ADEnosine testing to determine the need for Pacing Therapy with the additional use of an Implantable Loop Recorder

(ADEPT-ILR)

Permanent pacing in patients with unexplained syncope and a positive adenosine test: a randomised, double blind, placebo-controlled, crossover trial

A thesis presented for the degree of
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Abstract

Aim: To determine the efficacy of permanent pacing in preventing syncopal episodes in patients with unexplained syncope and a positive adenosine test via a randomised double-blind placebo-controlled crossover trial with an accompanying negative adenosine test implantable loop recorder arm.

Methods: Individuals presenting to secondary care with unexplained syncope underwent adenosine testing as defined by the European Society of Cardiology. Those with a positive test had a permanent pacemaker implant and were randomised to pacemaker on or off for 6 months before crossing over to the alternative mode. Those with a negative adenosine test underwent a loop recorder implantation. The primary outcome was cumulative syncope burden as reported by monthly syncope diaries.

Results: Fifty-two patients were included in the trial and had adenosine testing. There were 35 positive adenosine tests (67%) and 17 negative adenosine tests (33%). There was a mean of 0.4 fewer syncopal episodes per patient during the pacemaker on period compared to the pacemaker off period (1.2 vs. 1.6 episodes) with a higher relative risk of syncope in the pacemaker off period compared with the pacemaker on (RR 2.1, 95% CI 1.0 to 4.4, p=0.048). In the adenosine negative arm, one patient developed bradycardia requiring permanent pacing, giving a negative predictive value of the adenosine test for identifying a bradycardia pacing indication of 0.94 (95% CI 0.69 to 1.0).

Conclusion: Permanent pacing reduces the syncope burden in patients with unexplained syncope and a positive adenosine test, whilst a high negative predictive value demonstrates the low likelihood of a missed opportunity for pacemaker implantation. Our study suggests that a positive adenosine test unmasks bradycardia pacing indications without the need for

prolonged and invasive investigations, providing opportunity for early and effective intervention.

Dedication

This work is dedicated to my wife, Irene, and my three children, Anna, Charlie and Ruairi for understanding and permitting my need to persist with it. I love you all.

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1.1 Syncope

1.1.1 Definition of syncope

The term syncope comes from the Greek 'synkopḗ' meaning to 'cut short' and is precisely defined in a medical context by the European Society of Cardiology as 'transient loss of consciousness secondary to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous recovery' (Task Force for the *et al.*, 2009). The transient global hypoperfusion is the consequence of a variety of cardiovascular disorders that result in impaired cerebral blood flow with consequent loss of consciousness and postural tone.

1.1.2 Epidemiology of syncope

Whether one examines the incidence of a first episode of syncope or the lifetime prevalence of syncope, either in the general population, in those attending the Emergency Department or in those admitted to hospital, the numbers differ significantly. The primary reason for this is that a significant number of those suffering a syncopal episode do not seek medical attention. Estimates range from 44% in a cohort from the seminal cardiovascular epidemiological study of the Framingham population in Massachusetts, USA, the most frequently cited report into the incidence of syncope (Soteriades *et al.*, 2002) to 73% in a more contemporary population of Dutch middle-aged adults (Ganzeboom *et al.*, 2006). It is most useful for the purpose of this thesis, as it is built around a randomised controlled trial assessing unexplained syncope presenting to acute medical services, to examine the incidence of syncope in those presenting to the Emergency Department or Medical Assessment Suite. However, this incidence must be placed in the context of the general population for a fuller understanding of the clinical picture.

1.1.2.1 *Incidence of Syncope in the General Population*

Syncope is common in the general population, more so in females, and presents in a bimodal pattern at characteristic ages, with peaks in late childhood/early adulthood and in those over 65 years. Contemporary data from the Framingham Heart Study and Framingham Offspring Study involving 7814 participants with a mean age of 51 ± 14 years followed up for a mean of 17 years report a prevalence of first syncope of 6.2 per 1000 person years (Soteriades *et al.*, 2002). The rate increases with age and rises sharply at age 70 years from 5.7 events per 1000 person years in men aged 60-69 years to 11.1 in men aged 70-79 years and a further jump to 16.9 in men aged ≥ 80 years. The incidence was equal amongst men and women when adjusted for age (7.2 per 1000 person years).

Others, studying different populations and reporting either incidence of first syncope or lifetime prevalence of syncope, report different findings (**Table 1.1**). The other principal study reporting incidence of first syncope concerns a cohort from a Belgian general practice register from 1994-2008. This comprised 2,485 patients with syncope and 13,909 age and sex-matched controls (Vanbrabant *et al.*, 2011). The incidence of first syncope was 1.91 per 1000 person years (95% CI 1.83-1.98) and significantly greater in females (2.42 per 1000 person years [95% CI 2.32-2.55] in females versus 1.4 [95% CI 1.32-1.49] for males). Similar to the Framingham data, there was a peak in incidence in those over 65 years but also an additional earlier peak in those aged 15-24.

Study	Setting	Timeframe	Number	Age Mean ± SD	Measure	Incidence/ Prevalence
Vanbrabant 2011	General practice network, Belgium	1994-2008	16694	Not available	First incidence of syncope	1.91 per 1000 person years
Serletis 2006	Medical students and first degree family members, Canada	2006	Offspring: 166 Parents: 124	Offspring: 26 ± 5 years Parents: 57 ± 5 years	Lifetime prevalence of syncope	Offspring: 31% Parents: 35%
Chen 2006	Randomly selected residents ≥ 45 years in Minnesota, USA	1998-2000	1925	63 ± 12 years	Lifetime prevalence of syncope	19%
Thijs 2006	Randomly selected control population aged 20-60 years in epidemiological study into migraine, Netherlands	2004	153	48 ± 8 years	Lifetime prevalence of syncope	31%
Ganzeboom 2006	Randomly selected 35-60 years old from population register Netherlands	2011-2003	549	48 ± 7 years	Lifetime prevalence of syncope	35% or 18.1 per 1000 person years
Ganzeboom 2003	Medical students returning anonymous questionnaire, Netherlands	2002	394	21 years*	Lifetime prevalence of syncope	39% or 39.7 per 1000 person years
Soteriades 2002	Participants in Framingham studies, USA	1971-1998	7814	51 ± 14 years	First incidence of syncope	6.2 per 1000 person years

Table 1.1. Contemporary data reporting the incidence or lifetime prevalence of syncope in the general population. *Median value; no IQ range reported.

1.1.2.2 *Lifetime Prevalence of Syncope in the General Population*

Contemporary studies that report the lifetime prevalence of syncope in the general population have focused on differing populations (Table 1.1). Ganzeboom *et al* reported a lifetime prevalence of syncope of 39% (39.7 per 1000 person years) in a cohort of 394 Dutch medical students with a median age of 21 years(Ganzeboom *et al.*, 2003). Syncope was more common in females rather than males (47% versus 24% RR 1.9 95% CI 1.3-2.7). The median age at presentation with a first episode of syncope was 15 years in both men and women. An additional study in 290 Canadian medical students and their first degree relatives reports a lifetime incidence of syncope of 31% in the offspring (n=166, mean age 26 ± 5 years) and 35% in the parents (n=124, mean age 27 ± 5 years)(Serletis *et al.*, 2006). The median age of first syncope was 14 years (IQ range 12-18 years) in the offspring and 13 years (IQ range 10-25 years) in the parents.

A further paper from the group that had previously reported on Dutch medical students focused on the prevalence of syncope in a randomly selected sample of 549 adults aged 35-60 years (mean age 48 ± 7 years) from a Dutch population register (Ganzeboom *et al.*, 2006). The lifetime prevalence of syncope was 35% (95% CI 31-39%) or 18.1 per 1000 person years, with syncope more common in women (41% [95% CI 35-47%] versus 28% [95% CI 23-34%], p=0.003) and the median age of the first episode of syncope was 18 years (IQ range 13-28). These figures are very similar to a smaller study (n=154) of another Dutch population, this time the control group in a case-control study concerned with migraine, with a mean age of 48 ± 8 years, that reports a lifetime prevalence of syncope of 31% (Thijs *et al.*, 2006). Again, syncope was more common in women (32%) than in men (26%) and the mean age at first syncope was 15-24 years (23 ± 13 years). Lastly, Chen *et al* reported the lifetime prevalence of syncope in a cohort of 1925 randomly selected age and sex matched controls in a study concerning the prevalence of cardiac dysfunction and cardiovascular disease in the community of Olmsted County, Minnesota, USA (Chen *et al.*, 2006). The mean age was 63 years and lifetime prevalence syncope 19% (95% CI 17-21%); higher in women than in men (22% versus 15%, p=0.001). The median age of the first episode of syncope was 25 years. This was higher for men than women (33 years versus 22 years, p =0.04). Interestingly, the

prevalence of syncope did not rise with age (20% in those aged 45-54 years, 20% in 55-64 years, 15% in those aged 65-74 years and 21% for those ≥ 75 years, p=0.86).

