinct demonstration of this is provided by the baseline characteristics of the ECLIPSE cohort described in section 8.2.5.1: 53% had a past history of cardiovascular disease but only 26% were taking statins.[635]

Related to QRISK3 scoring, lipid profiles were tested at exacerbation, with a high proportion of normal results conspicuous on inspection of

Figure 81, section 7.4.3.3. Given the high rates of known cardiovascular disease and adverse cardiovascular events in the population, this requires explanation. Of relevance is the fact that lipid profile changes are well documented during periods of acute illness and inflammation, with reductions in total cholesterol, HDL cholesterol and triglyceride levels potentially masking abnormalities in the stable lipid profile.[701,702] Also, importantly, statins were prescribed to 64.9% of patients at admission and were demonstrated in STATCOPE to effectively improve lipid profiles in patients with COPD.[400] Interestingly, a meta-analysis of serum lipid levels found no difference in lipid levels between patients with COPD and healthy controls, apart from for triglyceride levels, which were slightly higher in patients with COPD not taking statins.[703] Taken together, these results imply that atherosclerosis and acute adverse cardiovascular events in COPD are primarily driven by dyslipidaemia-independent processes, such as systemic inflammation and accelerated senescence.[704]

A final result for discussion relates to fibrinogen measurement. Fibrinogen has been identified as marker of COPD severity, exacerbation frequency and mortality, and has been hypothesised to be a biomarker of comorbid cardiovascular disease in COPD.[647] In keeping with the findings for NT-proBNP and troponin, fibrinogen levels during exacerbation did not appear to differ for patients who did and did not experience adverse cardiovascular events during follow-up. However, at stability, the median fibrinogen level of the 4 patients who experienced late adverse cardiovascular events was noticeably higher than for those that did not. The clear cautionary factor here is the tiny number of patients being studied, but once again the potential role of a stable state biomarker to aid cardiovascular risk stratification is suggested.

8.3 Strengths of this research

This study investigated the impact of a structured cardiovascular assessment that had several positive attributes. Firstly, it involved tests that are available in most hospitals and are all low cost. Likewise, the interventions recommended in the management summaries were predominantly inexpensive, generic drug therapies already embedded in clinical practice for supply and monitoring purposes. This means the SCA could easily be tested at multiple study centres with a range of levels of resource. Almost all patients were able to receive the investigations in a timely way, despite suffering from a severe ECOPD on the background of, in general, advanced COPD. The data obtained from the SCA investigations was of sufficient quality to enable diagnostic and therapeutic clinical decisions in the majority of cases, despite anticipated difficulties in performing cardiac tests in the setting of severe ECOPD. Lastly, there was no evidence that receiving the SCA was harmful, either through serious adverse events related to drugs started as a result of its use or patient experience: the drop-out rate from the SCA arm was the same as in the control arm.

The inclusion and exclusion criteria meant that a broad sample of patients was recruited, which closely matched the inpatient COPD populations described by large scale national audits.[615] This lends the study findings generalisability, and mitigates against the risk that any suggested effects would attenuated if tested in a larger sample size across multiple sites, a common pitfall in clinical research.[705] The importance of pragmatic randomised controlled trials, in which the study population and setting closely mirror real-world clinical practice, in directing COPD research in an increasingly patient-centred direction, has been emphasised in prominent editorials.[706,707] The SCATECOPD study could reasonably, and creditably, be described as a pragmatic RCT in the sense that it investigated the improved delivery of already-proven treatments in a highly representative population.

Regarding the study findings, it is a strength that a broad range of outcome measures were examined, given the exploratory, pilot nature of the research. It was important to gather data on DAOH, as the nature of the distribution of this variable in this population was unknown. It was discovered that even in a high-mortality, regularly readmitted population such as the one studied DAOH over 1 year is heavily left skewed, and that longer follow-up is required to yield data for which differences between groups can be more efficiently discerned. This will be valuable for the design of future trials using this outcome measure. The identification of a potential effect on adverse cardiovascular event rates, utilising robust mortality adjudication, is also advantageous for planning future research. It is consistent with the previous research findings discussed in the previous subsection, of non-effect of statins on COPD-specific outcomes such as lung function decline,[400] but

significantly higher adverse cardiovascular event rates for patients who have cardiac damage during ECOPD but no known heart disease.[708] The diagnostic rates observed in the SCA group demonstrate that a significant proportion of these patients with the label of 'no known heart disease' are better described as having 'as yet untreated heart disease' – it is in these patients that beneficial effects on cardiovascular events rates may be effected through SCA.

Regarding the economic analysis, a strength of this aspect of the research was that its design, conduct and analysis were supervised by an experienced professor of health economics. Secondly, healthcare resource use was captured precisely by synthesis of information held in primary and secondary care records with patients' reported healthcare use. This ensured that healthcare resource use that occurred out of area was captured in several cases, and that patients who had not consented for their primary care records to be visible to clinicians outside their GP practice, to contribute full healthcare resource use data.

Finally, it should be reiterated that the SCATECOPD study was a pilot randomised trial, and was therefore intended to generate hypotheses for future research. The fact that multiple avenues for further investigations are suggested by the results of the study therefore represents a success of the work: these are discussed in detail in section 8.5.

8.4 Limitations of this research

This research also possesses limitations that require discussion. Some relate to its nature as a pilot study, for example the fact that all recruitment was conducted at a single centre, which, notwithstanding the points already made in support of the generalisability of the results, inevitably introduces caution as to whether the observed effects would be seen in a multicentre trial. Also related to the pilot nature of the work is the lack of a powered sample size, which means that the type II error rate is unknown for the tests conducted between the study arms. In other words, it is not clear how likely it is that negative results for difference in, for example, DAOH, result from a real absence of a difference in these outcomes, or a lack of statistical power to detect the signal of a difference from the noise created by variance within the sample collected. A further consequence of this being a pilot study is that follow-up was relatively short, at one year. This is particularly short for a study where the primary effect transpired to be on cardiovascular outcomes, which are generally examined over follow-up periods of the order of 2-5 years.[709] This was necessary for expedient conduct of the research and timely generation of results, but may have masked effects of SCA that became manifest after 1 year.

Regarding the components of the SCA itself, the timing of the design of the management summaries was unfortunate in that it fractionally preceded the publication of research supporting the use of SGTL2-inhibitor agents, outside of diabetes treatment, for patients with heart failure without significant LVSD. Given the favourable outcomes seen with these agents in terms of cardiovascular mortality and hospitalisation,[130] as well as quality of life and exercise capacity,[710] and the prevalence within the SCA arm of heart failure without moderate-severe LVSD, their inclusion would be expected to have positively augmented the effect of the SCA.

Another aspect of the study design that requires discussion is the fact that treatment allocation was not blinded. This was not practical in a study with limited resources conducted largely by a single researcher, but has potential implications both for patients and for study conduct. For patients, knowledge of their study arm may have altered perceptions of their care, for example those in the SCA arm may have felt more confident knowing they had had additional tests they might not have otherwise had, or they may have felt more uncertain due to feeling like they were part of an experimental process with unknown effects. In terms of study conduct, unconscious bias can ensue from knowledge of an individual's study arm, particularly in assessment of subjective outcome measures. In mitigation of this, objective, patient-generated measures were used throughout in assessment of outcomes such as quality of life. Furthermore, a key subjective measure – cause of death – was adjudicated by independent clinicians who were fully blinded to treatment allocation, improving the robustness of this outcome measure to the unblinded nature of the study.

The nature of the population recruited was discussed in detail above, and the fact that broad inclusion criteria led to the recruitment of a cohort with real-world validity was advanced as a strength of the research. However, it must be recognised that the SCA was an intervention that involved multi-modality investigation and inevitable exacerbation of polypharmacy for the patients who received it. There comes a point in an individual patient's deterioration from a life-limiting, progressive chronic disease such as COPD where interventions of this intensity become inappropriate. This was acknowledged by the inclusion of a life expectancy under 1 year for non-COPD reasons in the exclusion criteria, but this a is challenging judgement to make outside of metastatic malignancy.[711] It may be that, perhaps influenced by the time period during which study recruitment took place (see section 8.2.2.1), an overabundance of patients were recruited that had passed the point where, for them, receiving SCA and its downstream consequences resulted in as many negative impacts on outcome and quality of life as it did benefits. A finding that supports this is the fact that 20 of 107 (18.7%) patients who were offered 90-day follow-up did not attend this to some extent due to fatigue and general ill health.

Inspection of the length of stay data for the two arms reveals that patients undergoing SCA had a median length of stay of 6 days, versus 4 days for those in usual care. The interquartile ranges were very similar (3-8 for SCA; 3-9 for usual care) and p-value for difference 0.553. Nevertheless, vigilance is required against the possibility that SCA resulted in prolonged admissions due to the introduction of additional complexity into patients' care, for example through the introduction of new medications. Also related to the inpatient time course, it should be highlighted that, in some cases, coronary artery calcium score was not available prior to patient discharge, thereby delaying prescription of aspirin until after the highest-risk post-exacerbation period for adverse cardiovascular events. This could represent a limitation of SCA, particularly if expanded to centres without ready access to specialist radiology and cardiology services. This issue could be addressed by introduction of automated image analysis, which has been shown to produced CAC scores that have high levels of agreement with those generated by expert cardiac CT readers.[712]

Limitations of the economic analysis were discussed in detail in section 8.2.4. These included a very high degree of variance for costs, partly accounted for by the existence of outliers in both arms, and laborious data collection in order to ensure precise measurement of costs. It was also noted that the regular recording of health states with a negative utility index to patients may not have accurately represented subjective quality of life judgments, and potentially biased conclusions about change in quality of life when health status 'improved' due to death.

8.5 Implications for future research

8.5.1 Future research relating to SCA

8.5.1.2 A multicentre RCT comparing SCA and usual care following admission with ECOPD

Chief among the research directions suggested by the study findings discussed in this chapter is the evaluation of the effect of SCA delivered during admission with ECOPD in a multicentre RCT, with ACE as a primary outcome. Based on the hazard ratio for this outcome observed, a sample size of 528 patients would be required to adequately power such a study if the follow-up period were extended to two years, in line with other trials using cardiovascular events as an outcome.

Lessons from the results of the SCATECOPD study should be applied to the design of such a trial, to ensure its findings would be robust and to maximise the efficacy of the intervention. Firstly, it would be logical to expand the definition of ACE to include heart failure hospitalisations, given the high rates of undiagnosed heart failure identified and treated among patients who underwent SCA. The

intervention itself should also be updated based upon the latest research; at a minimum this should include integration of SGLT2-inhibitor agents into management summaries to guide treatment of heart failure without moderate-severe LVSD.

The method of identifying coronary artery disease should also be considered. In this pilot study, coronary artery calcium scoring was used, due to low cost, low radiation exposure, lack of need to for intravenous contrast and anticipated rapidity of reporting. However, as noted above in section 8.2.5.1, CTCA has the potential to more accurately identify coronary artery disease associated with critical arterial obstruction, enabling better targeting of antiplatelet therapy. This approach was successful in halving adverse cardiovascular outcome in patients without COPD with non-anginal chest pain, of which 9.5% had obstructive CAD.[713] Investigation of patients with COPD was higher yield than this, with 28% having severe stenosis.[685] This counters concerns that truly obstructive CAD would be a rare finding in the population, in comparison to non-obstructive vessel wall calcification. Moreover, the cost increase with CTCA is relatively modest: CTCA was quoted at £195 in a recent RCT, compared with a cost of £69 used in the economic analysis of this pilot study.[714] The rate of complications also appears low: in an RCT in which 1793 patients underwent CTCA, with the only major exclusion criteria being receipt of haemodialysis and absence of sinus rhythm, only one complication was reported (bradycardia).[715] Use of CTCA might also better target the use of invasive coronary angiography and percutaneous coronary intervention: as noted in section 8.2.5.5, 5.3% of patients underwent this procedure on the basis of very high troponin, but with a negative outcome – it is therefore already being carried out, but needs to be deployed with greater accuracy.

Also requiring consideration are the optimal inclusion and exclusion criteria. As discussed in section 8.2.2, the population recruited in the pilot study was characterised by high levels of frailty and overall comorbidity, and some patients were recruited for whom an increase in the intensity and complexity of their healthcare was probably inappropriate given their overall health status and life expectancy. However, broad inclusion criteria are necessary for generalisability and also ethical, fair access to treatment. A trial design that involves the inclusion of a patient decision that, if randomised to SCA, they could opt for the lower-intensity option of usual care (with an intention-to treat analysis of the primary outcome) may be worth exploring. The specifics of such a trial design should be guided by input of patients with COPD themselves, through well-conducted patient and public involvement.

Finally, qualitative research into the experience of patients in both arms of the trial would be valuable. This could explore the validity of some of the suggested explanations for results seen in this pilot study, for example that patients' health seeking behaviour may have been altered by

increased diagnoses given to them as a result of SCA. It could also improve insight into the experiences of patients with negative EQ-5D-5L scores and test the implication that, for these patients, dying represented an improvement in quality of life.

8.5.1.3 An RCT of SCA carried out in primary care

Several findings of this pilot study suggest that there would be benefit in conducting structured cardiac assessment in an outpatient setting. Firstly, over 20% of patients had already experienced an adverse cardiovascular event prior to recruitment, signifying previously missed opportunities to intervene to reduce cardiac risk. Furthermore, 7.7% of patients in SCA invited to return to hospital for repeat echocardiography declined to do so, indicating a preference for community treatment. Lastly, mid-exacerbation findings such as elevated biomarkers and ventricular dysfunction, had often resolved by the point of stability, when any persistent abnormalities appeared to have greater prognostic significance.

The pragmatic RCT mentioned in section 8.2.1.1, TargetCOPD, provides an apposite model for a study of this nature: here, active case and opportunistic case finding for COPD took place in 27 GP practices, while in 27 control practices usual practice continued – see the CONSORT diagram, Figure 96. The active approach identified approximately 4 times as many cases of COPD as usual practice, and was more cost-effective than this approach, as well as opportunistic case finding.[650] The results of the SCATECOPD pilot detailed above suggest positive results would be obtained from comparable study, in which patients with known COPD registered at randomly selected practices are invited for a community-based structured cardiac assessment, and diagnostic rates and outcomes compared with those at control practices using traditional symptoms and signs based diagnosis.

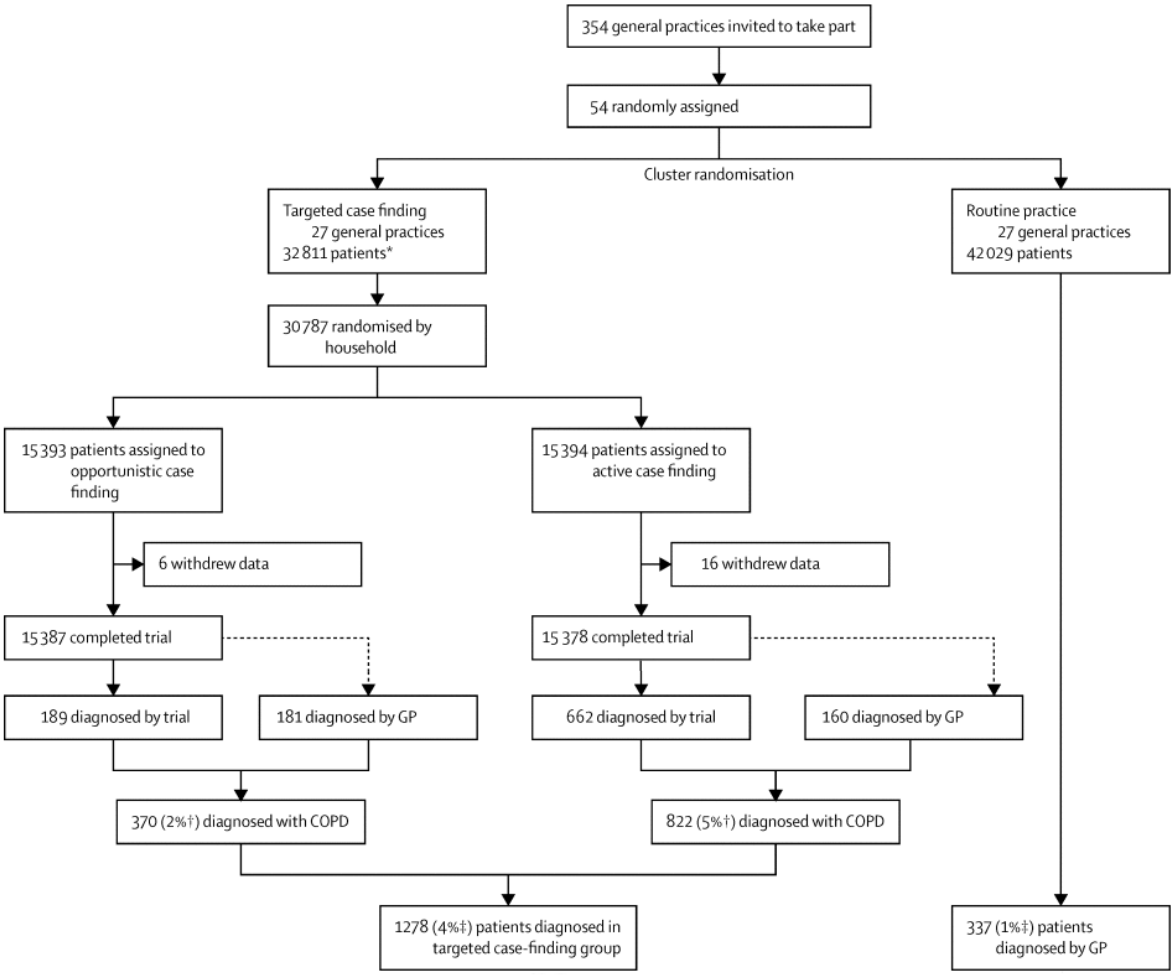


Figure 96: TargetCOPD trial profile, showing that active case finding resulted in a higher proportion of spirometrically-confirmed COPD diagnoses than opportunistic case finding or diagnosis resulting from standard GP practice. Adapted with permission from Jordan, et al.[650] © Elsevier Ltd.