1.1.2.3 *Summary*

The reported incidence of first syncope in selected sample of the general population in contemporary literature ranges from 1.9 – 6.2 per 1000 person years. This is lower than the reported lifetime prevalence of syncope in the general population that ranges from 19-39%. This is simply explained- only those episodes of syncope occurring during the study periods were included with no reference to a prior syncope history.

There are two peaks of increased syncope: in those aged 15-24 years, when most first episodes of syncope tend to present and is more common in women; and in the older population starting around 60 years and rising with increasing age. The lifetime prevalence of syncope is higher in women than in men.

1.1.2.4 *Incidence of Syncope in those presenting to Acute Medical Services*

The proposed participants in this study are to be selected from those presenting to acute medical services (ED or Medical Assessment Suite) and thus it is important to understand the published burden of syncope presenting this way (**Table 1.2**).

Study	Setting	Timeframe	Number	Age Mean ± SD or Median (IQ range)	Measure	Incidence/ Prevalence
Ruwald 2012	Danish National Patient Register Denmark	1997-2009	127508	65 yrs (IQ range 49-81 yrs)	First time episode of syncope presenting to ED, admitted to hospital or seen as an out-patient	17.2 per 1000 person years 0.6% of ED attendances 0.9% of hospital admissions
Malasana 2011	Network of 9 hospitals Utah, USA	2008-2009	2701	48 ± 21 years	Presentation to ED/out-patient clinic or admitted to hospital	0.29% of all attendances 9.5 patients per 1000 inhabitants
Baron-Ezquevias 2010	Registry of 19 hospitals Spain	2009	124037	57.3 ± 22.8 yrs	Presentation with syncope	1.14% of ED attendances
Numeroso 2010	Teaching hospital ED Italy	2008	42087	60.3 yrs	Presentation with syncope	2.3% of attendances
Alshekhlee 2009	National Inpatient Sample USA	2000-2005	305932	69 ± 17.7 yrs	Attendance at hospital with syncope	0.80-0.93 admissions per 1000 person years 0.6% of hospital admissions
Olde-Nordekamp 2009	City centre ED Netherlands	2000-2002	71309	46 yrs (IQ range 30-65 yrs)	Attending ED or chest pain unit with syncope	0.94% of attendances
Disertori 2003	Registry of 27 hospital, Italy	2001	105173	60 ± 23 yrs	Presentation with syncope	0.95% of attendances
Blanc 2002	Network of hospital, France	1999-2000	37475	57 ± 23 yrs	Attending ED with syncope	1.21% of attendances
Sarasin 2001	Teaching hospital ED Switzerland	1997-1999	67387	60 ± 23 yrs	Presentation with syncope	1.1% of attendances

Table 1.2. Contemporary data reporting the incidence or lifetime prevalence of syncope presenting to acute medical services

Unsurprisingly, the incidence of syncope in those attending acute medical services is lower than the incidence of first syncope and lifetime prevalence of syncope in the general population. This is because significant numbers of people do not seek medical attention following an episode of syncope. It is estimated that for every syncopal event in the general population, a ratio of between 1:2 and 1:4 seek medical attention and only between 1:10 and 1:50 attend acute medical services (Brignole and Hamdan, 2012).

Two studies have examined the prevalence of syncope on a national level – the first examining presentations to the ED, out-patient clinic or admitted to hospital across the whole of Denmark (Ruwald *et al.*, 2012); and the second concerning hospital admissions with syncope across the USA (Alshekhlee *et al.*, 2009).

1.1.2.5 ***Incidence of Syncope in those presenting to Acute Medical Services on a National Level***

The Danish study (Ruwald *et al.*, 2012) comprised 127, 508 patients identified from the National Inpatient Register as seeking medical attention for syncope between 1997-2009 and reports an overall incidence of a first-time episode of syncope of 17.2 per 1000 person years. Three peaks were identified, the first involving females around aged 20, a second smaller peak around aged 60 and a significant third peak around 80 years of age. The incidence rate in those of 20 years was 9.0 per 1000 person years compared to 40.2 per 1000 person years in those of 70 years and rising to 81.2 per 1000 person years in those over aged 80 years. Interestingly, the incidence rate rose with time from 13.8 per 1000 person years in 1997 to 19.4 per 1000 person years in 2009, suggesting a rising syncope burden as the population ages and/or improved rates of diagnosis over time.

The study from the USA (Alshekhlee *et al.*, 2009) focuses on 305,932 patients admitted to hospital with syncope (including those presenting to ED and being discharged home) from the National Inpatient Sample database between 2000-2005. The incidence rate was fairly static across the five year period (0.80, 0.85, 0.91, 0.93, 0.91 and 0.88 admissions per 1000 person years for 2000, 2001, 2002, 2003, 2004 and 2005

respectively), in contrast to the data from Denmark. Only a small proportion of attenders were aged under 40 years (n=23,713, 7.7%). No further age-specific data are provided but the incidence rate is much lower in the USA; perhaps reflecting differing healthcare systems in the two countries. The hospital admission rates were very similar, however, suggesting similar management strategies.

1.1.2.6 *Incidence of Syncope in those presenting to Acute Medical Services on an Individual Hospital Level*

A number of further studies have examined the incidence of people presenting with syncope to either individual hospitals or a regional or city network of hospitals (**Table 1.2**). Sarasin *et al* published data from their own teaching hospital ED in Switzerland (n=67,387, mean age 60 ± 23 years) (Sarasin *et al.*, 2001) where syncope accounted for 1.1% of attendances. A similarly sized study of a slightly younger population (median age 46 years [IQR 30-65 years]) from a city centre ED in the Netherlands reported an incidence of syncope of 0.94% (Olde Nordkamp *et al.*, 2009); and a slightly smaller one (n=42,087, mean age 60.3 years) one from a single centre in Northern in Italy reports a slightly higher incidence of 2.4% (Numeroso *et al.*, 2010).

Contemporary studies that have examined the incidence of syncope presenting to acute medical services across a network of hospitals come from a range of countries (**Table 1.2**). *Blanc et al* report an incidence of 1.21% in a small network of hospitals in a large city in Northern France (Blanc *et al.*, 2002), very similar to slightly larger networks in Italy (0.95% of ED attendances) (Disertori *et al.*, 2003) and Spain (1.14% of attendances) (Baron-Esquivias *et al.*, 2010). Lastly, data from a network of hospitals in Utah, USA showed a lower incidence of 0.29% of ED attendances, corresponding to a yearly prevalence of 9.5 patients per 1000 inhabitants (Malasana *et al.*, 2011). The yearly prevalence of syncope increased with age rising to 40 per 1000 inhabitants in those over 80 years.

1.1.2.7 *Summary*

Overall, the mean age of those presenting to acute medical services is older than the reported incidence of syncope in the general population; generally in the late fifties

compared to the late forties. The proportion of ED attendances with syncope is remarkably consistent in different settings across different countries at around 1%. The data on changes in the incidence of syncope over time are not consistent but it is certainly conceivable that this is rising with the ageing population and clear evidence that syncope is more prevalent in later years.

1.1.3 Aetiology of syncope

Syncope is not in itself a diagnosis. Rather, it is a symptom, for which the underlying mechanism must be identified and treated accordingly. There are three broad categories under which syncope is classified:

- Reflex (neurally-mediated) syncope;
- Syncope due to orthostatic hypotension; and
- Cardiac (cardiovascular) syncope.

The approximate frequencies of presentation under these categories, based on multiple international data sources, are provided by Sutton (Sutton, 2013). Reflex syncope accounts for approximately 60%, orthostatic hypotension 15%, cardiac arrhythmia 10%, structural cardiovascular 5% and unexplained/unclassified 10%. Subsequent sub-classification as outlined by the European Society of Cardiology (Task Force for the *et al.*, 2009) is given in Table 1.3. These figures from Sutton do not take into account age; although neurally-mediated syncope is the most frequent cause of syncope across all age groups (Parry and Tan, 2010); cardiac syncope and orthostatic hypotension are more frequent in the older population (Kenny, 2003; Del Rosso *et al.*, 2005). Similarly, they do not take into account the site of presentation; neurally-mediated syncope dominates presentation to acute medical services whilst arrhythmia makes up a greater proportion of referrals to specialist syncope units. Nonetheless, these approximations give a good indication of the aetiology of syncope in the real world published literature.