The SCA would need to be adapted for use in the community, and it is likely that an algorithmic approach that selects patients for the most intensive investigation would be required. Use of NT-proBNP to select patients for echocardiography would be logical, and results from this pilot suggest it would more accurate in this setting than during ECOPD. Likewise, cardiovascular risk scoring could select for investigation for coronary artery disease. The implementation of NHS community diagnostic centres, initiated in 2021 and now numbering over 165, widens access to these investigations and represents an opportunity to provide diagnostic tests to patients who would be less willing to attend hospital. Ultimately, the design of such a study would be best founded on a reliable method of quantifying cardiopulmonary risk: this currently remains an unanswered research question,[716] although potential components of such a risk assessment are suggested by the findings of this pilot study (see section 8.5.2 below).

In both inpatient and community-initiated trials of SCA, robust economic analysis will be needed to assess the effects of the intervention on healthcare costs and quality of life. Again, findings from this pilot study inform the optimal conduct of this. The method of assessing quality of life should be considered, with the assignment of negative health status scores questioned, given the discordance between the implication that these states are worse than death, and the subjective descriptions of quality of life by patients experiencing them. It has even been argued that this practice is unethical[717] – given that the scenario of negative health status is at least not rare (occurring 1 in 20 times quality of life was assessed in this pilot study), its handling should be specifically planned for. Additionally, a prospective method for handling outlying results should be generated to limit the breadth of confidence intervals for costs and QALYs, as discussed in section 8.2.4.

8.5.2 Future research relating to heart disease and COPD

Besides specific research into the benefits and cost-effectiveness and best implementation of SCA, additional avenues for future research as suggested the results of this pilot study, taken in the context of the existing literature in the field of heart disease associated with COPD.

8.2.5.1 Cardiopulmonary risk quantification

It has been a key conclusion of this pilot study that relying on the detection of symptoms or signs suggestive of heart disease is an inadequate diagnostic strategy in patients with COPD, and that active case finding based on individual cardiac disease risk must instead become the standard. The need to risk stratify patients for the most intensive investigations stems from the resource implications that would be associated with offering a full battery of cardiac tests to every patient with COPD: this would overwhelm services and have a very low chance of being cost effective. However, because the best method by which to risk stratify patients is as yet unknown, this represents an area where further research could greatly benefit patients with COPD as well as COPD care providers. A cardiopulmonary risk score would need to strike a balance between usability and accuracy, while using the minimum possible healthcare resources. Ideally, it would be possible to complete the assessments required for scoring in a single patient encounter, given the documented prevalence of low health literacy – 59% in a Spanish cross-sectional study - amongst patients with COPD, and the association of this attribute with lower uptake of preventative healthcare in preference to emergency services.[718]

Components of a cardiopulmonary risk score could be derived from a retrospective cohort study: variables independently associated with adverse cardiovascular outcomes would be combined to

create a novel scoring system, which could then be validated separately. This would rely on clinical data already gathered in the course of standard care, with variables such as age, spirometric COPD severity and exacerbation frequency likely to be included, along with blood eosinophil count, increasingly recognised as a biomarker for cardiovascular disease,[719] and QRISK4 score. However, data from the SCATECOPD study suggest that additional variables, including NT-proBNP, troponin and fibrinogen levels, which are less commonly collected, may also be associated with increased risk when abnormal during COPD stability. Therefore, a longitudinal study that involves measurement of these variables, while more resource intensive, could be expected to produce a risk assessment strategy with greater discriminatory power. Additionally, although less practical due to the prolonged nature of the test, 24-hour ECG recording with measurement of ectopic burden could also be added to the assessment, as there was a signal that this was associated with adverse outcomes in the SCATECOPD study.

8.2.5.2 Cardiac function changes during and after ECOPD

Several intriguing findings emerged from the analysis of echocardiography performed during exacerbation and at stability. However, significant caution needed to be attached to any conclusions drawn, for three principal reasons: firstly, numbers involved were very small, particularly when the cohort was subdivided, e.g. into those with persistent and reversible RV dysfunction; secondly, most patients with moderate-severe LVSD received new or intensified treatment that is associated with LVEF improvement, obscuring the extent to which LV dysfunction reversed spontaneously on recovery from ECOPD; and thirdly, a large number of patients either died or dropped out, meaning the trajectory of their cardiac function changes remained unknown. It would be possible to mitigate the first two challenges by recruiting greater numbers, to allow for subgroup and regression analyses, and the third by selecting a cohort with fewer traits associated with high mortality, such as severely limiting breathlessness, severe frailty and multiple recent admissions.

A larger study involving cardiac functional assessment at exacerbation and stability would be valuable in furthering understanding of what factors relating to background COPD and acute exacerbations lead to cardiac dysfunction. This could guide holistic exacerbation management in the future, by aiding identification of the patients at highest risk of heart failure, and suggesting how to target interventions to reduce cardiac dysfunction and risk of adverse events. For example, such a study could further illuminate why it was that patients with markers of pulmonary hypertension – such as increased PA:A and right ventricular dysfunction, did not experience worse outcomes in terms of readmissions, when these findings have previously been observed to be associated with

higher admission rates. If either the influence of treatment of concomitant left heart disease or the predominance of different COPD subtypes in those with and without signs of right sided cardiac dysfunction were found to be significant, this would have important implications for treatment during and after ECOPD. More accurate methods of non-invasively assessing pulmonary artery pressure could be used in such a study, based on data from the IMPULSE study that revealed that 36% of patients with low echocardiographic probability of pulmonary hypertension actually have significantly elevated pulmonary artery pressures on right heart catheterisation (with the most common cause being left heart disease).[587] An algorithm incorporating RV free wall longitudinal strain and RV isovolumetric relaxation time by tissue Doppler imaging reduced false negatives in these patients by 44%.

Finally, the finding in this pilot study that approximately 5% of patients admitted with ECOPD had very high troponin levels (>300) and negative angiography represents a knowledge gap: it is not clear what the mechanism of troponin release was in these patients, and how they should best be investigated and managed. In an observational study of the relationship between troponin level and adverse cardiovascular events in the year after ECOPD, hazard ratios rose linearly with the log-transformed peak troponin level, up to a point between 50 and 100x the upper limit of normal, after which the hazard ratio fell back below 1 (see Figure 97).[720] This implies an alternative pathological process, that could be better characterised by a larger dataset that includes analysis of other clinical variables at the time of ECOPD, along with post-discharge outcomes.

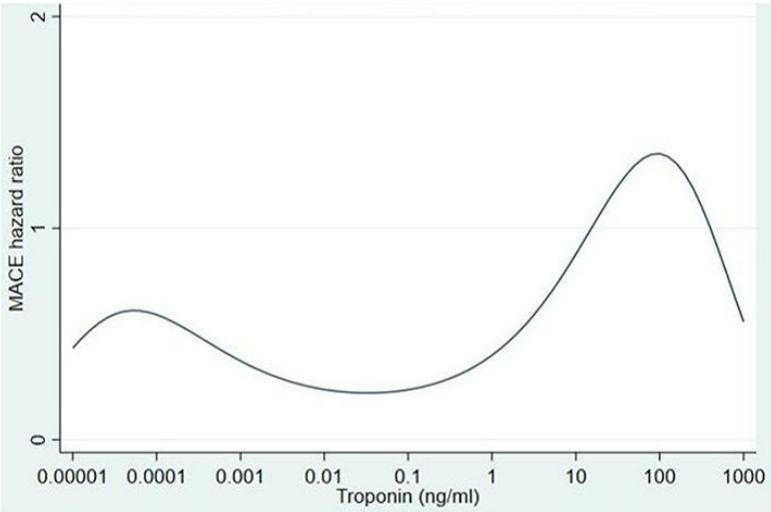


Figure 97: Predicted adjusted hazard ratio for ACE following admission for ECOPD. The X-axis is a logarithmic plot of the highest troponin level recording during admission, divided by the upper limit of normal to create a standardised troponin value that allows for differing troponin assays. Reproduced with permission from Kallis, et al[720] © Dove Medical Press Ltd.

8.6 Final conclusions

Patients with COPD suffer from an excess burden of heart disease. Their treating clinicians are often unaware of comorbid CVD, with systematic review and meta-analysis indicating that 10-20% of patients admitted with ECOPD having undiagnosed left ventricular systolic dysfunction. Underdiagnosis likely arises because COPD guidelines advocate investigating for heart disease if symptoms and signs are present, but this approach is evidently not accurate in this population. Even when heart disease is recognised, it is often not treated as comprehensively as it is patients who do not have COPD.

COPD exacerbations are a pivotal moment when risk of adverse cardiovascular events is highest. In a pilot study, patients hospitalised with ECOPD were randomised to receive a structured cardiovascular assessment designed to diagnose heart disease and prompt its appropriate treatment. The key findings were:

- The proportion of patients diagnosed with heart disease was significantly increased in the SCA group.
- The number of patients who received evidence-based treatment was significantly higher in the SCA group
- The frequency of adverse cardiovascular events emerged as the most suitable primary outcome for a definitive trial of the efficacy of structured cardiac assessment and treatment following ECOPD. The total sample size required to adequately power a study using this outcome, with two years of follow-up, would be 528.

Several other research directions are suggested by the findings of the pilot study, including a trial of structured cardiac assessment delivered in the outpatient setting, the derivation of an accurate method of predicting cardiopulmonary risk, and further observational work to understand the mechanisms by which both cardiac dysfunction and adverse event risk are increased during ECOPD.

Appendix A: Publications, presentations and prizes from this research

ERS Congress 2022

Undiagnosed and undertreated heart disease in hospitalised patients with exacerbations of chronic obstructive pulmonary disease (COPD)

J Kibbler, D P Ripley, S C Bourke, J Steer

Poster presentation; Barcelona, Spain, September 2022

BTS Winter Meeting 2022

P216 Effect of structured cardiac assessment on survival without readmission after hospitalisation with exacerbation of chronic obstructive pulmonary disease (COPD)

JCT Kibbler, DP Ripley, SC Bourke, J Steer

Poster presentation, London, November 2022

Sir John Halliday Croom Lecture 2023

COPD: Changing hearts and minds

Delivered at the Royal College of Physicians, Edinburgh, 3rd February 2023

ERS Congress 2023

Rigorous cardiac assessment helps clarify causes of recurrent admission in patients with COPD

Joseph Kibbler, Eduwin Pakpahan, Arun Prasad, David P Ripley, Stephen C Bourke, John Steer

Poster presentation, Milan, Italy

BTS Winter Meeting 2023

S87 Prevalence, persistence and outcomes of left ventricular (LV) and right ventricular (RV) dysfunction in patients admitted with exacerbation of chronic obstruction pulmonary disease (ECOPD)

JCT Kibbler, R Webb-Mitchell, E Pakpahan, DP Ripley, SC Bourke, J Steer

Spoken session, London, November 2023

ERJ Open Research

Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD

Joseph Kibbler, Clare Wade, Grace Mussell, David P. Ripley, Stephen C. Bourke, John Steer

Journal article, published November 2023

Biomedicines

Structured Cardiac Assessment and Treatment Following Exacerbations of COPD (SCATECOPD): A Pilot Randomised Controlled Trial

Joseph Kibbler, Eduwin Pakpahan, Stephen McCarthy, Rebecca Webb-Mitchell, Arun Prasad, David P. Ripley, Joanne Gray, Stephen C. Bourke and John Steer

Journal article, published March 2025

Appendix B: Search terms and additional data tables from systematic review and meta analysis (Chapter 3)

Searches performed 7th April 2021

MEDLINE (HF):

1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
4. "obstructive lung disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
9. "obstructive airway* disease".mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp heart failure/ or heart failure, diastolic/ or heart failure, systolic/
13. "heart failure".mp.
14. "cardiac failure".mp.
15. ccf.mp.
16. "systolic failure".mp.
17. "systolic dysfunction".mp.
18. exp ventricular dysfunction/ or ventricular dysfunction, left/
19. lvsd.mp.
20. lvsf.mp.
21. diastolic failure.mp.
22. diastolic dysfunction.mp.
23. hfref.mp.
24. hfpef.mp.
25. hfmref.mp.
26. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp Echocardiography/
28. echocardiogra*.mp.
29. echo.mp.
30. exp Radionuclide Ventriculography/
31. ventriculogra*.mp.
32. exp cardiac imaging techniques/ or exp cardiac-gated imaging techniques/ or cardiac-gated single-photon emission computer-assisted tomography/ or gated blood-pool imaging/ or tomography, x-ray computed/
33. computed tomogra*.mp.
34. CT.mp.
35. magnetic resonance.mp.

36. exp cardiac imaging techniques/ or exp myocardial perfusion imaging/ or exp magnetic resonance imaging/ or exp magnetic resonance angiography/ or exp diagnostic techniques, cardiovascular/ or exp heart function tests/ or magnetic resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/
37. mri.mp.
38. brain natriuretic peptide.mp. or Natriuretic Peptide, Brain/
39. bnp.mp.
40. exp tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
41. ("single photon emission computed tomography" or spect).mp.
42. exp Positron-Emission Tomography/
43. ("positron emission tomography" or pet).mp.
44. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 11 and 26 and 44
46. limit 45 to (yr="1980 -Current" and english)

MEDLINE (CAD):

1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
4. "obstructive lung disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
9. "obstructive airway* disease".mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp coronary disease/ or exp coronary artery disease/ or coronary occlusion/ or coronary stenosis/ or coronary thrombosis/
13. "coronary artery disease".mp.
14. exp myocardial ischemia/ or exp acute coronary syndrome/ or exp angina pectoris/ or exp myocardial infarction/
15. "isch*emic heart disease".mp.
16. "isch*emic cardiac disease".mp.
17. "coronary heart disease".mp.
18. "myocardial infarct*".mp.
19. "cardiac infarct*".mp.
20. "acute coronary syndrome".mp.
21. Angina, Stable/ or angina.mp. or exp Angina Pectoris/ or Angina, Unstable/
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. angiocardiography/ or exp coronary angiography/
24. "coronary angiogra*".mp.
25. exp Electrocardiography/
26. electrocardiogra*.mp.

27. ecg.mp.
28. ekg.mp.
29. exp echocardiography/ or exp echocardiography, stress/
30. echocardiogra*.mp.
31. echo.mp.
32. exp cardiac imaging techniques/ or exp cardiac-gated imaging techniques/ or cardiac-gated single-photon emission computer-assisted tomography/ or gated blood-pool imaging/ or tomography, x-ray computed/
33. "computed tomography".mp.
34. ct.mp.
35. exp cardiac imaging techniques/ or exp myocardial perfusion imaging/ or exp magnetic resonance imaging/ or exp magnetic resonance angiography/ or exp diagnostic techniques, cardiovascular/ or exp heart function tests/ or magnetic resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/
36. troponin.mp. or exp Troponin/
37. exp tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
38. ("single photon emission computed tomography" or spect).mp.
39. exp Positron-Emission Tomography/
40. ("positron emission tomography" or pet).mp.
41. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 11 and 22 and 41
43. limit 42 to (yr="1980 -Current" and english)

MEDLINE (AF):

1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
4. "obstructive lung disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
9. "obstructive airway* disease".mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. "atrial fibrillation".mp. or exp Atrial Fibrillation/
13. exp Atrial Flutter/
14. "atrial flutter".mp.
15. "atrial arrhythmia*".mp.
16. "supraventricular arrhythmia*".mp.
17. 12 or 13 or 14 or 15 or 16
18. exp Electrocardiography/
19. electrocardiogra*.mp.
20. ecg.mp.