Reflex (neurally-mediated) syncope	Syncope due to orthostatic hypotension	Cardiac (inc. structural cardiovascular) syncope
Vasovagal • Mediated by emotional distress: pain, fear, instrumentation, blood phobia • Mediated by orthostatic stress	Primary autonomic failure • Pure autonomic failure • Multiple system atrophy • Parkinson's disease • Lewy body dementia	Primary arrhythmia <u>Bradycardia</u> • Sinus node dysfunction (including bradycardia-tachycardia syndrome) • Atrio-ventricular conduction system disease • Cardiac implanted electronic device malfunction <u>Tachycardia</u> • Supraventricular • Ventricular (idiopathic, secondary to structural heart disease or to channelopathies)
Situational • Cough. sneeze • Gastrointestinal stimulation (swallow, defecation, visceral pain) • Micturition (post micturition) • Post-exercise • Post-prandial • Others e.g. laugh, weight-lifting, brass instrument playing	Secondary autonomic failure • Diabetes mellitus • Amyloidosis • Uraemia • Spinal cord injuries	Drug-induced bradycardia and tachycardia
Carotid sinus syndrome	Drug-induced orthostatic hypotension • Alcohol • Vasodilators • Diuretics • Phenothiazines • Anti-depressants	Structural Disease <u>Cardiac</u> • Valvular • Ischaemia/infarction • Hypertrophic cardiomyopathy • Cardiac masses e.g. atrial myxoma • Pericardial disease/tamponade • Congenital anomalies of cardiac valves, chambers or coronary arteries • Prosthetic valve dysfunction Others • Pulmonary embolus • Aortic dissection • Pulmonary hypertension
Atypical forms (without apparent triggers and/or atypical presentation	Volume depletion • Haemorrhage • Diarrhoea • Vomiting	

Table 1.3 Classification of syncope

1.1.3.1 *Reflex (neurally-mediated) syncope*

Reflex syncope incorporates the dominant presentation of syncope across all age ranges - the simple (vasovagal) faint. In vasovagal syncope, concurrent stimulation of the parasympathetic nervous system and inhibition of the sympathetic nervous system in response to an external stimulus results in haemodynamic disturbance comprising either:

1. Slowing of the sinus rate and/or atrio-ventricular block (cardio-inhibition);
2. Fall in blood pressure (vasodepression);
3. Or a combination of cardio-inhibition and vasodepression (mixed type).

Situational syncope refers to a specific situation, e.g. micturition which brings about the same sympathetic and parasympathetic imbalance and subsequent haemodynamic derangement as that of vasovagal syncope.

Carotid sinus syndrome refers to syncope secondary to an oversensitive carotid baroreceptor reflex. Classically, inadvertent stimulation of the carotid region on turning the head or on hyperextension of the neck is described. Diagnosis requires the reproduction of spontaneous symptoms (syncope or near syncope) during 10 seconds of sequential left and right carotid sinus massage performed supine and erect under continuous heart rate and periodic blood pressure measurement (Puggioni *et al.*, 2002; Parry *et al.*, 2009b). It accounts for around 1% of presentations with syncope (van Dijk *et al.*, 2008) and is a disease of the older person, being very rare under the age of 40 years. It is well recognised that due to amnesia for loss of consciousness in the older patient group affected by carotid sinus syndrome (Parry *et al.*, 2005) this condition may present as 'falls' rather than syncope and the incidence is higher when one includes this group (Richardson *et al.*, 1997; Kenny *et al.*, 2001; Parry *et al.*, 2009c).

1.1.3.2 *Orthostatic hypotension*

This is the second most frequent cause of syncope in clinical practice. There is a degree of overlap with reflex syncope as orthostatic stress in itself may be a precipitant.

However, it is a separate entity in its own right. It is defined as a sustained fall from baseline of ≥ 20 mm Hg in systolic blood pressure and/or ≥ 10 mm Hg in diastolic blood pressure within 3 minutes of active standing that may or may not be accompanied by symptoms (Freeman *et al.*, 2011). It comes in two principal forms: secondary to a failure of the autonomic nervous system to facilitate the compensatory haemodynamic mechanisms associated with a change in posture; or more commonly, secondary to an alteration in intravascular volume status, either due to a drug(s) induced effect(s) or to direct volume depletion. It is more common in the older patient, in those taking vasoactive medication and in Addison's disease.

1.1.3.3 ***Cardiac (cardiovascular) syncope***

Cardiovascular syncope is broken down into syncope secondary to cardiac rhythm disturbance, either bradycardia or tachycardia; and syncope secondary to structural heart disease (with a resultant reduced cardiac output). It is more common in those over 65 years (Del Rosso *et al.*, 2005)

Primary cardiac rhythm disturbance, that is, rhythm disturbance related to intrinsic conducting system disease rather than due to drug side effects/toxicity, accounts for around 10% of syncope. Bradycardia causing syncope, either sinus node disease or atrioventricular block, is more common than tachycardia, particularly in the absence of structural heart disease (Brignole *et al.*, 2001), and is more common in the older person (Parry and Tan, 2010). The identification of a cardiac rhythm disturbance is vital as it is readily treatable by intervention – most frequently permanent pacemaker implantation for bradycardia but also drug therapy, radiofrequency ablation or implantable cardiac defibrillator implantation in tachycardia.

Syncope secondary to structural cardiac disease refers to mechanical restriction e.g. pericardial effusion or obstruction e.g. severe valvular aortic stenosis or a pulmonary embolus resulting in reduced cardiac output and subsequent cerebral hypoperfusion; or an intrinsic pathological process of myocardial tissue, either inherited or acquired, resulting in predilection for arrhythmia e.g. hypertrophic cardiomyopathy.

1.1.3.4 ***Low adenosine syncope***

Recent work primarily by Brignole's group has postulated the distinct clinical entity of "low adenosine syncope" (Brignole *et al.*, 2011; Guieu *et al.*, 2015; Aste and Brignole, 2017; Brignole *et al.*, 2017). This consists of paroxysmal AV block associated with low levels of plasma adenosine and presents with unexplained syncope without prodrome. Whether it represents a form cardiovascular or neurally-mediated syncope is as yet undetermined. For now, it remains an area of ongoing research.

1.1.4 Investigation of syncope

The diagnostic armoury in the investigation of syncope is substantial (Table 1.4).

Initial investigations	ECG monitoring	Provocation tests	Imaging
History	In-patient telemetry	Tilt table testing	Echocardiography
Clinical examination	External ambulatory monitoring	Carotid sinus massage	Cardiac CT
12 lead ECG	External event (loop) recorder	Adenosine testing	Cardiac MRI
Blood tests e.g. serum electrolytes	Implantable loop recorder	Exercise treadmill testing	Cardiac catheterisation
		Drug testing	Brain CT
		Electrophysiological study	Brain MRI
			EEG

Table 1.4 Diagnostic tools frequently used syncope.

ECG = electrocardiography; CT = computed tomography; MRI = magnetic resonance imaging; EEG = electroencephalography.

The 3 key steps, ones that should be undertaken in every person presenting with syncope, comprise:

I. A detailed history, with particular emphasis on the circumstances of the syncopal episode, any prior syncopal episodes, family history of syncope, current drug history and current co-morbid conditions (Krahn *et al.*, 2013);

II. Clinical examination, which should include examination of the cardiovascular and neurological systems examination and supine and upright blood pressure; and
III. A 12-lead electrocardiogram.

In most cases these three features will lead to a definitive or provisional diagnosis (Croci *et al.*, 2002; Parry and Tan, 2010). Subsequent investigations will be directed by this diagnosis, itself influenced by the mode of presentation, age at presentation and underlying co-morbid conditions. It is important that the supine and upright blood pressure is measured correctly to assess for the presence of orthostatic hypotension (serial blood pressure measurement at a minimum of 1 minute intervals for 3 minutes after active standing assessing for a fall from baseline of ≥ 20 mm Hg in systolic blood pressure or≥ 10 mm Hg in diastolic blood pressure)

1.1.4.1 *ECG Monitoring*

If arrhythmic syncope is suspected, as it is likely to be in the older patient with unheralded syncope or falls, then prolonged ECG monitoring will be the cornerstone of investigation. The duration of this monitoring is determined by the frequency of syncope and is concisely outlined in clinical guidance from the National Institute of Clinical Excellence (Westby *et al.*, 2010): in those experiencing syncope several times a week or those with evidence of conducting system disease on 12 lead ECG ambulatory monitoring for up to 48 hours is recommended; in those with syncope every 1-2 weeks an external event recorder fitted for 1-2 weeks is recommended; and those with syncope occurring at a frequency of less than every 2 weeks an implantable ECG loop recorder should be offered as first line.

1.1.4.2 *Imaging*

Imaging of the cardiovascular system, and neurological system where felt appropriate, is used to investigate the presence of structural disease. The chosen modality will depend on the suspected underlying pathology. Examples include transthoracic echocardiography to assess ventricular and valvular function, cardiac CT to assess for congenital coronary artery anomalies and cardiac MRI to assess for hypertrophic

cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, inherited conditions that predispose to arrhythmia. Imaging of the brain and electroencephalography is performed when epilepsy is the suspected cause of loss of consciousness rather than syncope.

1.1.4.3 ***Provocation testing***

One of the more important aspects in the investigation of syncope is provocation testing. Here, the aim is to reproduce the clinical symptoms i.e. syncope or near syncope, under controlled conditions that allows a definitive diagnosis to be made.

The most frequent provocation test in use is tilt-table testing. It has long been established that the orthostatic challenge of tilting is a stimulus to vasovagal syncope (McMichael and Sharpey-Schafer, 1944; Fascenelli and Lamb, 1966) but formalised tilt testing in syncope did not enter routine clinical practice until the 1980s (Kenny *et al.*, 1986). Various different protocols exist (Kenny *et al.*, 2000; Parry *et al.*, 2009b) but all have a similar basis – the utilisation of tilting with or without the aid of a pharmaceutical agent to potentiate haemodynamic disturbance and to demonstrate a propensity to vasovagal syncope. Should the presenting clinical symptoms be reproduced in combination with the characteristic haemodynamic disturbances on testing then a diagnosis of vasovagal syncope can be made. Depending on the nature of this haemodynamic disturbance the test is classified as vasodepressor (hypotension only), cardioinhibitory (bradycardia only) or mixed (combination of hypotension and bradycardia) (Brignole *et al.*, 2000b). This classification is important because treatment options differ; pacemaker implantation may have a role to play in cardioinhibitory or mixed vasovagal syncope but not in vasodepressor vasovagal syncope. However, this classification is not straightforward as it has been clearly established that the response on tilt testing does not necessarily correlate with spontaneous symptoms (Brignole *et al.*, 2006a; Deharo *et al.*, 2006) and randomised trials of pacing in vasovagal syncope have failed to demonstrate efficacy (Sutton *et al.*, 2000; Connolly *et al.*, 2003; Occhetta *et al.*, 2004; Raviele *et al.*, 2004). Indeed, it has been recognised that pacing therapy can be effective in those with syncope and a cardioinhibitory response on tilt testing but only if bradycardia at the time of spontaneous syncope is demonstrated. The Third

International Study on Syncope of Unexplained Etiology (ISSUE 3) (Brignole *et al.*, 2012) involved 511 patients with at least three neurally-mediated syncopal events in the last two years that underwent implantable ECG loop recorder (ILR) implantation. Eighty nine patients had recurrent syncope with asystole documented on ILR. Seventy-seven then underwent permanent pacemaker implantation and were randomized to either dual chamber or placebo pacing. Syncope recurred in 57% of those in the placebo group and in 25% of those paced ($p = 0.039$). Whilst an impressive result, the population were highly selected with the authors estimating only 9% of all patients with vasovagal syncope would benefit from this strategy.

Another provocation test that may be undertaken is carotid sinus massage. This can facilitate a diagnosis of carotid sinus syndrome in those over 40 years of age with syncope or falls. The test involves eliciting spontaneous symptoms (syncope or near syncope) during sequential left and right carotid sinus massage performed supine and erect (Puggioni *et al.*, 2002; Parry *et al.*, 2009b). It carries a 0.1% risk of stroke (Richardson *et al.*, 2000) and should be avoided in those with a recent history of stroke or TIA and in those with carotid bruits unless imaging has excluded carotid artery stenosis > 70% (Task Force for the *et al.*, 2009).

Electrophysiology studies have been performed as part of the investigation of syncope in the past but their sensitivity and specificity are low. They are now done only when there is a clinical suspicion of tachycardia, particularly in the presence of structural heart disease (Linzer *et al.*, 1997), or for invasive investigation of atrioventricular conduction.

The final provocative test to mention is the adenosine or adenosine triphosphate (ATP) test. This is the subject of the next chapter.

1.1.4.4 ***Unexplained syncope***

There is no consensus definition of unexplained syncope but it is taken to mean an absence of a diagnosis after a minimum of:

- Clinical history;

- Clinical examination;
- 12-lead electrocardiogram; and
- Supine and upright blood pressure.

Other investigations which have formed part of the diagnostic work-up in the published literature have included many of the tests outlined in **Table 1.4**; with the most prominent being:

- Ambulatory electrocardiography;
- Head-up tilt testing;
- Carotid sinus massage;
- Transthoracic echocardiography; and
- Electrophysiology study

The proportion of syncope that remains unexplained ranges from 5-20% in dedicated syncope referral units (Alboni *et al.*, 2001; Chen *et al.*, 2003; Shen *et al.*, 2004; Brignole *et al.*, 2006b; Ammirati *et al.*, 2008) to 17-33% in patients presenting to acute medical services (Ammirati *et al.*, 2000; Blanc *et al.*, 2002; Disertori *et al.*, 2003; Olde Nordkamp *et al.*, 2009). This heterogeneity can be explained by the lack of a consensus definition and the different sites of presentation with different investigation protocols.

1.1.4.5 ***Economic impact of syncope***

Syncope, particularly when recurrent, can be devastating to sufferers, resulting in soft tissue and head injuries, fractures and road traffic accidents, with attendant loss of independence and adverse effects on work and driving. Thus, the economic impact of syncope is felt not only in direct medical care costs but also in a broader sense across the workforce and economy. The cost of syncope to the US economy has been estimated at $US 2.4 billion per annum and a mean $5,400 (95% CI $5,100 -$5,600) per hospitalisation in one study (Sun *et al.*, 2005) and a median $8,579 (IQ range $5,247 -

$14,137) in another (Alshekhlee *et al.*, 2009). This latter figure rises significantly with age ($7,908 for patients less than 50 years versus $8,579 for those aged 50 to 70 years versus $8,783 for those older than 70 years ($p<0.001$).

In Israel, a study at a single tertiary referral centre reported mean hospital costs per admission of 11,210 ± 8133 NIS (approximately £2,140± 1,476 in 2013) (Shiyovich *et al.*, 2008); and in Europe, others have shown an average cost for hospital stay and related diagnostic tests and treatments for patients with syncope of € 11,587 (Baron-Esquivias *et al.*, 2006). Finally, a study from a single district general hospital in the UK reports a mean cost of investigation and hospital stay of £1,384 per patient and cost per diagnosis of £1,949 (Farwell and Sulke, 2004).

So, because it is common in the general population and often requires extensive investigation that may include hospitalisation, syncope is costly. Strategies to mitigate this cost, principally involving earlier, accurate diagnosis and the instigation of timely, appropriate therapy are attractive not only to the individual patient but to healthcare systems.

1.1.4.6 ***Impact of syncope on quality of life***

Not only does syncope have an impact on the physical morbidity of an individual, it has significant impact on quality of life. This is through a combination of reduced mobility and capability to undertake daily living activities, either through direct injury or through fear of future syncopal events, and impaired mental health, with elevated anxiety and depression levels.

Various different instruments have been used to examine health related quality of life in syncope but regardless of the tool used results have been consistent. Linzer *et al* assessed functional and psychosocial impairment in 62 patients with recurrent syncope presenting to a specialist syncope service using the Sickness Impact Profile and the Symptom Checklist-90 measures (Linzer *et al.*, 1991). Functional impairment was found to be similar in severity to severe rheumatoid arthritis and chronic low back pain. Psychosocial impairment was greater than that observed in psychiatric in-patients. Similarly, using the EuroQoL EQ -5D instrument was used to measure quality of life in

136 individuals with recurrent syncope (mean age 40 ±17 years, 58% male). Health related quality of life was significantly impaired in all five domains of the tool (Rose *et al.*, 2000). This was particularly pronounced in those with a greater syncope burden; in those with more than six lifetime episodes of syncope, there was a significant ($p < 0.001$) negative relationship between the frequency of syncope and overall perception of health compared to those with less than six syncopal episodes.

Even in patients with a lower syncope burden, quality of life is impaired. In 382 Dutch adults (mean age 52 ± 19 years, 58% male, median number of syncopal episodes in last 12 months 2 [IQ range 1-3]) completing the Short Form 36 (SF-36) quality of life questionnaire, scores were lower on all scales compared to an age and sex-matched reference population (van Dijk *et al.*, 2006). In the same population, the Syncope Functional Status Questionnaire (SQFS), a disease specific quality of life measure in syncope, revealed that female gender, greater co-morbidity, and a higher syncope burden were associated with poorer quality of life. Interestingly, one year follow-up data from this population (van Dijk *et al.*, 2007) demonstrated that quality of life improves over time but that older age, greater co-morbidity and syncope recurrence were predictive of poorer quality of life.