21. ekg.mp.
22. exp Pacemaker, Artificial/ or pacemaker.mp. or exp Cardiac Pacing, Artificial/
23. exp Electrocardiography, Ambulatory/
24. holter.mp.
25. exp monitoring, ambulatory/ or exp telemetry/
26. "cardiac monitor*".mp.
27. "heart monitor*".mp.
28. defibrillator.mp.
29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 11 and 17 and 29
31. limit 30 to (yr="1980 -Current" and english)

Embase (HF):
1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. chronic bronchitis.mp.
8. "obstructive airway* disease".mp.
9. "chronic airway* obstruction".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp heart failure/
13. ("heart failure" or "cardiac failure").mp.
14. exp systolic heart failure/ or exp heart failure with reduced ejection fraction/
15. ("systolic heart failure" or "systolic cardiac failure").mp.
16. exp congestive heart failure/
17. ("congestive cardiac failure" or "congestive heart failure" or ccf).mp.
18. exp diastolic dysfunction/ or exp diastolic heart failure/ or exp heart failure with preserved ejection fraction/
19. ("diastolic dysfunction" or "diastolic heart failure" or "diastolic cardiac failure" or "diastolic failure" or "heart failure with preserved ejection fraction" or "hfpef").mp.
20. ("heart failure with medium range ejection fraction" or hfmref).mp.
21. exp left ventricular systolic dysfunction/ or exp heart left ventricle failure/
22. ("left ventricular systolic dysfunction" or "left ventricular systolic failure" or lvsd or lvsf).mp.
23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. exp echocardiography/ or exp contrast echocardiography/ or exp doppler echocardiography/
25. (echocardiogra* or echo).mp.
26. exp heart ventriculography/
27. exp radionuclide ventriculography/ or exp heart scintiscanning/
28. ventriculogra*.mp.
29. exp computer assisted tomography/
30. ("computed tomography" or ct).mp.
31. exp single photon emission computed tomography/
32. ("single photo emission compute* tomography" or spect).mp.

33. exp positron emission tomography/
34. ("positron emission tomography" or pet).mp.
35. exp nuclear magnetic resonance imaging/ or exp cardiovascular magnetic resonance/
36. ("magnetic resonance imaging" or mri or "cardiovascular magnetic resonance" or cmr).mp.
37. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 11 and 23 and 37
39. limit 38 to (english and yr="1980 -Current")

Embase (CAD):
1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. chronic bronchitis.mp.
8. "obstructive airway* disease".mp.
9. "chronic airway* obstruction".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp coronary artery disease/ or exp coronary artery atherosclerosis/ or exp coronary artery calcification/ or exp coronary artery obstruction/ or coronary artery occlusion/ or exp coronary artery thrombosis/
13. exp ischemic heart disease/ or exp ischemic cardiomyopathy/ or exp silent myocardial ischemia/
14. ("isch*emic heart disease" or "isch*emic cardiac disease").mp.
15. ("coronary arter*" or "coronary heart disease").mp.
16. exp heart infarction/
17. ("myocardial infarct*" or "cardiac infarct" or mi).mp.
18. exp acute coronary syndrome/
19. ("acute coronary syndrome" or acs).mp.
20. exp angina pectoris/
21. angina.mp.
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp echocardiography/ or exp doppler echocardiography/ or exp stress echocardiography/
24. (echocardiogra* or echo).mp.
25. exp computer assisted tomography/
26. ("computed tomography" or ct).mp.
27. exp single photon emission computed tomography/
28. ("single photo emission compute* tomography" or spect or "myocardial perfusion imaging" or mpi).mp.
29. exp positron emission tomography/
30. ("positron emission tomography" or pet).mp.
31. exp nuclear magnetic resonance imaging/ or exp cardiovascular magnetic resonance/
32. ("magnetic resonance imaging" or mri or "cardiovascular magnetic resonance" or cmr).mp.
33. exp coronary angiography/
34. coronary angiogra*.mp.
35. exp computed tomographic angiography/

36. exp electrocardiography/
37. (electrocardiogra* or ecg or ekg).mp.
38. troponin.mp. or exp troponin/
39. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 11 and 22 and 39
41. limit 40 to (english and yr="1980 -Current")

Embase (AF):

1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. "chronic bronchitis".mp.
8. "obstructive airway* disease".mp.
9. "chronic airway* obstruction".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp atrial fibrillation/ or exp heart atrium arrhythmia/ or exp paroxysmal atrial fibrillation/
13. ("atrial fibrillation" or af).mp.
14. "atrial flutter".mp. or exp heart atrium flutter/
15. "atrial arrhythmia*".mp. or exp heart atrium arrhythmia/
16. exp heart supraventricular arrhythmia/ or "supraventricular arrhythmia*".mp.
17. 12 or 13 or 14 or 15 or 16
18. exp electrocardiography/
19. (electrocardiogra* or ecg or ekg).mp.
20. exp ambulatory electrocardiography/ or exp electrocardiography monitoring/ or exp holter monitoring/
21. ("cardiac monitor*" or "heart monitor*" or holter or "ambulatory electrocardiography" or "ambulatory ecg").mp.
22. pacemaker.mp. or exp cardiac rhythm management device/
23. exp defibrillator/ or defibrillator.mp.
24. 18 or 19 or 20 or 21 or 22 or 23
25. 11 and 17 and 24
26. limit 25 to (english and yr="1980 -Current")

Scopus (HF): (TITLE-ABS-KEY((chronic obstructive pulmonary disease)) OR TITLE-ABS-KEY(copd) OR TITLE-ABS-KEY((obstructive lung disease)) OR TITLE-ABS-KEY(coad) OR TITLE-ABS-KEY((chronic airflow obstruction)) OR TITLE-ABS-KEY((chronic bronchitis)) OR TITLE-ABS-KEY(emphysema) OR TITLE-ABS-KEY((obstructive airway* disease)) OR TITLE-ABS-KEY((chronic airway* obstruction))) AND (TITLE-ABS-KEY((heart failure)) OR TITLE-ABS-KEY((cardiac failure)) OR TITLE-ABS-KEY(ccf) OR TITLE-ABS-KEY((systolic failure)) OR TITLE-ABS-KEY((systolic dysfunction)) OR TITLE-ABS-KEY(lvsd) OR TITLE-ABS-KEY(lvsf) OR TITLE-ABS-KEY((diastolic failure)) OR TITLE-ABS-KEY((diastolic dysfunction)) OR TITLE-ABS-KEY(HFrEF) OR TITLE-ABS-KEY(HFpEF) OR TITLE-ABS-KEY(HFmrEF)) AND (TITLE-ABS-KEY(echocardigra*) OR TITLE-ABS-KEY(echo) OR TITLE-ABS-KEY(ventriculogra*) OR TITLE-ABS-

KEY((computed tomography)) OR TITLE-ABS-KEY(CT) OR TITLE-ABS-KEY((magnetic resonance)) OR TITLE-ABS-KEY(CMR) OR TITLE-ABS-KEY(MRI) OR TITLE-ABS-KEY((Brain natriuretic peptide)) OR TITLE-ABS-KEY(BNP) OR TITLE-ABS-KEY((single photon emission computed tomography)) OR TITLE-ABS-KEY(SPECT) OR TITLE-ABS-KEY((positron emission tomography)) OR TITLE-ABS-KEY(PET)) AND (PUBYEAR > 1980) AND (LIMIT-TO (LANGUAGE,"English"))

Scopus (CAD): (TITLE-ABS-KEY((chronic obstructive pulmonary disease)) OR TITLE-ABS-KEY(copd) OR TITLE-ABS-KEY((obstructive lung disease)) OR TITLE-ABS-KEY(coad) OR TITLE-ABS-KEY((chronic airflow obstruction)) OR TITLE-ABS-KEY((chronic bronchitis)) OR TITLE-ABS-KEY(emphysema) OR TITLE-ABS-KEY((obstructive airway* disease)) OR TITLE-ABS-KEY((chronic airway* obstruction))) AND (TITLE-ABS-KEY((coronary artery disease)) OR TITLE-ABS-KEY((isch*emic heart disease)) OR TITLE-ABS-KEY((isch*emic cardiac disease)) OR TITLE-ABS-KEY((coronary heart disease)) OR TITLE-ABS-KEY((myocardial infarct*)) OR TITLE-ABS-KEY(MI) OR TITLE-ABS-KEY((cardiac infarct*)) OR TITLE-ABS-KEY((acute coronary syndrome)) OR TITLE-ABS-KEY((coronary artery)) OR TITLE-ABS-KEY(angina)) AND (TITLE-ABS-KEY((coronary angiogra*)) OR TITLE-ABS-KEY(ecg) OR TITLE-ABS-KEY(ekg) OR TITLE-ABS-KEY(electrocardiogra*) OR TITLE-ABS-KEY(echocardigra*) OR TITLE-ABS-KEY(echo) OR TITLE-ABS-KEY((computed tomography)) OR TITLE-ABS-KEY(CT) OR TITLE-ABS-KEY((magnetic resonance)) OR TITLE-ABS-KEY(CMR) OR TITLE-ABS-KEY(MRI) OR TITLE-ABS-KEY(troponin) OR TITLE-ABS-KEY((single photon emission computed tomography)) OR TITLE-ABS-KEY(SPECT) OR TITLE-ABS-KEY((positron emission tomography)) OR TITLE-ABS-KEY(PET) OR TITLE-ABS-KEY((myocardial perfusion imaging)) OR TITLE-ABS-KEY(MPI)) AND (PUBYEAR > 1980) AND (LIMIT-TO (LANGUAGE,"English"))

Scopus (AF): (TITLE-ABS-KEY((chronic obstructive pulmonary disease)) OR TITLE-ABS-KEY(copd) OR TITLE-ABS-KEY((obstructive lung disease)) OR TITLE-ABS-KEY(coad) OR TITLE-ABS-KEY((chronic airflow obstruction)) OR TITLE-ABS-KEY((chronic bronchitis)) OR TITLE-ABS-KEY(emphysema) OR TITLE-ABS-KEY((obstructive airway* disease)) OR TITLE-ABS-KEY((chronic airway* obstruction))) AND (TITLE-ABS-KEY((atrial fibrillation)) OR TITLE-ABS-KEY (af) OR TITLE-ABS-KEY((atrial flutter)) OR TITLE-ABS-KEY((atrial arrhythmia*)) OR TITLE-ABS-KEY((supraventricular arrhythmia*))) AND (TITLE-ABS-KEY((electrocardiogra*)) OR TITLE-ABS-KEY(ECG) OR TITLE-ABS-KEY(EKG) OR TITLE-ABS-KEY(Holter) OR TITLE-ABS-KEY(pacemaker) OR TITLE-ABS-KEY(defibrillator) OR TITLE-ABS-KEY((cardiac monitor*)) OR TITLE-ABS-KEY((heart monitor*))) AND (PUBYEAR > 1980) AND (LIMIT-TO (LANGUAGE,"English"))

Web of Science (HF):
ALL=(“chronic obstructive pulmonary disease” OR copd OR “chronic obstructive lung disease*” OR co ad OR “chronic airflow obstruction” OR “chronic bronchitis” OR emphysema OR “obstructive lung dis ease*” OR “obstructive airway* disease*” OR “chronic obstructive airway* disease*” OR “chronic air way* obstruction”) AND ALL=(“heart failure” OR “cardiac failure” OR ccf OR “systolic failure” OR “syst olic dysfunction” OR lvsd OR lvsf OR “diastolic failure” OR “diastolic dysfunction” OR HFrEF OR HFpEF OR HFmrEF) AND ALL=(echocardiogra* OR echo OR ventriculogram* OR “computed tomography” OR CT OR “magnetic resonance” OR CMR OR MRI OR “brain natriuretic peptide” OR BNP OR SPECT OR “single photon emission computed tomography” OR PET or “positron emission

tomography") AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021

Web of Science (CAD): (ALL=("chronic obstructive pulmonary disease" OR copd OR "chronic obstructive lung disease*" OR coad OR "chronic airflow obstruction" OR "chronic bronchitis" OR emphysema OR "obstructive lung disease*" OR "obstructive airway* disease*" OR "chronic obstructive airway* disease*" OR "chronic airway* obstruction") AND ALL=("coronary artery disease" OR isch*emic heart disease OR "isch*emic cardiac disease" OR "coronary heart disease" OR "myocardial infarct*" OR "cardiac infarct*" OR "acute coronary syndrome" OR angina) AND ALL=("coronary angiogram*" OR ecg OR electrocardiagra* OR echocardiagra* OR echo OR "computed tomography" OR ct OR "magnetic resonance" OR CMR OR MRI OR troponin OR SPECT OR "single photon emission computed tomography" OR PET or "positron emission tomography" OR "myocardial perfusion imaging" OR MPI)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021

Web of Science (AF):
ALL=("chronic obstructive pulmonary disease" OR copd OR "chronic obstructive lung disease*" OR coad OR "chronic airflow obstruction" OR "chronic bronchitis" OR emphysema OR "obstructive lung disease*" OR "obstructive airway* disease*" OR "chronic obstructive airway* disease*" OR "chronic airway* obstruction") AND ALL=("atrial fibrillation" OR af OR atrial flutter OR "atrial arrhythmia*" OR "supraventricular arrhythmia*") AND ALL=(electrocardiogra* OR ecg OR ekg OR Holter OR pacemaker OR defibrillator OR "cardiac monitor*" OR "heart monitor*")
AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021

	COPD severity									
Study ID	**GOLD1 (%)**	**GOLD2 (%)**	**GOLD3 (%)**	**GOLD4 (%)**	**LTOT (%)**	**FEV1% (x̄)**	**FEV1% (s.d.)**	**Other Measure**	**Other inclusion**	**Other exclusion**
Akpinar 2020[457]	2.3	32.6	33.7	31.4					Nil relevant	Renal/other lung disease, ACS, high Well's
Boudestein 2009[468]	32.4	49.2	18	0.4					over 65	Known HF
Freixa 2013[458]	6	48	39	8		52.4	16.2		1st hospitalisation	Patients without CVD presented separately
Guo 2018[459]						60.8	20.4		Nil relevant	Acute cardiorespiratory condition, LVF
Lee 2013[461]						35.4	12.43		Fit for TTE <48h	Renal failure, ACS, clinical HF, other respiratory
Leong 2021[366]					20	42.8	18.5		Nil relevant	117 patients without HF
Lopez-Sanchez 2013[469]								FEV1 30-50%	Nil relevant	IHD, AF, PVD, Charlson score> 5
Nishimura 2014[462]	18	36.1	32.8	13.1		56	23.8		Nil relevant	Intubation, pneumothorax, HF
Noordegraaf 1997[463]								FEV1 0.34- 1.47L	Emphysematous	History of cardiac failure
Paudel 2008[721]	31.6	46.7	21.7						Nil relevant	IHD, AF, HTN, bundle branch block
Pothal 2018[464]	2.5	42.5	35	20					Nil relevant	Other lung disease, HTN, acquired CVD
Rachakonda 2016		92.8	5.2	2.1					Nil relevant	Other lung disease, HF, IHD, poor TTE images
Rahman 2022[722]	12	34	44	10					Nil relevant	Known CV disease
Vonk-Noordegraaf 2005[470]						41	15		Nil relevant	HTN, IHD, known HF
Watz 2008[467]	20	34	25	21		56.3	22.2		Nil relevant	Clinical HF

Table A: Additional data extracted from 15 studies of LVSD. Abbreviations: GOLD: Global initiative for chronic Obstructive Lung Disease, LTOT – long term oxygen therapy, FEV1% - % predicted forced expiratory volume in 1 second, , HF – heart failure, LVF - left ventricular failure, ACS - acute coronary syndrome IHD - ischaemic heart disease, AF – atrial fibrillation, PVD - peripheral vascular disease, HTN – hypertension, TTE – transthoracic echocardiography

	COPD severity								
Study ID	**GOLD1 (%)**	**GOLD2 (%)**	**GOLD3 (%)**	**GOLD4 (%)**	**LTOT (%)**	**FEV1% (x̄)**	**FEV1% (s.d.)**	**Other inclusion**	**Other exclusion**
Bhatt 2018[471]	*Unclear: classes not presented for COPD cohort*							Nil relevant	Other respiratory disease; 928 patients without CAD
Gaisl 2015[472]	5	23	16	56		28*	22-	Previous CACS available	Coronary symptoms, congenital heart
Kahnert 2022[473]	11.8	47.4	32.3	22.6				Nil relevant	45 of +ve cases had known CAD
Leong 2021[366]					20	42.8	18.5	Nil relevant	100 patients without ASCVD (personal communication from author)
Ozylimaz 2016[474]		100						GOLD 2	Known CAD, LVSD

*Table B: Additional data extracted from 5 studies of CAD. *Median and interquartile range. Abbreviations. ASCVD – atherosclerotic cardiovascular disease, LVSD – left ventricular systolic dysfunction*