It is worthy of note that the variety of quality of life questionnaires applied throughout the syncope literature makes comparisons between different studies/populations difficult. With this in mind, an effort was made by authors in Canada to tie together aspects of the EQ-5D, SQFS and others and to produce a readily applicable validated disease specific questionnaire assessing the impact of syncope of the quality of life (Rose *et al.*, 2009). The result was the 12 item Impact of Syncope of the Quality of Life (ISQL) score assessing functional impairment, fear, depression, and physical limitations in syncope. The brief but comprehensive nature of the ISQL along with its syncope specific nature make it attractive for use and, indeed, the ISQL has been used in the course of this clinical trial.

1.2 Adenosine

1.2.1 Physiology of adenosine

Adenosine is a ubiquitous purine nucleoside present in virtually all organ systems. It was initially discovered to play a role in cardiac function; in an elegant experiment in which heart muscle tissue extract was injected into the whole animal resulting in bradycardia and increased coronary arterial blood flow (Drury and Szent-Gyorgyi, 1929). Adenosine is now known to be involved in a regulatory capacity of all organs systems studied. Indeed, so abundant is adenosine that its precursor, adenosine 5'-triphosphate (ATP) is produced and metabolised by the human body in amounts approximately equal to its own weight each day (Pelleg and Belhassen, 2010).

All cells in the body are able to use free energy from the breakdown of ATP to perform a host of functions and thus all cells in the body are a potential source of adenosine. Many cells are capable of using this adenosine to reduce the individual work of that cell. This negative feedback loop is a vital component of the physiology of adenosine and has led to adenosine being aptly described as a "retaliatory molecule" (Newby, 1984).

1.2.2 Role of adenosine in the heart

In the heart, the principal role of adenosine as a "retaliatory molecule", released from cells in response to changes in energy status, is to regulate the myocardial oxygen supply-demand balance (Lerman and Belardinelli, 1991). It does this by:

- Increasing oxygen supply by promoting coronary arterial vasodilatation; and
- Reducing oxygen demand by decreasing myocardial contractility, counteracting catecholamine effects and slowing conduction within the sinoatrial (SA) and atrioventricular (AV) nodes.

It is this reduction in oxygen demand by slowing conduction in the SA and AV nodes that is of principal interest in this research.

1.2.2.1 *The adenosine regulatory system*

The regulatory adenosine system with respect to the heart comprises three essential components:

- Adenosine formation;
- Receptor-effector complex; and
- Adenosine removal.

1.2.2.2 *Adenosine formation*

Formation of adenosine is via two primary pathways, the first of which is dephosphorylation of adenosine monophosphate (AMP), catalyzed by the enzyme 5'-nucleotidase (**Figure 1.1**). This pathway is tightly regulated, attendant to bioenergetic state, and is the most important source of adenosine. The enzyme 5'-nucleotidase is present both intra- and extra-cellularly and, therefore, adenosine is formed both intra- and extra-cellularly. The adenosine generated from the intra-cellular AMP pool is the major source of adenosine in the physiological state and under ischaemic/hypoxic conditions; however, as evidenced by knockout or extra-cellular 5'-nucleotidase studies, the adenosine generated in the extra-cellular space has a prominent role to play (Borst and Schrader, 1991; Headrick *et al.*, 1992; Darvish *et al.*, 1996).

The second pathway of adenosine formation occurs intracellularly by the breakdown of S-adenosylhomocysteine (SAH) catalysed by the enzyme S-adenosylhomocysteine hydrolase (**Figure 1.1**).

The relative contributions of each of the pathways vary with physiological conditions. For example, under normal tissue oxygenation conditions a significant proportion of adenosine is derived from the SAH pathway, whereas in hypoxic conditions adenosine is principally derived from AMP (Lloyd *et al.*, 1988).

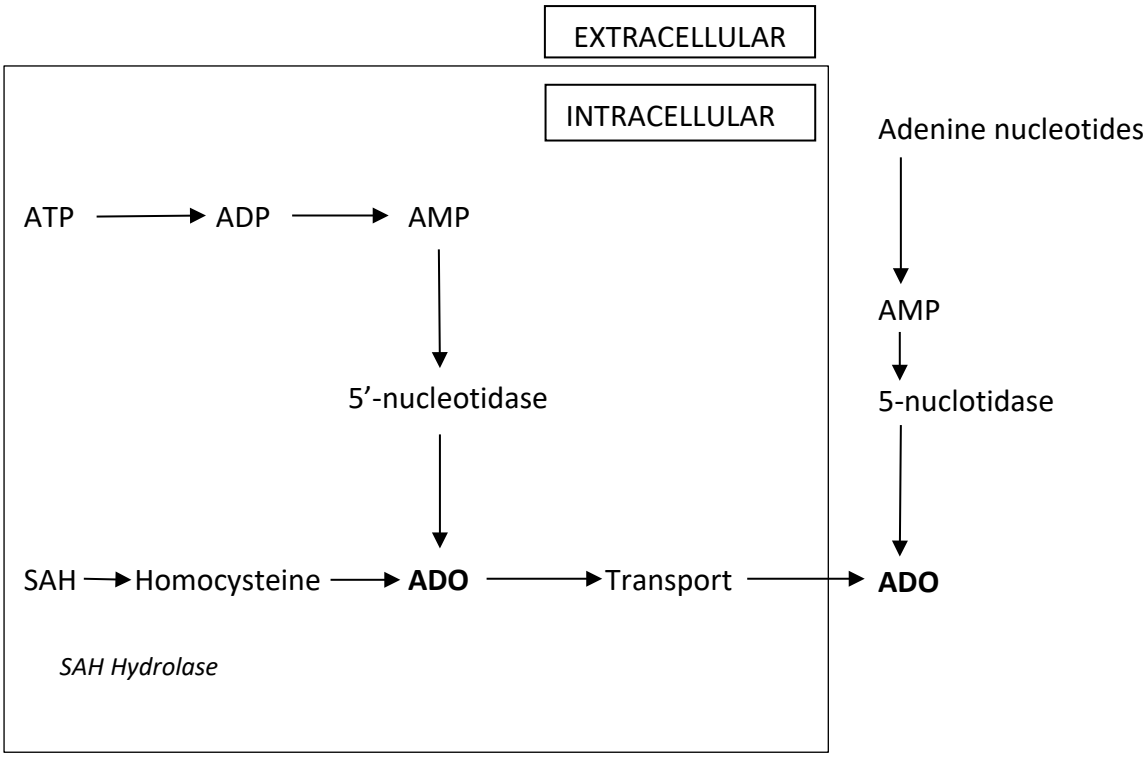

Figure 1.1. Schematic representation of adenosine formation

ATP = adenosine triphosphate, ADP = adenosine diphosphate, AMP = adenosine monophosphate, SAH = S-adenosylhomocysteine, ADO = adenosine.

1.2.2.3 ***Receptor-effector complex***

When adenosine is formed, a mechanism is required for it to exert its effects. This mechanism takes the form of a receptor-effector complex.

There are four identified subtypes of transmembrane adenosine receptor [A1, A2A, A2B and A3]. Each has a distinct distribution within body tissue and receptor-effector coupling within the superfamily of guanine nucleotide binding proteins [G-protein] coupled receptors (**Table 1.**).

Receptor	G-Protein coupling	Action on adenylyl cyclase activity	Most prominent human tissue distribution
A1	G_i	Inhibition	Brain (*cortex, hippocampus, cerebellum*) Spinal cord Eye Adrenal gland **Heart**
A2A	G_s	Stimulation	Brain (*caudate-putamen*, *nucleus accumbens, tuberculum olfactorium*) Thymus Spleen Leukocytes Platelets **Heart**
A2B	G_s	Stimulation	Large intestine Bladder
A3	G_i	Inhibition	Thyroid Adrenal gland Liver Kidney **Heart**

Table 1.5. Characterisation of adenosine receptor subtypes

Source: International Union of Pharmacology. XXV. Nomenclature and Classification of Adenosine Receptors (Fredholm *et al.*, 2001)

Traditionally, it was thought that adenosine receptor signalling occurs via the inhibition or stimulation of adenyl cyclase with a subsequent decrease or increase in intracellular cyclic adenosine monophosphate [cyclic AMP]. On this basis, adenosine receptors were initially classified as A1 [decreasing cyclic AMP] or A2 [increasing cyclic AMP] (van Calker *et al.*, 1979). This classification system has been refined by the discoveries of two distinct sub-types of the cyclic AMP-increasing A2 receptor – high affinity A2A receptors and low affinity A2B receptors (Daly *et al.*, 1981) and of a third type of receptor, the cyclic AMP decreasing A3 receptor (Church and Hughes, 1985).