	COPD severity				
Study ID	**LTOT (%)**	**FEV1% (x̄)**	**FEV1% (s.d.)**	**Other inclusion**	**Other exclusion**
Carta 2021[475]		63	10	Nil relevant	History or symptoms of CV disease
Einvik 2017[476]	13.44	43.4	11.4	Nil relevant	Known AF, psychiatric disease
Hanrahan 2008[477]		42.8	15.3	On no LABA	Abnormal ECG, CVD, beta blocker use
Morganroth 2014[478]		39		Nil relevant	Arrhythmia, MI, HF hospitalisation
Shivnitwar 2023[479]				Nil relevant	History of cardiac disease
Terzano 2014[480]		72.5	8.2	Hypercapnoeic	IHD, valvular heart disease

Table C: Additional data extracted from 6 studies of AF. Abbreviations: LABA – long acting beta agonist, ECG - electrocardiogram

Appendix C: Management Summaries

SCATECOPD Management summary: heart failure

Definitions

The following practical definitions reflect implementation of evidence and international guidelines by local cardiology services:

1. Heart failure with moderate-severe LV systolic impairment
   - LVEF < 45% at transthoracic echocardiography (echo)
2. Heart failure without moderate-severe LV systolic impairment
   - LVEF ≥ 45% with echo report of LV diastolic dysfunction
3. Right sided heart failure:
   - Echo evidence of RV impairment in patient with peripheral oedema

Echo should be performed as early as possible during admission. If NIV used, wait until weaned to periods of ≥ 4 hours off NIV

Treatment goals

1. In patients with moderate-severe LV impairment, establishment of maximum tolerated dose of beta blocker and ACE-inhibitor, +/- spironolactone, with referral to heart failure team for supervision of this
2. In all other patients with heart failure, euvolaemia and control of hypertension, AF and CAD if present

Acting on echo reports

1. In patients with moderate-severe LV systolic impairment refer to heart failure service for ongoing supervision of the below:

   a) Start bisoprolol 1.25mg provided heart rate (HR) above 65 bpm and ECG excludes 2nd/3rd degree AV block
      - If already on bisoprolol increase dose if HR > 65 bpm
      - If on carvedilol, this can be continued/increased depending on HR
      - If on a different beta blocker, switch to bisoprolol at equivalent dose

      Titrate beta blocker dose every 2 weeks initially, aiming for HR < 70 bpm

   b) At the same time, introduce ramipril 1.25mg OD provided not hypotensive or hyperkalaemic, or on ARB
      - If cough/other insensitivity to ACE-inhibitor, introduce losartan 12.5mg OD

      Titrate ACE-inhibitor/ARB dose every 2 weeks initially, aiming for normal BP and stable creatinine

   c) If clinically hypervolaemic and not on diuretics, introduce furosemide 40mg OD
      - If already on furosemide increase dose by 40mg/d

   d) When beta blocker and ACE inhibitor doses stabilised, introduce spironolactone 25mg OD if LVEF < 35%.

2. For all other patients with heart failure:

   If admission CXR shows pulmonary congestion/oedema but LVEF >45%, review echo and clinical presentation with cardiologist to determine if treatment as for patients with moderate-severe LV systolic impairment is recommended

   b) If clinically hypervolaemic and not on diuretics, start furosemide 40mg OD
      - If already on furosemide increased dose by 40mg/d up to maximum 360mg/d

   c) Address hypertension, AF, diabetes and CAD if present (see relevant recommendations)

3. If echo is of poor quality and LVEF cannot be accurately quantified, arrange contrast echo as inpatient

Specialist referral criteria

- Patients with echo report of heart failure with moderate to severe valve disease should be discussed with a cardiologist prior to initiation of new medications (see protocol for management of valve disease)
- Patients who have been established on maximally tolerated doses of beta blocker, ACE-I and spironolactone and remain symptomatic should be referred to cardiology for further specialist input (this should happen via the heart failure service)

References

1) Chronic heart failure in adults: diagnosis and management NICE guideline [NG106] Published date: 12 September 2018 https://www.nice.org.uk/guidance/ng106

2) Acute heart failure: diagnosis and management, NICE Clinical guideline [CG187] https://www.nice.org.uk/guidance/cg187

3) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure https://academic.oup.com/eurheartj/article/37/27/2129/1748921

4) British cardiology society Heart Failure with Preserved Ejection Fraction: Pathologies, Aetiology and Directions for Treatment http://www.bcs.com/documents/D38_HFpEF_Review_3.pdf
5) NICE clinical knowledge summary: Heart failure - chronic https://cks.nice.org.uk/heart-failure-chronic#!topicSummary

SCATECOPD management summary: lipids and coronary artery disease

Rationale and definitions

- Statins are likely to be required in a high percentage of patients in the SCATECOPD study, either because of known coronary artery disease (CAD) or because of high risk of future CAD-related events
- Known CAD is defined as previous myocardial infarction (MI) or coronary revascularisation
- CT calcium score ranges between 0 and 1000+
  - Scores **≥** 100 are regarded as moderate to severe and have been demonstrated to correlate with significant coronary artery stenosis and a risk benefit-ratio favouring primary prevention with aspirin

QRISK3

- Gives the likelihood of a patient without established cardiovascular disease developing it within the next 10 years
- ***Calculate for all patients*** at https://www.qrisk.org/three/index.php using admission HDL/total cholesterol level
  - If total cholesterol > 7.5 mmol/l or non-HDL cholesterol > 5.9 mmol/l QRISK3 should not be used; repeat fasting lipid profile and assess for familial hypercholesterolaemia using FATS7 strategy (see reference)

Treatment with statins

Switch any existing statin prescriptions to those recommended below. Before starting, check ALT is not > 3 x upper limit of normal and there is no unexplained muscle pain (see FATS7)

- ***Patients with known CAD should be taking atorvastatin 80mg OD***
- ***Patients without the above, but who have QRISK3 ≥ 10% should be taking atorvastatin 20mg OD***
  - Additionally, patients over 40 with type 1 diabetes, or with CKD at any age (defined as albuminuria or eGFR <60ml/min/1.73m^2), should be offered atorvastatin 20mg OD regardless of QRISK3 score
- ***Patients with QRISK3 < 10% but with CT calcium score ≥ 1 should be taking atorvastatin 20mg OD***

Treatment with aspirin

- ***All patients with known CAD should be taking aspirin 75mg OD***
- ***All patients with CT calcium score ≥ 100 should be taking aspirin 75mg OD***
  - If intolerant of aspirin prescribe clopidogrel 75mg OD
- Co-prescribe lansoprazole 15mg OD if age **≥** 75 and/or history of GI bleed/peptic ulcer disease/severe gastro-oesophageal reflux disease

Follow up and referral

- Patients prescribed statins should have lipid profile repeated at their GP practice at 3-4 months, as well as LFTs
  - If non-HDL cholesterol has not fallen by > 40%, double statin dose up to maximum of 80mg atorvastatin
  - If ALT has risen to > 3x upper limit of normal statin should be stopped
- Patients should be advised to report any new muscle pains to their GP for consideration of the need for treatment cessation, dose reduction and/or measurement of creatine kinase levels

- If non-fasting triglycerides > 4.5 mmol/l a fasting sample should be taken and secondary causes excluded (e.g. uncontrolled diabetes mellitus, hypothyroidism). If fasting level > 10 mmol/l consider lipid clinic referral (see FATS7 for further advice)

References

- NICE clinical guideline [CG95]: Recent onset chest pain of suspected cardiac origin: assessment and diagnosis https://www.nice.org.uk/guidance/cg95
- NICE clinical guideline [CG181]: Cardiovascular disease: risk assessment and reduction, including lipid modification https://www.nice.org.uk/guidance/cg181
- Coronary calcium score and cardiovascular risk, Journal of the American College of Cardiology https://www.onlinejacc.org/content/72/4/434
- FATS7 cholesterol lowering strategy http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2012/03/FATS7-final-updated-appendices-November-2016.pdf

Definition

Atrial fibrillation (AF) shown on ECG while in hospital or total AF burden > 5 mins on 24h ambulatory ECG monitor

Treatment goals

1. Assessment of stroke/bleeding risk and introduction of anticoagulation if appropriate
2. Control of heart rate to ≤ 110 bpm at rest
    - Use mean of multiple heart rate measurements if inpatient, otherwise single clinic measurement

Pharmacological therapy

- Send TFTs and if hyperthyroid address this first by obtaining urgent endocrinology advice on need for beta blockade e.g. with atenolol

Anticoagulation:

- Calculate CHA_2DS_2-VASc and HAS-BLED scores and review echo report for evidence of mitral stenosis
- Start anticoagulation if CHA_2DS_2-VASc score ≥ 1 in men or ≥ 2 in women, unless bleeding risk considered excessive, e.g. recent bleeding event, HASBLED score ≥ 3 with risk felt to outweigh benefit
    - If moderate-severe mitral stenosis start warfarin therapy according to local guideline
    - Otherwise start apixaban 5mg BD
        - Reduce to 2.5mg BD if creatine clearance 15-29 ml/min
        - Also reduce to 2.5mg BD if creatine > 133µmol/L is associated with
          weight < 61kg or age > 80 years
    - If eGFR < 15, do not use apixaban; offer warfarin
- Stop any antiplatelet drugs (aspirin or clopidogrel) being given for primary prevention of cardiovascular disease, or for secondary prevention after a vascular event (such as MI, stroke) more than 12 months ago
    - If on antiplatelets for a vascular event within 12 months, consult with the specialist who started the antiplatelets before stopping

Quick reference CHA_2DS_2-VASc and HAS-BLED scores (see references for full details)

CHA_2DS_2-VASc risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/VTE	2
Vascular disease	1
Age 65-74	1
Sex =Female	1

HASBLED risk	Score
Hypertension	1
Abnormal liver/renal function	1 or 2
Stroke	1
Bleeding history	1
Labile INR	1
Elderly (Age > 65)	1
Drugs causing bleeding or alcohol	1

Rate control:

- Start bisoprolol 2.5mg OD if HR > 110 bpm at rest
- If already on bisoprolol, increase dose by 2.5mg up to maximum 10mg OD
    - Do not increase bisoprolol if systolic BP < 90 mmHg
- If bisoprolol dose maximised, start digoxin (having corrected any hypokalaemia)
    - If in hospital, load with 0.75 to 1.5mg orally in divided doses over 24h, then give maintenance dose 125 micrograms OD (62.5 micrograms OD if eGFR < 15)
    - Out of hospital, slow loading with maintenance dose is acceptable

Follow up/specialist referral

- Refer patients started on warfarin to their local anticoagulation clinic for INR monitoring
- Review at GP should take place in 2 weeks following a change in rate control medication, for assessment of pulse rate and side effects and further dose titration if necessary
    - patients on digoxin may have dose increased if rate control poor, alternatively if toxicity suspected (nausea, fatigue, blurred vision) a trough level should be checked and dose reduced if level > 1ng/ml

- Cardiology referral should be made for patients if heart rate >110 bpm on maximal digoxin and bisoprolol dose

References

- 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management
- NICE Clinical guideline CG180: Atrial fibrillation: management (2014) https://www.nice.org.uk/guidance/cg180
- BMJ Best Practice – digoxin overdose https://bestpractice.bmj.com/topics/en-us/338
- $CH_{A2}D_{S2}$-VASc score https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk
- HAS-BLED score https://www.mdcalc.com/has-bled-score-major-bleeding-risk

Diagnosis and treatment target

Blood pressure (BP) ≥ 140/90 mmHg on two occasions in final 24 hours of admission

- Only one of systolic or diastolic BP needs to exceed the threshold

- Final 24 hours of admission chosen due to lack of evidence for diagnosing hypertension during acute illness

Treatment target is below 140/90 mmHg in patients under 80 and below 150/90 in patients over 80

Management of BP during inpatient admission - ***Consider drug interactions and contraindications and use lowest risk agent***

Do not start treatment in hospital if BP less than 180/120 mmHg

- Instead refer patients with BP ≥ 140/90 mmHg on two occasions in final 24 hours of admission for ambulatory blood pressure monitoring (ABPM)

Start treatment in hospital if BP ≥ 180/120 mmHg on two occasions

- These patients should also have urine tested for dipstick haematuria and albumin:creatinine ratio.

- If they have symptoms/signs attributable to hypertensive end-organ damage, such as headache, they will need specialist inpatient management of their hypertension, usually by an endocrinologist

- If <55, or co-morbid type II diabetes or heart failure at any age, start ramipril 1.25mg OD
- If >55, or of black African or African-Caribbean family origin, start amlodipine 5mg OD

On discharge, ask GP for review within 2 weeks for BP measurement and dose titration

Uptitrate medications in patients already on antihypertensives with BP ≥ 140/90 mmHg on two occasions

- If on ACE-i, double dose, up to maximum advised in BNF
- If already on maximal ACE-i dose, double CCB dose up to maximum advised in BNF
- If already on maximal ACE-i and CCB doses, add indapamide 2.5mg OD

On discharge, ask GP for review in 2-8 weeks for BP measurement and dose titration

Acting on ABPM

≥ 14 measurements taken during usual waking hours should be used

Hypertension is confirmed if daytime average is ≥ 135/85 mmHg

- If not on any antihypertensives, start ramipril or amlodipine as described for inpatients above
- If already on antihypertensives, uptitrate medications as described for inpatients above

Ask GP for review in 2-8 weeks for BP measurement dose titration

Monitoring/Follow up

Review should take place at GP between 2-8 weeks after any change and every 3-6 months otherwise.

- Review should involve BP measurement and enquiry about adverse effects of drugs started/adjusted

- U&E should be measured within 2 weeks of any change of dose of ACE-i/diuretic

- ACE-i will need to be stopped if eGFR reduces by ≥ 25% or creatinine increases by ≥ 30%

References

- 8th Joint National Committee Guidelines for Management of High Blood Pressure in Adults https://sites.jamanetwork.com/jnc8/

- NICE guideline [NG136] Hypertension in adults: diagnosis and management https://www.nice.org.uk/guidance/ng136/chapter/Recommendations#diagnosing-hypertension
- 2018 ESC/ESH guidelines for the management of arterial hypertension https://academic.oup.com/eurheartj/article/39/33/3021/5079119#186437943
- NICE clinical guideline [CG182] Chronic kidney disease in adults: assessment and management https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations

Definitions

- ***Type 2 diabetes (T2DM)***: $HbA_{1C} \geq 48$ mmol/mol detected at screening and confirmed on repeat
- ***Undertreated T2DM***: patients being treated for T2DM with confirmed $HbA_{1C} \geq 58$ mmol/mol

Goals of inpatient management

- Identification and confirmation of raised HbA_{1C} levels and initiation/escalation of treatment for T2DM with involvement of inpatient diabetes services
- Shared decision making and clinical judgement regarding target HbA_{1C} levels (likely to be higher in frail patients)

There is a possibility that patients could have type 1 diabetes identified during admission. They will typically have one or more of the following: age < 50, BMI < 25, weight loss, ketosis. They should be urgently referred to diabetes specialists during inpatient stay

Acting on HbA_{1C} results in hospital

- Patients without a diagnosis of T2DM with $HbA_{1C} \geq 48$ mmol/mol should have HbA_{1C} repeated in hospital
  - If T2DM confirmed: discuss lifestyle measures and initiation of metformin treatment with patient, involving inpatient diabetes service
- Patients with known T2DM with $HbA_{1C} \geq 58$ mmol/mol should have HbA_{1C} repeated in hospital, provided treatment escalation has not already taken place within the last 3 months
  - If $HbA_{1C} \geq 58$ mmol/mol is confirmed, escalation of therapy should be offered and referral made to inpatient diabetes service for advice and recommendations for follow up

Patients with heart disease and diabetes

- Patients with established atherosclerotic heart disease (history of MI, PCI + stent, CABG, angina) or heart failure with LV ejection fraction < 45% are likely to benefit from an SGLT2 inhibitor
  - NICE and local formulary guidance currently restricts prescribing to patients intolerant of other agents
  - Patients with the above heart conditions should nevertheless be referred to diabetes service as inpatients for consideration of switch to SGLT2 inhibitor or to plan for outpatient review to discuss this

GP Follow up

- Accurate communication in discharge letter to GP will be essential to ensure abnormal HbA_{1C} results are repeated and acted up; patients +/- relatives will also need to be fully appraised of the plan
- Patients who do have inpatient changes to medications should see their GP at 3 months for review of HbA_{1C} level, discussion of ongoing target HbA_{1C} and consideration of further treatment intensification
- Patients with HbA_{1C} 42-47 mmol/l should have HbA_{1C} repeated yearly due to high risk of progression to T2DM

References

- NICE public health guideline [PH38] Type 2 diabetes: prevention in people at high risk https://www.nice.org.uk/guidance/ph38
- The impact of corticosteroid treatment on haemoglobin A1C levels among patients with type-2 diabetes with chronic obstructive pulmonary disease exacerbation https://www.resmedjournal.com/article/S0954-6111(14)00288-1/fulltext
- NICE pathway: Type 2 diabetes in adults https://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults
- NICE technology appraisal guideline [TA390] Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes https://www.nice.org.uk/guidance/ta390

Appendix D: Source document worksheets

SCATECOPD SOURCE DOCUMENT WORKSHEET *VERSION 1.6*

TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

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PATIENT STUDY NUMBER _____

Screening

Eligibility Assessment:

Smoking history:	Current smoker ☐ Ex-smoker ☐ Pack years	*Source:*

Most recent spirometry Date / /20	*No spirometry* ☐			*Source:*
FEV1 L	% predicted	VC L	% predicted	
FEV1/VC 0.		Inspiratory capacity L	% predicted	

Inclusion criteria	Yes	No	**Exclusion criteria**	Yes	No
ECOPD primary cause for admission	☐	☐	Admission not due to ECOPD	☐	☐
Age > 35	☐	☐	Unable to consent	☐	☐
>10 PYH smoking	☐	☐	Life expectancy < 12 months (non-COPD reason)	☐	☐
Diagnosed COPD + FEV1/VC <0.7	☐	☐	Cannot have cardiac CT	☐	☐
			Pregnancy or breastfeeding	☐	☐

Informed Consent:

Patient Information Sheet given ☐	Version	Date / /202
Summary PIS given ☐	Version	Date / /202
Consent form signed ☐	Version	Date / /202

Randomisation:

Study number assigned:

PEARL score:
Low (0-1) ☐ Medium (2-4) ☐ High (5-9) ☐

Cardiovascular disease:
Present ☐ Not present ☐

Patient allocated to:

Usual care group ☐ Intervention group ☐

Completed by: ..... Signed ..... Date ..... / ..... / .....