It is now recognised that adenosine receptors are linked to multiple other cellular signalling pathways in addition to G-protein coupled inhibition or stimulation of adenyl cyclase (Fredholm *et al.*, 2001). In the heart these include A1 receptors and phospholipase C (Tawfik *et al.*, 2005), pertussis toxin-sensitive K^+ channels and 'funny' (I_f) channels (Belardinelli *et al.*, 1995); A1 and A2A receptors and p44/42 extracellular signal-regulated protein kinase (ERK) signalling (Reid *et al.*, 2005); and A3 receptors and K_{ATP} channels (Tracey *et al.*, 1998).

The predominant adenosine receptors in the heart are A1 and A2A. The A2A receptor is responsible for mediating coronary vasodilation whilst it is the A1 receptor that facilitates the electrophysiological actions of adenosine (**Table 1.**). These are discussed later.

Effect of adenosine	Adenosine receptor subtype
Anti β-adrenergic	A1
Depression of SA node activity (negative chronotropy)	A1
Depression of AV node activity (negative dromotropy)	A1
Depression of atrial contractility (negative inotropy)	A1
Inhibition of platelet aggregation	A2A
Vasodilation	A2A (A2B)

Table 1.6. Effects of adenosine of cardiovascular tissue by adenosine receptor subtype (Shryock and Belardinelli, 1997).

1.2.2.4 *Adenosine removal*

Adenosine is removed by enzymatic degradation; either deamination by adenosine deaminase to inosine or phosphorylation by adenosine kinase to AMP. Both of these enzymes are intra-cellular therefore adenosine must be taken up into cells via the ubiquitous cellular nuceloside transport system (**Figure 1.2**).

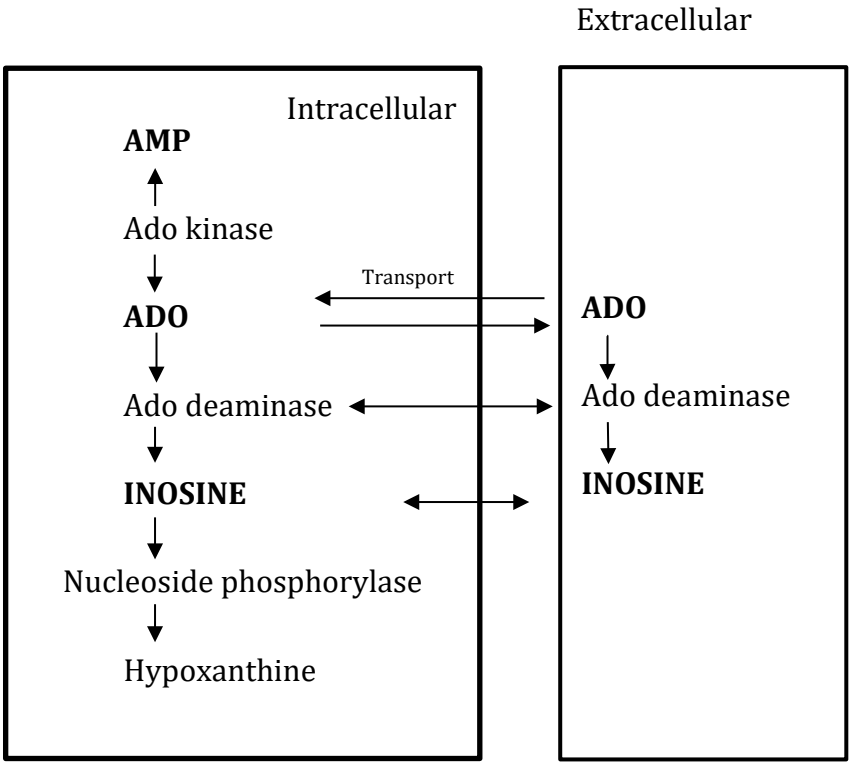

Figure 1.2. Mechanism of adenosine removal (Lerman and Belardinelli, 1991)

ADO = adenosine; AMP = adenosine monophosphate.

1.2.3 Cardiac electrophysiological effects of adenosine

Adenosine has specific cardiac electrophysiological actions:

1. Depression of sinoatrial node (SAN) activity
2. Depression of atrioventricular node (AVN) activity
3. Depression of ventricular automaticity
4. Depression of myocardial contractility

The first three of these actions can be regarded as effects on cardiac impulse generation and conduction (negative chronotropy and dromotropy); mediated by the direct action

of adenosine on local tissue in these locations and anti-adrenergic activity. The depression of myocardial contractility (negative inotropy) is specifically mediated by the anti-adrenergic action of adenosine.

1.2.3.1 *Cardiac impulse generation and conduction*

Bradycardia was the first documented clinical action of adenosine (Drury and Szent-Gyorgyi, 1929). It is now known that this negative chronotropism is mediated by A1 receptors and involves the complex interplay of inactivation of the inwardly rectifying K^+ current coupled with the inhibition of the inward Ca^{2+} (I_{Ca}) current and the "funny" hyperpolarization-activated current (I_f) within the sinus node, atrio-ventricular node and His-Purkinje system (Belardinelli *et al.*, 1995). The I_f and I_{Ca} currents are also modified by the indirect anti-adrenergic activity of adenosine. The relative roles of these currents differ between sites within conducting system (Pelleg *et al.*, 1990).

In addition to a negatively chronotropic effect, adenosine also exhibits a negative dromotropic effect (slowing of conduction) with prolongation of P-R and A-His intervals as well as causing AV block. This is mediated by A1 receptor activation of the inwardly rectifying K^+ current and inhibition of β-adrenergic activation of a subtype of the inward Ca^{2+} current ($I_{Ca,L}$) and is AV node-specific, as evidenced by the absence of His-V interval prolongation.

1.2.3.2 *Adrenergic control and inotropism*

Adenosine negatively modifies myocardial contractility via anti-adrenergic effects primarily mediated by A1 receptors involving G-protein coupled interactions with β-adrenoceptors (Dobson, 1983; Romano and Dobson, 1990; Fenton and Dobson, 2007).

1.2.4 The adenosine test

The adenosine test involves the intravenous administration of a 20mg bolus of adenosine or adenosine triphosphate (ATP) via a suitable large proximal upper limb vein (most commonly an antecubital vein) followed by a 20ml flush of 0.9% sodium chloride to a supine patient with continuous electrocardiographic (ECG) monitoring and preferably non-invasive beat-to-beat arterial blood pressure monitoring.

The European Society of Cardiology defines a positive test as the induction of ventricular asystole lasting ≥ 6 seconds or atrioventricular (AV) block lasting ≥ 10 seconds. (Task Force for the *et al.*, 2009).

It is only the ECG response to adenosine that is of clinical interest. Similar to carotid sinus massage (Moller *et al.*, 1987), undertaking the test with the patient in a supine position will attenuate the severity of any provoked symptoms and it is not expected that these will reproduce spontaneous clinical symptoms.

1.2.4.1 *Origin and validation of the adenosine test*

Interest in using adenosine as a diagnostic agent in syncope, and the subsequent development of the adenosine test, emerged in the late 1990's from two groups; one in Italy, led by Brignole; and the other in France, led by Flammang.

1.2.4.2 *Flammang study on the validation of the adenosine test*

In Flammang's study (Flammang *et al.*, 1997) a 20mg bolus of ATP was administered to 316 patients hospitalised for recurrent syncope (n=195) or presyncope (n=121) of undetermined origin and to 51 un-matched control subjects with no history of syncope over a period of 8 years between 1980 and 1992. The initial ATP tests were done as part of an electrophysiology study with back-up transvenous demand pacing in-situ. Later tests were performed in accordance with the accepted protocol outlined above (supine, at the bedside, with continuous ECG monitoring and automated intermittent external blood pressure monitoring).

This was the first documented clinical experience of ATP testing in the world literature and the authors elegantly described five phases of response to the ATP bolus:

1. Progressive slowing of the sinus interval ending with either abrupt PR prolongation (≥ 20% of preceding PR interval) or second-degree AV block (Phase I).
2. First or second-degree AV block with increasing slowing of the ventricular rate ending with complete AV block or sinus pause.

3. Cardiac pause of variable duration due to complete AV block or sinus pause. This phase is not universal (it did not occur in 30% of the patients in Flammang's study). Escape beats are usually observed during this phase – on average every 5.4 seconds in Flammang's study (Phase III).
4. Return to pre-test rhythm via resumption of rapid ventricular activity when phase 3 is present or less severe bradycardia or AV bock when it is not (Phase IV).
5. Reflex sympathetic tachycardia (Phase V).

Flammang described the total vagal (clinical) effect as being the sum of Phases II, III and IV; with Phase III representing the climax. The measured parameter of interest was the duration of the cardiac pause (Phase III) corresponding to either the duration of sinus pause or AV block, importantly, excluding any ventricular escape beats or rhythm.

In the control group, ATP provoked a cardiac pause (the duration of sinus pause or AV block excluding any ventricular escape beats or rhythm) in 23 subjects (45%); the majority of which were secondary to AV block (n=21 [91%]) with sinus pauses in only 2 [9%]). Only 3 control subjects (6%) had a cardiac pause > 10 seconds (mean duration 13.3 ± 0.7 seconds); the remaining normal subjects had a pause < 10 seconds (mean duration 5.1 ± 0.5 seconds). This led the authors to conclude that using a cardiac pause > 10 seconds as a cut-off, the ATP test had 94% specificity. It was thus considered that a cardiac pause > 10 seconds in response to 20mg ATP was an abnormal response (**Figure 1.3**).

In the 316 symptomatic patients, adenosine caused a cardiac pause in 234 (74%) secondary to either AV block in 196 (84%) or sinus pause block in 38 (16%). Eighty-two subjects (26%) had no cardiac pause. One hundred and thirty subjects (41%) had a cardiac pause > 10 seconds (mean duration 20.5 ± 0.7 seconds) and 104 (32%) had a cardiac pause < 10 seconds (mean duration 5.9 ± 0.2 seconds).

Comparing the control and recurrent syncope groups, the control group was younger (58.2 ± 2.4 years versus 73.7 ± 0.6 years, $p < 0.05$), more were male (58.8% versus 48.7%, $p < 0.05$) and they were less likely to suffer from metabolic disease (3.9% versus

17.1%, $p < 0.01$). The authors stated that in the symptomatic group, those with a cardiac pause were more likely to be older, to be female and to suffer a greater burden of arterial disease. The paper also describes pacing therapy – groups that were ATP test positive or negative were further divided into those who did or did not receive a pacemaker before being compared. This makes it difficult to interpret the stated differences between the ATP test positive and negative groups.

With regards to safety, there was a single case of severe bronchospasm in an asthmatic patient following the administration of ATP that was treated promptly and successfully with intravenous corticosteroid. Some individuals suffering syncope following ATP administration suffered short-lived episodes of seizure-like activity secondary to cerebral hypoperfusion with no associated tongue biting or micturition and others required external cardiac compression prior to the return of spontaneous circulation.

1.2.4.3 ***Brignole study on the validation of the adenosine test***

In Brignole's paper (Brignole *et al.*, 1997) the effects of a 20mg bolus of ATP were assessed in a group of 60 patients with syncope of unknown origin (SUO) and in a matched control group of 90 subjects without syncope. Details of the patient groups are shown in Table 1.. The maximum RR interval (RR_{max}) and maximum drop in systolic blood pressure (the difference between the observed value immediately before ATP administration and the lowest value observed after ATP administration) were the measured parameters.

Parameter	Control group	SUO group
Number	90	60
Age	55 ± 17 years	57 ± 19 years
Males (%)	46 (51%)	31 (52%)
Median RR_{max} (range)	1600ms (480-8000ms)	2200ms (7000-13000ms)
Mean systolic BP drop	31 ± 20 mmHg	38 ± 22 mmHg

Table 1.7. Characteristics of the control and syncope of unknown origin in the Brignole study (Brignole *et al.*, 1997)

SUO = syncope of unknown origin; RR_{max} = maximum RR interval; ms = milliseconds; mmHg = millimetres of mercury

In the control group, the adenosine test induced transient 3rd degree AV block in 26 subjects (29%) compared with 29 (48%) subjects in the SUO arm (p=0.01). The median RR_{max} in the control group was 1600ms (range 480 to 8000ms) compared with 2200ms (range 700 to 13000ms) in the SUO arm. Systolic blood pressure dropped by 31 ± 20mmHg in the control group compared with 38 ± 22mmHg (p=0.047). The number of individuals with an RR_{max} above the values corresponding to the 95th and 99th percentiles of the control group distribution (6000ms and 8000ms, respectively) was significantly higher in the SUO group than in the control group (4 [5%] control group versus 17 [28%] SUO group for 95th percentile [p=0.000] and 1 [1%] control group versus 9 [15%] SUO group for 99th percentile [p=0.001]). It was thus considered that an $RR_{max} \geq 6000$ms in response to a 20mg bolus of ATP was abnormal.

In the control arm, the mean RR_{max} was longer in women than in men (2943 ± 1847ms versus 1871 ± 1688ms, p=0.005) and in those older than 55 years (2743 ± 1787ms versus 2015 ± 1840ms, p=0.06). Interestingly, in the SUO group those with an abnormal response to ATP were more likely to be female (11 [65%] versus 6 [42%], p=0.028) and

more likely to be older (66 ± 20 years versus 53 ± 19 years, p=0.068). This suggests that a positive test is more likely in older female patients.

Pleasingly, no significant safety concerns related to the administration of 20mg ATP were identified. Light-headedness was the most frequently reported symptom associated with ventricular asystole. Short-lived bradycardia induced syncope with prompt recovery was encountered in no control subjects and in seven of the SUO group but did not require any treatment.

Thus, the identification of 6000ms as the value representing the 95th percentile of the control group distribution led to the adoption of a period of ventricular asystole lasting ≥ 6 seconds constituting a positive adenosine test (Figure1.3). These results and reassuring safety data together with the work of Flammang (Flammang *et al.*, 1997), piqued interest in utilising the adenosine test may in the investigation of unexplained syncope.

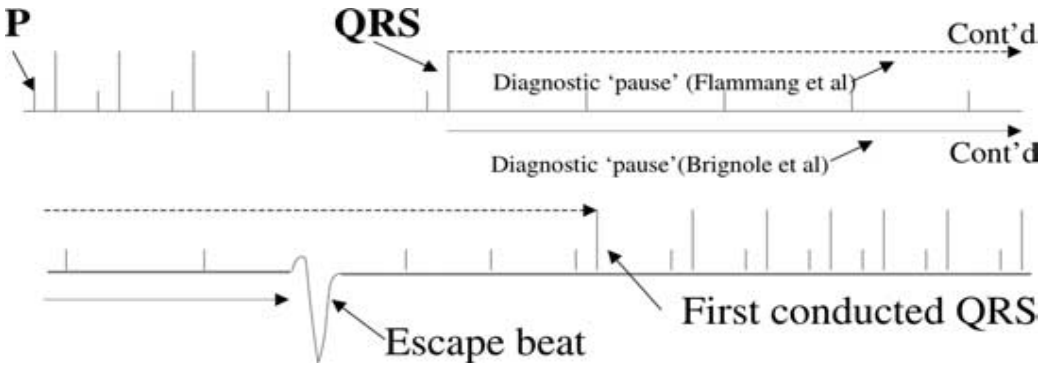

Figure1.3. Schematic electrocardiogram depicting the two criteria considered to constitute a positive ATP test (Flammang *et al.*, 2005).

The short vertical bars represent "P" waves and the taller vertical bars represent "QRS" complexes.

1.2.4.4 *Reproducibility of the adenosine test*

To assess the reproducibility of the adenosine test, Flammang *et al* undertook repeat adenosine testing in a cohort of 80 individuals with unexplained syncope (44 male, mean age 72 ± 12 years)(Flammang *et al.*, 1998). The initial adenosine test was positive in 31 (39%) and negative in 49 (61%). The cohort was then split into groups and repeat testing undertaken within 36 days (short term, n=43) or after more than 36 days (long term, n=37). It is not clear how individuals were selected for each group or why the 36 day cut-off was used. In the short-term group adenosine testing was performed after a mean of 7 ± 10 days (range 1 – 36 days) and the initial result was the same in 36 patients (84%). In the long-term group adenosine testing was repeated after a mean of 1361 ± 927 days (range 95 – 4,870 days) and the initial result was the same in 27 patients (79%). Thus, adenosine testing appears to have reproducibility, regardless of the outcome, over a significant length of time (up to 13 years).

1.2.4.5 *Adenosine or ATP?*

There is debate in the literature on whether only ATP, or both ATP and adenosine, reliably induce the desired negative chronotropic and dromotropic effects. A substantial proportion of the published literature involving the adenosine test comes from Flammang's group in France. They use exclusively ATP and cite enhanced cardiac vagal afferent stimulation over adenosine as the reason for doing so; supporting a hypothesis that a positive adenosine test identifies cardio-inhibitory vasovagal syncope amenable to pacing therapy.

Enhanced vagal effects have been most clearly demonstrated in a series of experiments, all originating from the same laboratory, showing that the these effects of ATP are independent of degradation to adenosine (Katchanov *et al.*, 1996; Pelleg *et al.*, 1996; Katchanov *et al.*, 1997; Pelleg *et al.*, 1997). However, these are canine experiments rather than human observations and different effects have been observed in different species, including the guinea pig, rabbit, cat and dog (Belhassen and Pelleg, 1984; West and Belardinelli, 1985; Clemo and Belardinelli, 1986).