SCATECOPD SOURCE DOCUMENT WORKSHEET *VERSION 1.6*

TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

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PATIENT STUDY NUMBER _____

Baseline information

Form 1 – Complete for all patients

Admission details	*Source:*
Admission date / /202 Admission time : Admitted from: Home ☐ Sheltered accom. ☐ Res. home ☐ Nursing home ☐ Other: Has formal carers ☐	
Symptoms & signs: ^ dyspnoea ☐ ^ sputum volume ☐ ^ sputum purulence ☐ Oedema: ankle ☐ below knee ☐ above knee ☐ sacral ☐	
Initial observations: Temp. . HR BP / RR SpO2 % on via . BM Weight . kg Height cm ↑ FiO2/LPM and device GCS New confusion ☐	
Admission ABG: pH . PaCO2 . PaO2 . HCO_3^- BE FiO_2/device: *ABG not done* ☐	
Admission ECG: Rate QRS axis Rhythm: Sinus ☐ AF ☐ Atrial flutter ☐ AV block ☐ Other: RBBB ☐ LBBB ☐ LVH ☐ RVH ☐ Dynamic ST deviation ☐ Other comment:	
Admission CXR: PA ☐ AP ☐ CTR 0. Consolidation ☐ Unilateral effusion ☐ Bilateral effusions ☐ Pulmonary congestion ☐ Diaphragm height cm Other comment:	
Bloods at admission: Na^+ K^+ . Ur . Cr eGFR *Leave any not done blank* Albumin Glucose . Lactate . CRP Troponin T HbA_{1c} NT-proBNP Hb WCC Plt Neuts Lymphs Eos	

Additional details:

Admissions history	*Source:*
Total admissions in past year	
Total previous COPD admissions COPD admissions in past year Self-reported exacerbations in past year Previous NIV ☐ Previous invasive ventilation ☐	
Any previous admission with CVD ☐ CVD admissions in past year	

Additional details:

Patient details sticker

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PATIENT STUDY NUMBER _____

COPD background	*Source:*
COPD care: Secondary care ☐ GP care only ☐ Undiagnosed at admission☐	
Current e-cigarette use ☐ Total duration of e-cigarette use ____ months ____ years	
eMRCD score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5a ☐ 5b ☐ NYHA class: 1 ☐ 2 ☐ 3 ☐ 4 ☐ PEARL score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐	
Rockwood Clinical Frailty Scale: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐	

Additional details:

CV comorbidities											
	o/a	d/c		o/a	d/c		o/a	d/c		o/a	d/c
LVSD	☐	☐	AF	☐	☐	V. Arrhythmia	☐	☐	^ Cholesterol	☐	☐
RV failure	☐	☐	PCI + stent	☐	☐	PPM	☐	☐	Stroke/TIA	☐	☐
HFpEF	☐	☐	CABG	☐	☐	ICD	☐	☐	PVD	☐	☐
MI	☐	☐	Angina	☐	☐	HTN	☐	☐	Valve disease	☐	☐
Other/details:											

Previous Echocardiogram *(if available)* Date / /20	*Source:*
Technical quality: Good ☐ Adequate ☐ Poor/limited ☐ Very poor/limited ☐ Not stated ☐ Other comment:	
LVEF: ____ % No measurement ☐ LVED diameter ____ cm LVED volume ____ ml LV abnormality: Global hypokinesis ☐ RWMA ☐ Outflow obstruction ☐ Thrombus ☐ Other: LV diastolic dysfunction: None ☐ Mild/Grade I ☐ Moderate/Grade II ☐ Severe/Grade III ☐ No comment ☐ Other: LA diameter ____ cm Septal E/e' ____ Lateral E/e' ____ Average E/e' ____	
RV function comment: Good ☐ Impaired ☐ Other: TR velocity ____ m/s TAPSE ____ cm FAC ____ % S' ____ cm/s RA volume ____ ml Estimated RA pressure ____ mmHg Estimated PASP ____ mmHg	
Valve disease: Aortic stenosis ☐ Aortic regurgitation ☐ Mitral stenosis ☐ *(moderate/severe)* Mitral regurgitation ☐ Tricuspid regurgitation (in absence of dilated RV) ☐ Aortic root dilatation ☐ Other:	

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PATIENT STUDY NUMBER _____

Other comorbidities:		*Source:*
Respiratory:	Asthma ☐ ILD ☐ PE ☐ Bronchiectasis ☐ OSA/OHS ☐ CPAP ☐	
Gastro/liver:	Cirrhosis ☐ Portal HTN ☐ Variceal bleeding ☐ Chronic hepatitis ☐ PUD ☐	
Renal/urology:	CKD ☐ Stage Baseline eGFR Dialysis ☐ Transplant ☐	
Neuro/psych:	Dementia ☐ Hemiparesis ☐	
Endocrine:	T1DM ☐ T2DM ☐ End organ damage ☐	
MSK:	Rheumatoid arthritis ☐ Other connective tissue disease ☐	
Malignancy:	Solid tumour ☐ Metastases ☐ Lymphoma ☐ Leukaemia☐ Presumed cured ☐ Active treatment ☐ More details:	
Other PMH:	VTE ☐ AIDS ☐ Other:	

Therapy:

	o/a	d/c		o/a	d/c		o/a	d/c		o/a	d/c
LABA	☐	☐	Aspirin	☐	☐	MRA	☐	☐	Fibrate	☐	☐
LAMA	☐	☐	Clopidogrel	☐	☐	Entresto	☐	☐	Metformin	☐	☐
ICS	☐	☐	Warfarin	☐	☐	Loop diuretic	☐	☐	Insulin	☐	☐
Theophylline	☐	☐	DOAC	☐	☐	Thiazide/TLD	☐	☐	Sulfonylurea	☐	☐
Oral steroid	☐	☐	Beta blocker	☐	☐	DHP CCB	☐	☐	DDP-4-i	☐	☐
Macrolide	☐	☐	ACE-inhibitor	☐	☐	Nitrate	☐	☐	SGLT2-i	☐	☐
Carbocisteine	☐	☐	ARB	☐	☐	Ivabradine	☐	☐	GLP-1	☐	☐
Home nebs	☐	☐	Non-DHP CCB	☐	☐	Nicorandil	☐	☐	Other anti-hypertensive	☐	☐
LTOT	☐	☐	Digoxin	☐	☐	Ranolazine	☐	☐			
Home NIV	☐	☐	Amiodarone	☐	☐	Statin	☐	☐			

Additional details/other meds:

In hospital events		*Source:*
Escalation decisions:	Existing DNACPR ☐ New DNACPR ☐ Ceiling of care: Level 3 ☐ Level 2 ☐ Ward ☐	
CV events:	MI ☐ AF ☐ PE ☐ DVT ☐ Stroke/TIA ☐ Decompensated HF: oral treatment ☐ IV treatment ☐ Other, including treatment details:	
Other events:	Sputum culture +ve ☐ Organism: Blood culture +ve ☐ Organism: Viral PCR +ve ☐ Organism: COVID -19 ☐ Influenza ☐ RSV ☐ Other: HAP ☐ DKA ☐ Fall(s) ☐ Delirium ☐ Cardiac arrest ☐ AKI ☐ AKI Stage Other/details:	

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PATIENT STUDY NUMBER _____

In-hospital treatment		*Source:*
COPD treatment:	Steroids ☐ Nebulised bronchodilators ☐ Oral Abx ☐ IV Abx ☐	
Smoking cessation:	Advice given ☐ Referral offered ☐ Drug prescribed ☐	
Ventilatory support:	NIV used ☐ Date/time started / /202 : Acute CPAP ☐ Invasive ventilation ☐	

Additional details:

Spirometry Date / /202				*Source:*
FEV1 L	% predicted	Inspiratory capacity L	% predicted	
VC L	% predicted			

SGRQ-C Date / /202				*Source:*
Symptoms	Activity	Impacts	Total	

EQ-5D-5L Date / /202		*Source:*
Descriptive system number	VAS	

4m gait speed Date / /202		*Source:*
Trial 1 time s	Trial 2 time s	

Discharge	*Source:*
Discharge date / /202 Discharge time :	
Discharged to: Home ☐ Sheltered accom. ☐ Res. home ☐ Nursing home ☐ Other: Has formal carers ☐ Supported discharge ☐ Hospital at home ☐	
ABG pre-discharge: *not done* ☐ Date / /202 pH . PaCO2 . PaO2 . HCO_3^- BE FiO_2/device	

Additional details:

Completed by: …… Signed …… Date …… / …… / ……..

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TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

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PATIENT STUDY NUMBER _____

Baseline Information
Form 2 – complete for all patients in Intervention Arm

Additional admission bloods:	*Source:*
Troponin T NT-pro-BNP Fibrinogen . HbA_{1c} Total cholesterol . HDL cholesterol . Non-HDL cholesterol . Triglycerides .	

Data for QRISK 3 score:		*Source:*
Ethnicity	White ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Other Asian ☐ Black Caribbean ☐ Black African ☐ Chinese ☐ Other ethnic group ☐	
Other risk factors:	Angina or MI in 1DR < 60? ☐ Migraine ☐ RA ☐ SLE ☐ Erectile dysfunction ☐ On atypical antipsychotic ☐ Schizophrenia/bipolar/moderate-severe depression ☐	

Additional details:

24h ECG Date / /202	*Source:*
Total recording duration: h m Technical comments:	
Predominant rhythm: Sinus ☐ AF ☐ Atrial flutter ☐ 1° AV block ☐ AV block II/III ☐ Other: Arrhythmias: AF > 5 min total ☐ SVT > 30 seconds ☐ AV block II/III ☐ Sinus pause > 3 seconds ☐ Other: Other findings:	

Blood Pressure review	*Source:*
Highest two inpatient BPs: 1) / mmHg 2) / mmHg *In last 24h before discharge*	

Cardiac/thoracic CT Date / /202	*Source:*
Dose length product mGycm Image quality comment: CAC scores: LM LAD Cx RCA Total Pulmonary trunk diameter mm Ascending aorta diameter mm	

Echocardiogram Date / /202 Contrast given ☐	*Source:*
Technical quality: Good ☐ Adequate ☐ Poor/limited ☐ Very poor/limited ☐ Not stated ☐ Other comment:	
LVEF: % No measurement ☐ LVED diameter cm LVED volume ml LV abnormality: Global hypokinesis ☐ RWMA ☐ Outflow obstruction ☐ Thrombus ☐ Other: LV diastolic dysfunction: None ☐ Mild/Grade I ☐ Moderate/Grade II ☐ Severe/Grade III ☐ No comment ☐ Other: LA diameter cm Septal E/e' Lateral E/e' Average E/e'	

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PATIENT STUDY NUMBER _____

RV function comment: Good ☐ Impaired ☐ Other: TR velocity ____ m/s TAPSE ____ cm FAC ____ % S' ____ cm/s RA volume ____ ml Estimated RA pressure ____ mmHg Estimated PASP ____ mmHg	
Valve disease: *(moderate/severe)* Aortic stenosis ☐ Aortic regurgitation ☐ Mitral stenosis ☐ Mitral regurgitation ☐ Tricuspid regurgitation (in absence of dilated RV) ☐ Aortic root dilatation ☐ Other:	

Additional details:

Summary of CV diagnoses and treatments during admission			*Source:*
Diagnosis:	Treatment indicated:	Reason if not given *(e.g. contraindication, SE)*	

Completed by: …… Signed …… Date …… / …… / ……..

Patient details sticker

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PATIENT STUDY NUMBER _____

Baseline Form 3 – complete for all patients in Usual Care Arm

Use this section to record inpatient cardiovascular investigations done outside of study protocol

Additional bloods:	*Source:*
Troponin T NT-pro-BNP Fibrinogen . HbA_{1c} Total cholesterol . HDL cholesterol . Non-HDL cholesterol . Triglycerides .	

Prolonged (e.g. 24h) ECG Date / /202	*Source:*
Total recording duration: h m Technical comments:	
Predominant rhythm: Sinus ☐ AF ☐ Atrial flutter ☐ 1° AV block ☐ AV block II/III ☐ Other: Arrhythmias: AF > 5 min total ☐ SVT > 30 seconds ☐ AV block II/III ☐ Sinus pause > 3 seconds ☐ Other: Other findings:	

Cardiac/thoracic CT Date / /202	*Source:*
Dose length product mGycm Image quality comment: CAC scores: LM LAD Cx RCA Total Pulmonary trunk diameter mm Ascending aorta diameter mm	

Echocardiogram Date / /202	*Source:*
Technical quality: Good ☐ Adequate ☐ Poor/limited ☐ Very poor/limited ☐ Not stated ☐ Other comment:	
LVEF: % No measurement ☐ LVED diameter cm/m^2 LVED volume ml LV abnormality: Global hypokinesis ☐ RWMA ☐ Outflow obstruction ☐ Thrombus ☐ Other: LV diastolic dysfunction: None ☐ Mild/Grade I ☐ Moderate/Grade II ☐ Severe/Grade III ☐ No comment ☐ Other: LA diameter cm Septal E/e' Lateral E/e'	
RV function comment: Good ☐ Impaired ☐ Other: TR velocity m/s TAPSE cm FAC % S' cm/s RA volume ml/m^3 Estimated RA pressure mmHg Estimated PASP mmHg	
Valve disease: *(moderate/severe)* Aortic stenosis ☐ Aortic regurgitation ☐ Mitral stenosis ☐ Mitral regurgitation ☐ Tricuspid regurgitation (in absence of dilated RV) ☐ Aortic root dilatation ☐ Other:	

Additional details:

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Patient details sticker

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PATIENT STUDY NUMBER _____

Summary of CV diagnoses and treatments during admission			*Source:*
Diagnosis:	Treatment indicated:	Reason if not given *(e.g. contraindication, SE)*	

Completed by: …… Signed …….. Date …… / …… / ……..

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PATIENT STUDY NUMBER _____

90-day review

Form 1 – Complete for all patients

Events since discharge Date of review / /202	*Source:*
Patient deceased ☐ Date of death / /202 Cause of death: COPD ☐ CVD ☐ Other/details:	
CVD admissions since discharge Date and times of admissions: / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 :	
Other admissions since discharge Date and times of admissions: / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 :	

Additional details:

Current COPD status	*Source:*
Residence: Home ☐ Sheltered accom. ☐ Res. home ☐ Nursing home ☐ Other: Has carers ☐	
Smoking: Current smoker ☐ Ex-smoker ☐ Current e-cigarette user ☐ Ex e-cigarette user ☐ Since discharge: Used smoking cessation service ☐ Used smoking cessation drug ☐	
eMRCD score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5a ☐ 5b ☐ NYHA class: 1 ☐ 2 ☐ 3 ☐ 4 ☐ PEARL score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐	

Additional details:

Current relevant therapy:

LABA	☐	LTOT	☐	ARB	☐	DHP CCB	☐	Insulin	☐
LAMA	☐	Home NIV	☐	Non-DHP CCB	☐	Nitrate	☐	Sulfonylurea	☐
ICS	☐	Aspirin	☐	Digoxin	☐	Ivabradine	☐	DDP-4-i	☐
Theophylline	☐	Clopidogrel	☐	Amiodarone	☐	Nicorandil	☐	SGLT2-i	☐
Oral steroid	☐	Warfarin	☐	MRA	☐	Ranolazine	☐	GLP-1	☐
Macrolide	☐	DOAC	☐	Entresto	☐	Statin	☐	Other anti-hypertensive	☐
Carbocisteine	☐	Beta blocker	☐	Loop diuretic	☐	Fibrate	☐		
Home nebs	☐	ACE inhibitor	☐	Thiazide/TLD	☐	Metformin	☐		

Other/details:

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Patient details sticker

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PATIENT STUDY NUMBER _____

CV comorbidities									
LVSD	☐	AF	☐	Angina	☐	ICD	☐	Stroke/TIA	☐
RV failure	☐	PCI + stent	☐	V. Arrhythmia	☐	HTN	☐	PVD	☐
HFpEF	☐	CABG	☐	PPM	☐	^ Cholesterol	☐	Valve disease	☐
MI	☐	Other:							

Additional details:

Health service utilisation					*Source:*
COPD exacerbations: Total number		Rescue packs used		Nurse encounters	
GP visits		Ambulances		A&E attendances	Admissions
Acute NIV episodes		I&V episodes			
Date and times of admission:	/ /202 :	to	/ /202 :		
	/ /202 :	to	/ /202 :		
	/ /202 :	to	/ /202 :		
	/ /202 :	to	/ /202 :		
Other health service utilisation:					
GP:	Home visits		Surgery appointments	Telephone	
Practice nurse:	Home visits		Surgery appointments	Telephone	
OT:	Home visits		Surgery appointments	Telephone	
PT:	Home visits		Surgery appointments	Telephone	
	Day unit		Hospital		
OP clinic:	Total number				
Hospital:	Ambulances called		A&E attendances	Ward (day only)	

Additional details:

Spirometry Date / /202	*Source:*
FEV1 L % predicted Inspiratory capacity L % predicted	
VC L % predicted	

SGRQ-C Date / /202	*Source:*
Symptoms Activity Impacts Total	

EQ-5D-5L Date / /202	*Source:*
Descriptive system number VAS	

4m gait speed Date / /202	*Source:*
Trial 1 time s Trial 2 time s	

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TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

Patient details sticker

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PATIENT STUDY NUMBER _____

Additional details:

Summary of CV diagnoses and treatments since discharge			*Source:*
Diagnosis:	Treatment indicated:	Reason if not given *(e.g. contraindication, SE)*	

Completed by: …… Signed …… Date …… / …… / ……..

SCATECOPD SOURCE DOCUMENT WORKSHEET *VERSION 1.6*

TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

Patient details sticker

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PATIENT STUDY NUMBER _____

90-day review

Form 2 - complete for patients in Intervention Arm

Blood tests: Date of sample / /202	*Source:*
Troponin T NT-pro-BNP Fibrinogen	

ECG: Date / /202	*Source:*
Rate QRS axis Rhythm: Sinus ☐ AF ☐ Atrial flutter ☐ AV block ☐ Other: RBBB ☐ LBBB ☐ LVH ☐ RVH ☐ Dynamic ST deviation ☐ Other comment:	

Echocardiogram: Date / /202 Contrast given ☐	*Source:*
Technical quality: Good ☐ Adequate ☐ Poor/limited ☐ Very poor/limited ☐ Not stated ☐ Other comment:	
LVEF: % No measurement ☐ LVED diameter cm LVED volume ml LV abnormality: Global hypokinesis ☐ RWMA ☐ Outflow obstruction ☐ Thrombus ☐ Other: LV diastolic dysfunction: None ☐ Mild/Grade I ☐ Moderate/Grade II ☐ Severe/Grade III ☐ No comment ☐ Other: LA diameter cm Septal E/e' Lateral E/e' Average E/e'	
RV function comment: Good ☐ Impaired ☐ Other: TR velocity m/s TAPSE cm FAC % S' cm/s RA volume ml Estimated RA pressure mmHg Estimated PASP mmHg	
Valve disease: Aortic stenosis ☐ Aortic regurgitation ☐ Mitral stenosis ☐ *(moderate/severe)* Mitral regurgitation ☐ Tricuspid regurgitation (in absence of dilated RV) ☐ Aortic root dilatation ☐ Other:	

Additional details:

Completed by: ..... Signed ..... Date ..... / ..... / .....

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TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

Patient details sticker

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PATIENT STUDY NUMBER _____

6-month telephone review – complete for all patients

Date of review / /202

Current relevant therapy:											
LABA	☐	LTOT	☐	ARB	☐	DHP CCB	☐	Insulin	☐
LAMA	☐	Home NIV	☐	Non-DHP CCB	☐	Nitrate	☐	Sulfonylurea	☐
ICS	☐	Aspirin	☐	Digoxin	☐	Ivabradine	☐	DDP-4-i	☐
Theophylline	☐	Clopidogrel	☐	Amiodarone	☐	Nicorandil	☐	SGLT2-i	☐
Oral steroid	☐	Warfarin	☐	MRA	☐	Ranolazine	☐	GLP-1	☐
Macrolide	☐	DOAC	☐	Entresto	☐	Statin	☐	Other anti-hypertensive	☐
Carbocisteine	☐	Beta blocker	☐	Loop diuretic	☐	Fibrate	☐		
Home nebs	☐	ACE inhibitor	☐	Thiazide/TLD	☐	Metformin	☐		
Other/details:											

Health service utilisation					*Source:*
COPD exacerbations: Total number		Rescue packs used		Nurse encounters	
GP visits		Ambulances		A&E attendances	
Other health service utilisation:					
GP:	Home visits		Surgery appointments		Telephone
Practice nurse:	Home visits		Surgery appointments		Telephone
OT:	Home visits		Surgery appointments		Telephone
PT:	Home visits		Surgery appointments		Telephone
	Day unit		Hospital		
OP clinic:	Total number				
Hospital:	Ambulances called		A&E attendances		Ward (day only)

Additional details:

Completed by: …… Signed …… Date …… / …… / ……..

Patient details sticker

✂----------

PATIENT STUDY NUMBER _____

Section 7 – Complete at 9-month telephone review for all patients

Date of review / /202

Current relevant therapy:									
LABA	☐	LTOT	☐	ARB	☐	DHP CCB	☐	Insulin	☐
LAMA	☐	Home NIV	☐	Non-DHP CCB	☐	Nitrate	☐	Sulfonylurea	☐
ICS	☐	Aspirin	☐	Digoxin	☐	Ivabradine	☐	DDP-4-i	☐
Theophylline	☐	Clopidogrel	☐	Amiodarone	☐	Nicorandil	☐	SGLT2-i	☐
Oral steroid	☐	Warfarin	☐	MRA	☐	Ranolazine	☐	GLP-1	☐
Macrolide	☐	DOAC	☐	Entresto	☐	Statin	☐	Other anti-hypertensive	☐
Carbocisteine	☐	Beta blocker	☐	Loop diuretic	☐	Fibrate	☐		
Home nebs	☐	ACE inhibitor	☐	Thiazide/TLD	☐	Metformin	☐		
Other/details:									

Health service utilisation				*Source:*
COPD exacerbations: Total number		Rescue packs used	Nurse encounters	
GP visits		Ambulances	A&E attendances	
Other health service utilisation:				
GP:	Home visits	Surgery appointments	Telephone	
Practice nurse:	Home visits	Surgery appointments	Telephone	
OT:	Home visits	Surgery appointments	Telephone	
PT:	Home visits	Surgery appointments	Telephone	
	Day unit	Hospital		
OP clinic:	Total number			
Hospital:	Ambulances called	A&E attendances	Ward (day only)	

Additional details:

Completed by: …… Signed …… Date …… / …… / ……..

Patient details sticker

✂----------

PATIENT STUDY NUMBER _____

12-month review – complete for all patients

Events since last review Date of review / /202	*Source:*
Patient deceased ☐ Date of death / /202 Cause of death: COPD ☐ CVD ☐ Other/details:	
CVD admissions since last review Date and times of admissions: / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 :	
Other admissions since last review Date and times of admissions: / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 : / /202 : to / /202 :	

Additional details:

Current COPD status	*Source:*
Residence: Home ☐ Sheltered accom. ☐ Res. home ☐ Nursing home ☐ Other: Has carers ☐	
Smoking: Current smoker ☐ Ex-smoker ☐ Current e-cigarette user ☐ Ex e-cigarette user ☐ Since last review: Used smoking cessation service ☐ Used smoking cessation drug ☐	
eMRCD score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5a ☐ 5b ☐ NYHA class: 1 ☐ 2 ☐ 3 ☐ 4 ☐ PEARL score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐	

Current relevant therapy:

LABA	☐	LTOT	☐	ARB	☐	DHP CCB	☐	Insulin	☐
LAMA	☐	Home NIV	☐	Non-DHP CCB	☐	Nitrate	☐	Sulfonylurea	☐
ICS	☐	Aspirin	☐	Digoxin	☐	Ivabradine	☐	DDP-4-i	☐
Theophylline	☐	Clopidogrel	☐	Amiodarone	☐	Nicorandil	☐	SGLT2-i	☐
Oral steroid	☐	Warfarin	☐	MRA	☐	Ranolazine	☐	GLP-1	☐
Macrolide	☐	DOAC	☐	Entresto	☐	Statin	☐	Other anti-hypertensive	☐
Carbocisteine	☐	Beta blocker	☐	Loop diuretic	☐	Fibrate	☐		
Home nebs	☐	ACE inhibitor	☐	Thiazide/TLD	☐	Metformin	☐		

Other/details:

CV comorbidities

LVSD	☐	AF	☐	Angina	☐	ICD	☐	Stroke/TIA	☐
RV failure	☐	PCI + stent	☐	V. Arrhythmia	☐	HTN	☐	PVD	☐
HFpEF	☐	CABG	☐	PPM	☐	^ Cholesterol	☐	Valve disease	☐
MI	☐	Other:							

Additional details:

SCATECOPD SOURCE DOCUMENT WORKSHEET *VERSION 1.6*

TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

Patient details sticker

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PATIENT STUDY NUMBER _____

Health service utilisation							*Source:*
COPD exacerbations: Total number		Rescue packs used		Nurse encounters			
GP visits		Ambulances		A&E attendances		Admissions	
Acute NIV episodes		I&V episodes					
Date and times of admission:	/ /202	:	to	/ /202	:		
	/ /202	:	to	/ /202	:		
	/ /202	:	to	/ /202	:		
	/ /202	:	to	/ /202	:		
Other health service utilisation:							
GP:	Home visits		Surgery appointments		Telephone		
Practice nurse:	Home visits		Surgery appointments		Telephone		
OT:	Home visits		Surgery appointments		Telephone		
PT:	Home visits		Surgery appointments		Telephone		
	Day unit		Hospital				
OP clinic:	Total number						
Hospital:	Ambulances called		A&E attendances		Ward (day only)		

Additional details:

Spirometry	Date / /202					*Source:*
FEV1	L	% predicted		Inspiratory capacity	L	% predicted	
VC	L	% predicted					

SGRQ-C	Date / /202				*Source:*
Symptoms		Activity		Impacts		Total	

EQ-5D-5L	Date / /202		*Source:*
Descriptive system number		VAS	

4m gait speed	Date / /202			*Source:*
Trial 1 time	s	Trial 2 time	s	

Additional details:

SCATECOPD SOURCE DOCUMENT WORKSHEET *VERSION 1.6*

TO BE FILED IN 'CLINICAL TRIALS' SECTION OF CLINICAL NOTES

Patient details sticker

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PATIENT STUDY NUMBER _____

Summary of CV diagnoses and treatments since 90-day review			*Source:*
Diagnosis:	Treatment indicated:	Reason if not given *(e.g. contraindication, SE)*	

Completed by: …… Signed …….. Date …… / …… / ……..

Appendix E: Costs associated with healthcare use

Costing References

NHS Business Services Authority. Drug Tariff. 2021. https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

Jones, K. & Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. DOI: 10.22024/UniKent/01.02.92342

Care DoHaS. NHS Reference Costs 2020 to 2021. In: Care DoHaS, ed. London, 2021.

Wilson ECF, Usher-Smith JA, Emery J, Corrie P, Walter FM. A Modeling Study of the Cost-Effectiveness of a Risk-Stratified Surveillance Program for Melanoma in the United Kingdom. Value Health. 2018;21(6):658-668. doi:10.1016/j.jval.2017.11.009

Dretzke J, Blissett D, Dave C, Mukherjee R, Price M, Bayliss S, et al. The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. Health Technol Assess 2015;19(81)

Holmes GR, Ward SE, Brennan A, et al. Cost-Effectiveness Modeling of Surgery Plus Adjuvant Endocrine Therapy Versus Primary Endocrine Therapy Alone in UK Women Aged 70 and Over With Early Breast Cancer. Value Health. 2021;24(6):770-779. doi:10.1016/j.jval.2020.12.016

Kuruvilla, T., Phillips, E., Justin, B., Rose, P. and Lyburn, I. (2015), Functional neuroimaging for dementia: commissioning and evaluating a service. Prog. Neurol. Psychiatry, 19: 27-32. https://doi.org/10.1002/pnp.367

HRU Items

HRU Item	**Cost**	**Source**
Rescue packs used	£30.45	NHS Drugs Tariff 2021
GP Visits	£39.23	PSSRU 2021
GP Home Visits	£100.62	PSSRU 2021
GP Surgery Appointments	£39.23	PSSRU 2021
GP Telephone	£15.32	PSSRU 2021
Nurse Encounters	£11.37	PSSRU 2021
Practice Nurse Home Visits	£17.16	PSSRU 2021
Practice Nurse Surgery Appointments	£11.37	PSSRU 2021
Practice Nurse Telephone	£7.62	PSSRU 2021
OT Nurse Home Visits	£33.80	PSSRU 2021
OT Surgery Appointments	£26.00	PSSRU 2021
OT Telephone	£4.26	PSSRU 2021
PT Home Visits	£34.67	PSSRU 2021
PT Surgery Appointments	£26.67	PSSRU 2021
PT Telephone	£4.37	PSSRU 2021
PT Day unit	£67.00	PSSRU 2021
PT Hospital	£67.00	PSSRU 2021

OP Clinic F2F	£137.00	PSSRU 2021
OP Clinic Tel	£137.00	PSSRU 2021
Ambulances (COPD)	£134.00	PSSRU 2021
Ambulances (Other)	£134.00	PSSRU 2021
A&E	£170.00	NHS Reference costs 2022/23
A&E Attendances	£170.00	NHS Reference costs 2022/23
Ward (Day Only)	£392.00	NHS Reference costs 2022/23
Nursing Home	£119.93	PSSRU 2021
Residential Home	£102.71	PSSRU 2021

Hospital Admission

Hospital Admission Reason	**Cost**	**Source**
CVD hospital nights	£290.00	NHS Reference costs 2022/23
COPD hospital nights	£275.00	NHS Reference costs 2022/23
Readmitted from rehab with COVID19 and died in hospital	£275.00	NHS Reference costs 2022/23
abdo pain	£292.00	NHS Reference costs 2022/23
wound infection	£275.00	NHS Reference costs 2022/23
syncope	£290.00	NHS Reference costs 2022/23
Fall complicated by COVID-19 and PE	£275.00	NHS Reference costs 2022/23
UTI	£291.00	NHS Reference costs 2022/23
Osteoporotic #	£304.00	NHS Reference costs 2022/23
Hyperglycaemia	£279.00	NHS Reference costs 2022/23
colostomy revision	£292.00	NHS Reference costs 2022/23
falls	£275.00	NHS Reference costs 2022/23
Transient neurological symptoms, unexplained	£271.00	NHS Reference costs 2022/23
Urinary retention	£291.00	NHS Reference costs 2022/23
pneumonia/fall	£275.00	NHS Reference costs 2022/23

glaucoma (acute) +rehab	£365.00	NHS Reference costs 2022/23
Hip #	£304.00	NHS Reference costs 2022/23
delirium + hyperglycaemia + orthostatic hypotension	£279.00	NHS Reference costs 2022/23
Covid + AF	£275.00	NHS Reference costs 2022/23
collapse/infection	£291.00	NHS Reference costs 2022/23
anxiety	£275.00	NHS Reference costs 2022/23
migraine	£271.00	NHS Reference costs 2022/23
Covid-19	£275.00	NHS Reference costs 2022/23
Pneumonia	£270.00	NHS Reference costs 2022/23
Pneumothorax	£270.00	NHS Reference costs 2022/23
Collapse	£290.00	NHS Reference costs 2022/23
colitis/diverticulitis	£286.00	NHS Reference costs 2022/23
starvation ketoacidosis	£274.00	NHS Reference costs 2022/23
heat exhaustion	£290.00	NHS Reference costs 2022/23
copd progression (not exac.)	£275.00	NHS Reference costs 2022/23
Confusion	£290.00	NHS Reference costs 2022/23
hip dislocation	£299.00	NHS Reference costs 2022/23
elective prostatectomy	£286.00	NHS Reference costs 2022/23
hyperkalaemia	£286.00	NHS Reference costs 2022/23
acute pancreatitis	£277.00	NHS Reference costs 2022/23
CAP	£270.00	NHS Reference costs 2022/23
Fall, HAP	£275.00	NHS Reference costs 2022/23
hip pain	£270.00	NHS Reference costs 2022/23

haematuria	£286.00	NHS Reference costs 2022/23
COVID19	£275.00	NHS Reference costs 2022/23
Fall	£275.00	NHS Reference costs 2022/23
Chest pain (not cardiac)	£285.00	NHS Reference costs 2022/23
oropharyngeal Ca, died in hospital	£270.00	NHS Reference costs 2022/23
COPD (baseline, not exac.)	£275.00	NHS Reference costs 2022/23
gallstones	£270.00	NHS Reference costs 2022/23
shoulder pain	£270.00	NHS Reference costs 2022/23
gastritis	£270.00	NHS Reference costs 2022/23
fall/aki/lowK+	£275.00	NHS Reference costs 2022/23
AKI, hyperkalaemia	£286.00	NHS Reference costs 2022/23
urosepsis	£270.00	NHS Reference costs 2022/23
High stoma output	£270.00	NHS Reference costs 2022/23

Index Procedure Costs

Procedure	Cost	Source
Echocardiogram	83.00	NHS Reference costs 2022/23
CT coronary artery calcium score	69.00	NHS Reference costs 2022/23
24h ECG	98.22	Locally agreed tarriff and inflated
Coronary angiogram	1685.00	NHS Reference costs 2022/23

Scans

Item	Cost	Source
BP&24h tape (at same time)	£98.22	Data from John and inflated
Cardiac MRI	£465.00	NHS Reference costs 2022/23
X ray	£28.00	NHS Reference costs 2022/23

Computerised Tomography Scan of One Area	£81.33	NHS Reference costs 2022/23
Computerised Tomography Scan of Two Areas	£86.00	NHS Reference costs 2022/23
Computerised Tomography Scan of Three Areas	£94.00	NHS Reference costs 2022/23
Ultrasound Scan	£72.00	NHS Reference costs 2022/23
DEXA scan	£61.00	NHS Reference costs 2022/23
ECG	£127.00	NHS Reference costs 2022/23
Echo	£83.00	NHS Reference costs 2022/23
Lung function	£245.00	NHS Reference costs 2022/23
PFTs	£245.00	NHS Reference costs 2022/23
Synacthen test	£38.00	NHS Drugs Tariff 2022
XR calcaneus	£28.00	NHS Reference costs 2022/23
Skin biopsy (RVI)	£150.66	Wilson et al. (2018) PSSRU 2021
ABG	£54.85	Dretzke et al. (2015) PSSRU 2021
Mammogram	£56.89	Holmes et al. (2021)
NM bone scan	£200.00	NHS Reference costs 2022/23
MRI	£151.67	NHS Reference costs 2022/23
OGD	£458.00	NHS Reference costs 2022/23
NM DAT scan	£1,002.50	Kuruvilla et al. (2015) PSSRU 2021
bronchoscopy	£746.00	NHS Reference costs 2022/23
Sleep study	£377.00	NHS Reference costs 2022/23
US urinary tract	£72.00	NHS Reference costs 2022/23
cystoscopy	£251.00	NHS Reference costs 2022/23
PETCT	£979.14	NHS Reference costs 2022/23

Appendix F: Reasons for undertreatment post-SCA

		Indicated medication			
		Antiplatelet	Beta-blocker	ACE-inhibitor	Statin
At 90 days:	MI *n=8*	-	-	Stopped: Hypotension x 2	Allergy x 1
	LVEF <40% *n=4*		-	Stopped: Hypotension x 1	
	LVEF 40-44% *n=2*		-	-	
	CAD *n=36*	Stopped: low platelets x 1 Stopped after fall x 1 Not initiated x 3			Patient declined x 2 Stopped (LFTs) x 2 CI: prev. hepatitis x 1 Not initiated x 1
At 12 months:	MI *n=7*	-	-	-	-
	LVEF <40% *n=3*		-	-	
	LVEF 40-44% *n=2*		-	-	
	CAD *n=30*	Not initiated x 1			Stopped (LFTs) x 1 CI: prev. hepatitis x 1 Stopped by patient x 2 Patient declined x 1

Appendix G: Additional analyses relating to right heart function

Changes in right heart function and ECOPD severity

In section 7.3.4., the relationship between change in right heart function, as measured by overall RV function assessment, and ECOPD severity, was explored. As mentioned in this section, other

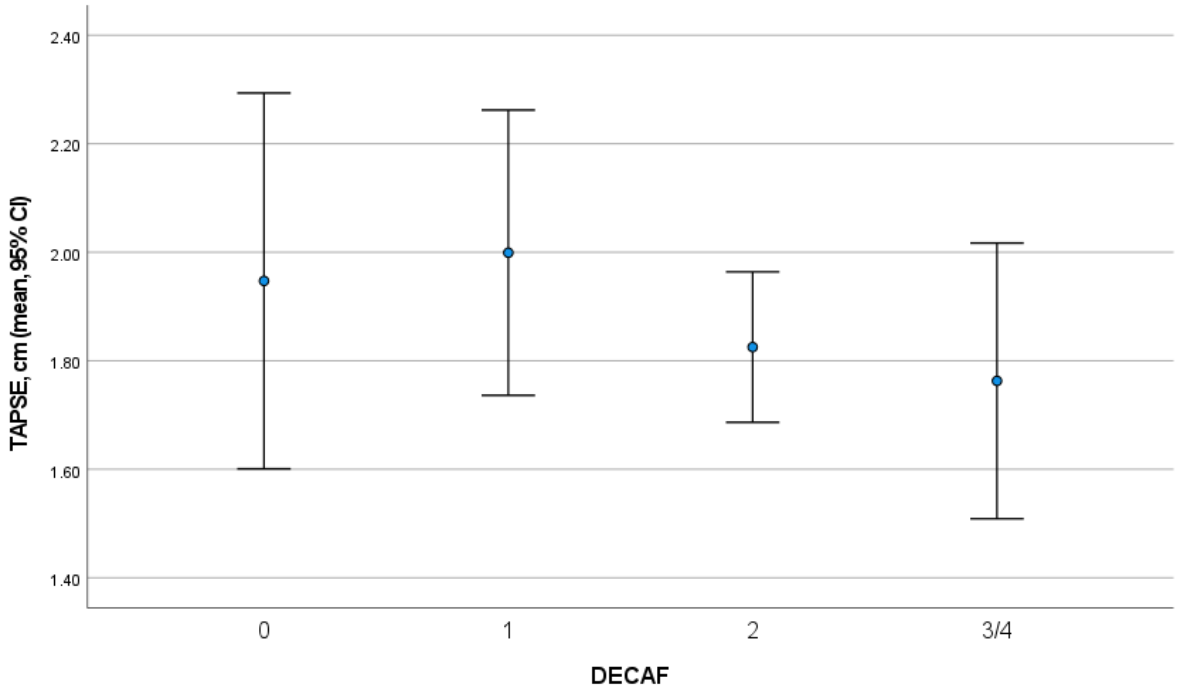
methods of assessing RV function was also acquired, namely TAPSE and pulmonary hypertension probability. In this appendix, the relationship between these measures and ECOPD severity is analysed.

TAPSE

Although analysis contained in section 7.3.4, using overall assessment of RV function, provided the most complete dataset, the majority of patients had TAPSE measurable at baseline and follow-up, therefore it was possible to evaluate mean TAPSE at the two time points for different levels of ECOPD severity, as measured by DECAF score. As only one patient had a DECAF score of 4, this patient was combined with the group of patients with score 3 for this analysis.

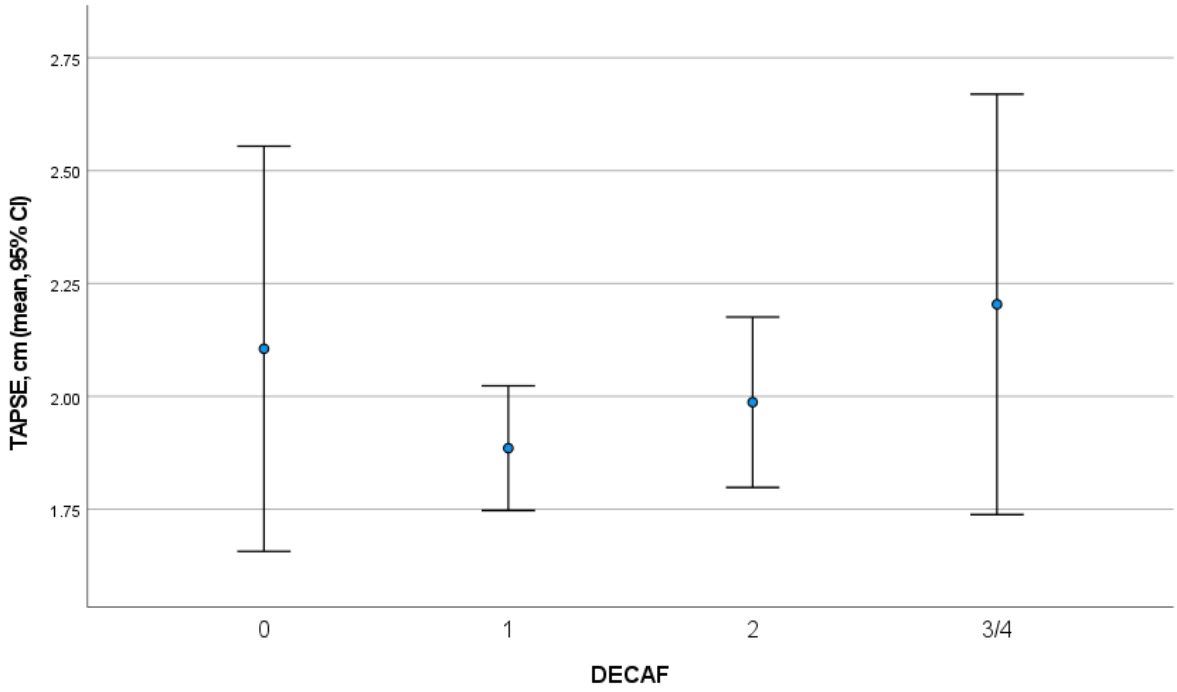
There was a weak graphical trend for mean TAPSE to be lower in cases of more severe ECOPD, although within-group variability was considerable; one-way ANOVA showed no statistically significant difference between groups (n=50, F=0.889; p=0.454).

Figure A198: Mean (95% confidence interval) TAPSE at baseline according to DECAF score



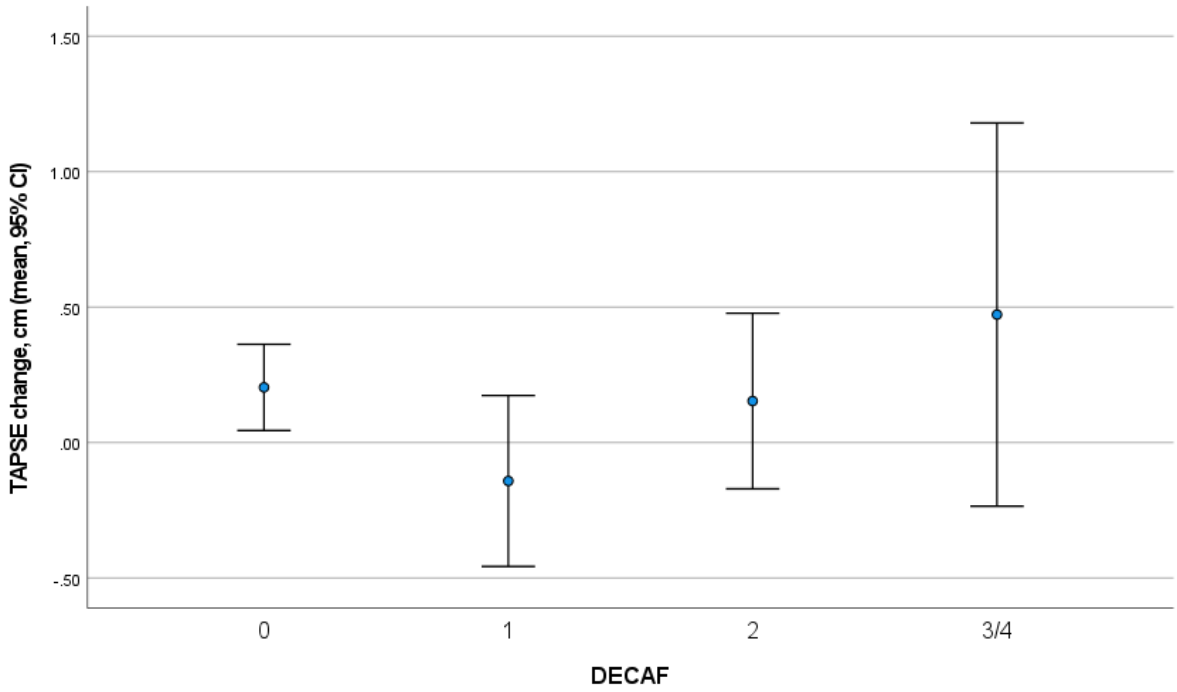
From echocardiography performed on those surviving to follow-up (n=41 with measurable TAPSE), there was no relationship between the index ECOPD severity, as measured by DECAF score, and RV function at 90-day follow-up, as measured by TAPSE. (one-way ANOVA, F=1.114; p=0.356)

Figure A2: Mean (95% confidence interval) TAPSE at 90-day follow-up according to DECAF score of index ECOPD admission



There was a trend for TAPSE *change* to be more positive between baseline and follow-up with higher DECAF scores; one-way ANOVA did not show a significant difference between means, however (n=35, F=2.299, p=0.097).

Figure A3: Mean (95% confidence interval) of TAPSE change between baseline and 90-day follow-up according to DECAF score of index ECOPD admission

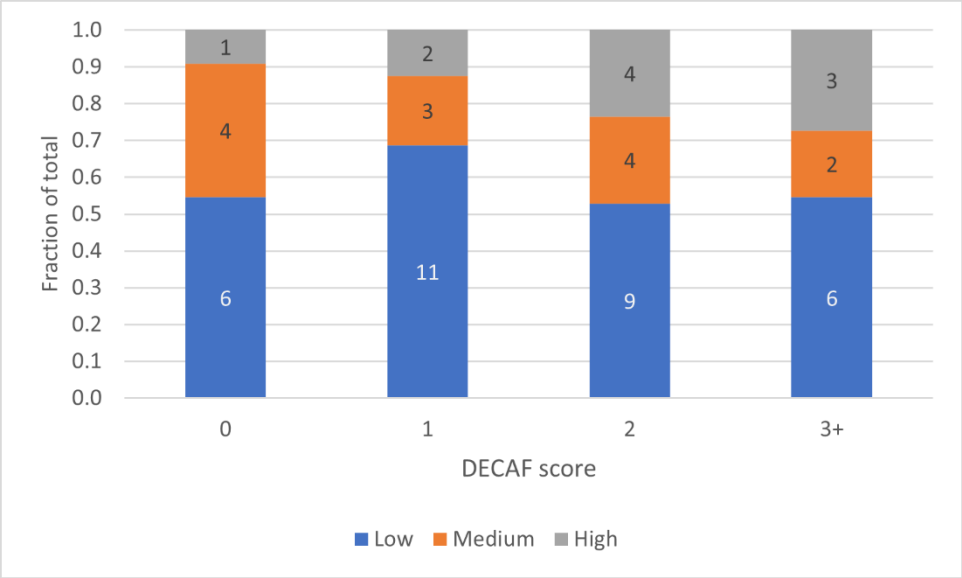


Taken together, these results suggest a possible signal of more significant transient impairment of longitudinal RV function in patients who had more severe ECOPD, as measured by DECAF.

Estimated pulmonary artery pressure/pulmonary hypertension probability

An alternative objective method of assessing right heart function is via the velocity of tricuspid regurgitation. Pulmonary hypertension probability was calculated from TR velocity in line with guideline recommendations. In the cohort studied, only 70% of patients had measurable TR, whereas all could have pulmonary hypertension probability estimated.

Figure A4: Baseline pulmonary hypertension probability classes according to DECAF score of index ECOPD admission



There appeared to be a graphical trend for a greater proportion of patients with the highest DECAF scores to have a high probability of pulmonary hypertension, in keeping with TAPSE measurements. However, there was no statistically significant association between DECAF score and pulmonary hypertension probability (p=0.839; Fisher's exact test).

Regarding *change* in right heart function specifically, 43 pairs of pulmonary hypertension probability assessments were available. The most common outcome for patients in each category of pulmonary hypertension probability at baseline was to remain in the same category at follow-up (if still alive and in face-to-face follow-up):

Table A1: Pulmonary hypertension probability class at baseline and 90-day follow-up

		Pulmonary hypertension probability at baseline		
		Low	Medium	High
Pulmonary HTN probability at follow-up	Low	**17**	4	2
	Medium	5	**5**	2
	High	2	0	**6**

However, as demonstrated above, changes in the classification of pulmonary hypertension probability were not uncommon. 8 patients demonstrated a reduction in from medium or high probability at baseline to a lower probability at follow-up. DECAF scores were not significantly

different in those whose pulmonary hypertension probability fell vs. the rest of the cohort (p= 0.247, MWU test).

Changes in right heart function and cardiovascular comorbidity

In section 7.3.5, relationships between RV function, based on the global assessment by the sonographer, and comorbid heart disease, were assessed. Analyses using TAPSE and pulmonary hypertension probability are contained in this section of the appendix.

Mean TAPSE change between baseline and follow-up assessments, measured in 35 patients, was compared between patients with and without diagnoses of major cardiac comorbidities post-SCA:

Table A2: Comparison of TAPSE change between baseline and 90-day follow-up in patients with and without heart disease comorbidity. NB: only one patient included in this analysis had AF.

	TAPSE change, mean (SD, n)		
Heart disease comorbidity following SCA	Comorbidity present	Comorbidity absent	P value‡
Moderate-severe LVSD	0.43 (0.32, 3)	0.08 (0.46, 32)	0.189
HF without moderate-severe LVSD	0.08 (0.57, 11)	0.12 (0.42, 24)	0.857
Myocardial infarction	-0.02 (0.61, 6)	0.14 (0.43, 29)	0.567
Atrial fibrillation	0.06 (n/a,1)	0.11 (0.47, 34)	-
Moderate-severe coronary artery disease*	0.15 (0.45, 22)	0.04 (0.50, 13)	0.517
Any major treatable heart disease†	0.13 (0.49, 28)	0.02 (0.32, 7)	0.572
* CACS >100 or PCI, without diagnosis of MI † At least one of moderate-severe LVSD, MI, moderate-severe CAD ‡ Fisher's exact test			

None of the comparisons revealed a significant difference. The highest mean TAPSE change, 0.43 cm, was seen in the group who had moderate-severe LVSD, although this group comprised only 3 patients; the high mortality and non-attendance rate encountered with these patients reduced the group size substantially.

As shown in Table A1, the probability of pulmonary hypertension changed during follow-up in a substantial proportion of patients: in 8 patients the probability decreased from baseline to follow-

up, in 7 it increased; pulmonary hypertension probability was unchanged in 23.

Table A3: prevalence of heart disease comorbidity amongst patients with unchanged, decreased and increased probability of pulmonary hypertension between baseline and follow-up

	Pulmonary hypertension probability change			
Heart disease comorbidity following SCA	Unchanged *n=23*	Decreased *n=8*	Increased *n=7*	P value‡
Moderate-severe LVSD	10.7	0.0	28.6	0.216
HF without moderate-severe LVSD	21.4	75.0	0.0	0.003
Myocardial infarction	10.7	12.5	28.6	0.395
Atrial fibrillation	3.6	12.5	0.0	0.581
Moderate-severe coronary artery disease*	64.3	50.0	85.7	0.632
Any major treatable heart disease†	82.1	62.5	100.0	0.180

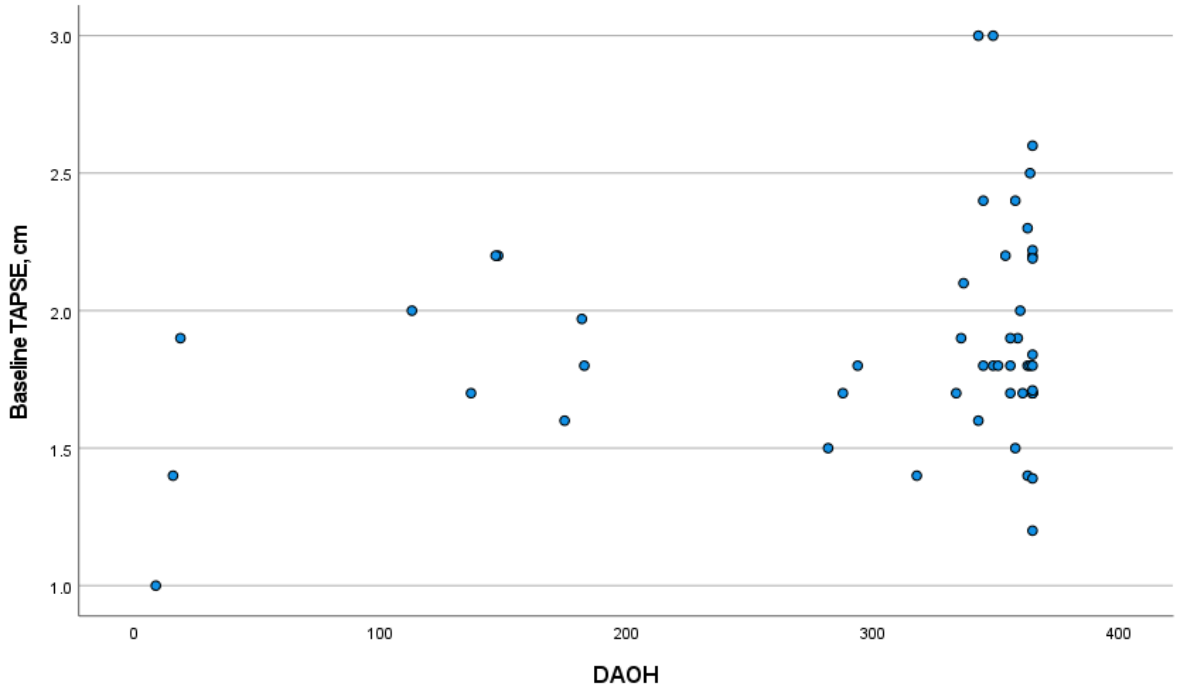
* CACS >100 or PCI, without diagnosis of MI
† At least one of moderate-severe LVSD, MI, moderate-severe CAD
‡ Fisher's exact test

In interpreting the comparison of comorbidity burden between the three pulmonary hypertension probability trajectories, it must be remembered that moderate-severe LVSD and HF without moderate-severe LVSD are mutually exclusive categories. This complicates interpretation of the proportions of patients with these diagnoses, and the accompanying statistical tests for association between the categories. Perhaps most informative, albeit statistically insignificant by Fishers' exact test, is the burden of any major heart disease: this was lowest in the group whose pulmonary hypertension probability decreased from baseline to follow-up; contrastingly, cardiac comorbidity was universal amongst those patients in whom pulmonary hypertension probability *increased* over this interval.

Right heart function and DAOH

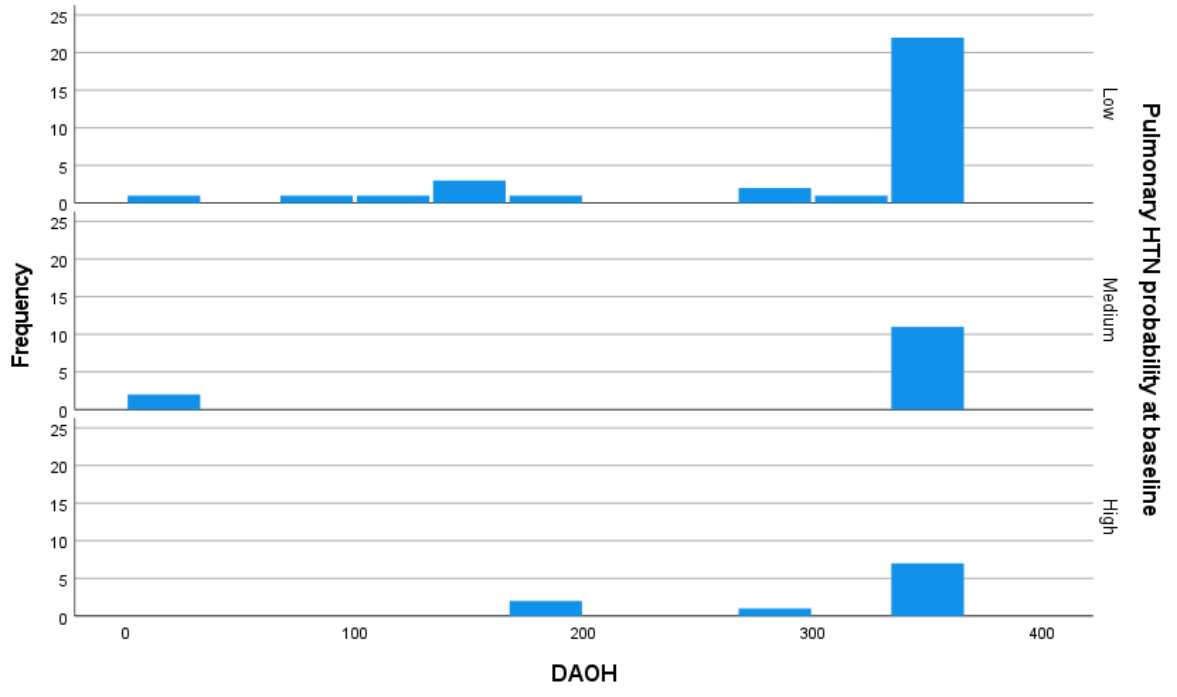
In section 7.3.6, the relationship between RV dysfunction, based on the global assessment by the sonographer, and DAOH was assessed. As an additional, continuous, measure of right heart function, TAPSE was plotted against DAOH. There was evidence of a weak positive correlation between TAPSE and DAOH, although the range of TAPSE values observed for patients with the highest values of DAOH was extremely broad, and the correlation was not statistically significant (Pearson correlation coefficient 0.224; p=0.117)

Figure A5: Scatter plot: DAOH vs. TAPSE at baseline



Finally, the distributions of DAOH for different classes of probability of pulmonary hypertension at baseline (low, n=32; medium, n=13; high, n=10), were compared. There was no visual or statistically significant difference in the distribution of DAOH across the 3 classes (p=0.778, Kruskal-Wallis test).

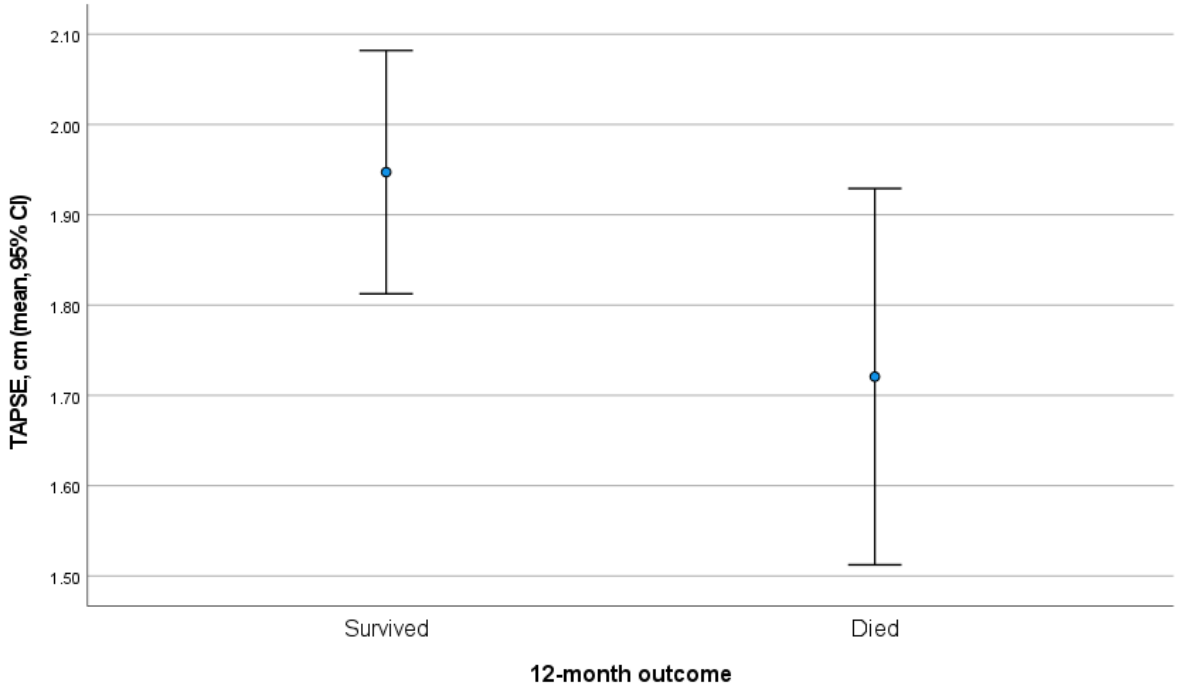
Figure A6: Distribution of DAOH according to pulmonary hypertension probability



Mortality and readmissions

Considering the objective measures of RV function, there was a trend towards those who died during follow-up having a lower mean TAPSE than those who survived (mean difference 0.23cm [95% CI -0.03 – 0.48, p=0.078]).

Figure A7: Mean (95% confidence interval) TAPSE according to survival



Mean (SD) TAPSE was 1.90 (0.41) cm in those who were readmitted during the 12 months of follow-up, and was not significantly different (1.85 [SD 0.39] cm) in those who survived with readmission (p=0.737; Student's T test).

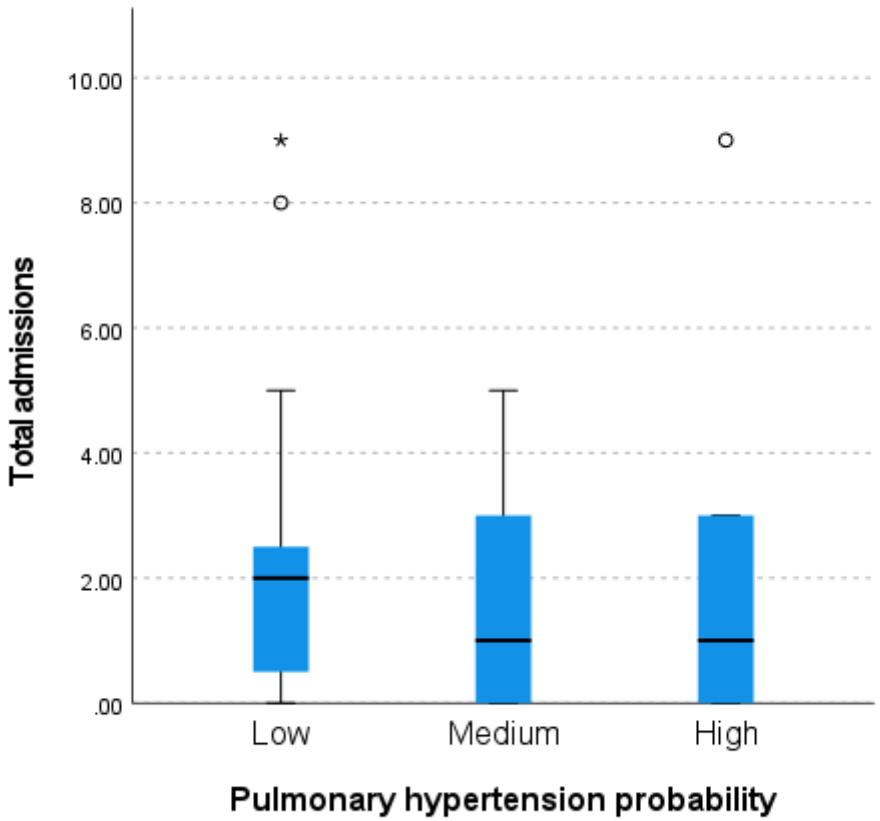
There was no significant difference in mortality, or the proportion of patients experiencing readmission, according to the classification of pulmonary hypertension probability made at baseline echocardiography:

Table A4: Mortality and readmission rates according to pulmonary hypertension probability at baseline

	Pulmonary hypertension probability			
	Low n=32	Medium n=13	High n=10	P value*
Mortality, %	28.1	15.4	30.0	0.690
Readmission, %	75.0	69.2	70.0	0.919
*Fisher's exact test				

Likewise, there was no difference in the number of admissions experienced by patients in the 3 classes of pulmonary hypertension probability (p=0.737, Kruskal-Wallis test).

Figure A8: Box plots: admissions in 1 year of follow-up according to pulmonary hypertension probability at baseline



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