Published data assessing the extent of involvement of the vagus nerve in mediating the actions of adenosine in humans is sparse. In the most recent of only two papers, Di Marco *et al* delivered a weight-adjusted intravenous adenosine bolus to 17 subjects undergoing electrophysiology studies(DiMarco *et al.*, 1983). This produced at least a ≥ 50% increase in sinus cycle length (suggesting a degree of sino-atrial nodal inhibition) and complete AV block (clearly demonstrating atrio-ventricular nodal involvement) in all subjects. Weight-adjusted administration of atropine, a potent antagonist of vagal activity, did not alter these effects, suggesting a lack of vagal involvement. In the second report, Lechat compared the effects of atropine and aminophylline (a non-selective adenosine receptor antagonist) on the transient complete atrio-ventricular nodal block induced by adenosine (Lechat, 1982). The atrio-ventricular nodal block was not affected by the administration of adenosine but was prevented by aminophylline, suggesting an absence of vagal involvement.

Importantly, there has been no observed difference in the efficacy of ATP or adenosine to treat supraventricular tachycardia; the most common use in clinical practice (Rankin *et al.*, 1990; Belhassen and Viskin, 1993).

There is thus no convincing evidence to favour either adenosine or ATP as an agent for this test (Fragakis *et al.*, 2015). This conclusion is consistent with European Society of Cardiology guidance (Task Force for the *et al.*, 2009). Adenosine was therefore selected for use in the clinical trial forming the basis of this thesis because of its local availability.

1.2.4.6 ***Safety profile of adenosine***

Common to all active pharmacological agents, the safety profile of adenosine is of paramount importance. Safety data specific to the adenosine test is most instructively provided by the Brignole and Flammang papers that validated the test (Brignole *et al.*, 1997; Flammang *et al.*, 1997). In Brignole's paper incorporating 150 subjects, there was a single case of non-sustained atrial tachyarrhythmia secondary to adenosine; whilst in Flammang's study including 367 participants, there was non-sustained atrial fibrillation recorded in only 11 subjects post adenosine.

A much larger volume of data comes from the literature reviewing the safety profile of adenosine used as a therapeutic agent to terminate supraventricular tachycardia. A comprehensive review covering the first 13 years of adenosine or ATP use since the introduction to market in the USA (Pelleg *et al.*, 2002), documents 12 cases of supraventricular arrhythmia (mostly atrial fibrillation/flutter), six cases of torsades de pointes (all cases had baseline prolonged QT intervals) and one case of ventricular fibrillation. There were no deaths directly attributable to adenosine.

The most commonly encountered side effects related to adenosine administration are syncope, presyncope, light-headedness, flushing, dyspnoea, chest pressure, nausea and a non-specific general sensation of 'discomfort'. These arise secondary both to the direct actions of adenosine on the specialised conducting tissue of the heart e.g. presyncope/syncope and its actions elsewhere in the body e.g. vasodilatation resulting in flushing. Although unpleasant, the short half-life of adenosine (less than 10 seconds) (Pelleg and Porter, 1990) means that these side effects are short-lived.

It should be noted that adenosine is contra-indicated in asthma and chronic obstructive pulmonary disease with reversibility due to the potential for bronchospasm.

Adenosine administration should be avoided with concomitant dromotropic- and chronotropic agents e.g. beta-blockers and calcium blockers to avoid a synergistic effect on the sino-atrial and atrio-ventricular nodes. However, it may not be practical or possible to do this in clinical practice.

1.2.4.7 *Clinical experience with the adenosine test*

Although, the adenosine test was not validated until 1997, the first published clinical experience of its use in the context of syncope appeared earlier (Brignole *et al.*, 1994). Seventy-nine subjects with syncope (neurally-mediated syncope, n= 26, mean age 64 ± 11 years; sinus node disease, n = 22, mean age 74 ± 8 years; or both, n= 31, mean age 75 ± 8 years) and 31 control subjects (mean age 62 ± 16 years) were given a 20mg intravenous bolus of adenosine. The sinus cycle length (a measure of the activity of the sinus node) was prolonged by more than 50% in none of the control group compared to 5% (n=1) of the neurally-mediated syncope group, 23% (n=5) of the sinus node disease group and 42% (n=13) of those with both (p=0.01). Atrio-ventricular block occurred in 45% (n=14) of controls, 38% (n=10) of those with neurally-mediated syncope, 18% (n=4) of those with sick sinus syndrome and 42% (n=13) of those with both (p=not significant). The authors concluded firstly that documented sinus node disease needed to be present for there to be an abnormal response of the sinus node to adenosine, suggesting a possible role for adenosine testing if sinus node disease was suspected as the cause of syncope; and secondly, that adenosine has similar effects on the sino-atrial and atrio-ventricular nodes of those with neurally-mediated syncope and controls, suggesting that adenosine testing has a limited role in the investigation of neurally-mediated syncope. However, there is an established overlap between sinus node disease and neurally-mediated syncope (Brignole *et al.*, 1991; Alboni *et al.*, 1993), prefacing the uncertainty about the significance of a positive test.

Brignole's validation study (Brignole *et al.*, 1997) concluded that the adenosine test could be used to identify patients with syncope secondary to paroxysmal AV block (who would benefit from pacing therapy). This was entirely contradictory to their initial clinical experience described. They did not postulate an underlying mechanism but called for future prospective studies to validate their assumption.

In Flammang's initial study (Flammang *et al.*, 1997) the working hypothesis was that the adenosine test would identify individuals with syncope secondary to vagally-mediated cardio-inhibition. This is an important distinction as pacing therapy has been proposed as a definitive treatment for cardio-inhibitory vasovagal syncope.

Mechanistically, this is logical. Indeed a number of investigators have identified higher endogenous adenosine levels in those with vasovagal syncope and proposed adenosine as a modulator of the process (Shen *et al.*, 1996; Saadjian *et al.*, 2002). However, in clinical practice, the issue is less clear-cut - the ISSUE 3 study showed that permanent pacing for cardio-inhibitory vasovagal syncope was effective although only in the small percentage (9%) of those with prolonged asystole demonstrable on a loop recorder (Brignole *et al.*, 2012).

The existence of these two incompatible theories requires the re-examination of the true significance of a positive adenosine test. The literature is principally divided into two camps: cardio-inhibitory vasovagal syncope and cardiac conducting system disease; although a third diagnosis of 'adenosine sensitive syncope' has been proposed.

1.2.4.8 ***The adenosine test and cardioinhibitory vasovagal syncope***

Flammang *et al* performed adenosine testing and head-up tilt testing (initially passive then, if negative, followed by isoproterenol provocation) in 72 patients (mean age 65 ± 2 years) hospitalised for unexplained presyncope (n=16) or syncope (n=56) (Flammang *et al.*, 1999b). Tilt testing was positive in 41 patients (57%) and adenosine testing was positive in 8 patients (11%). Both tests were negative in 36 patients (50%) and positive in 3 patients (4%). No correlation was observed between the tilt and ATP tests. The authors concluded that tilt and adenosine testing 'individually and jointly' determined the mechanism of vasovagal symptoms (suggesting that tilt testing identifies vasodepression and adenosine testing identifies cardioinhibition as the mechanism for vasovagal syncope) despite both tests being negative in 50% of patients. Those with a positive ATP test were older (78 ± 3 years versus 63 ± 2 years) and were more likely to have cardiac disease (62% versus 32%) supporting the theory that the diagnosis was conducting system disease rather than vasovagal syncope although this is very speculative.

In a similar vein, Brignole *et al* conducted adenosine and head-up tilt testing in 175 consecutive patients with unexplained syncope (Brignole *et al.*, 2000a). Seventy-seven (64%) had a positive tilt test, 18 (15%) had a positive adenosine test and both tests

were positive in 26 (21%). Compared to those with an isolated positive tilt test, those with an isolated positive adenosine test were older (68 ± 10 years versus 45 ± 20 years) and had a higher proportion of ECG abnormalities (28% versus 9%). The authors concluded that tilt and ATP testing identify a different population of patients with syncope and that 'adenosine sensitive syncope' is a distinct clinical entity. Additionally, Perennes *et al* demonstrated that in a cohort presenting with unexplained syncope (n=214, mean age 59 ± 18 years), a positive test was more likely in women (14.3% of women versus 2.2% of men) and in older patients (adenosine test positive 77 ± 12 years versus adenosine test negative 56 ± 19 years) (Perennes *et al.*, 2006). Overall, the adenosine test was positive in only 9% of the whole cohort, however.

Logically, the next step was to document the presence or absence of rhythm disturbance at the time of syncope and to examine any relationship to the adenosine test. The implantable loop recorder provides the ideal opportunity to do this. Deharo *et al* used an implantable loop recorder to document any rhythm disturbance in 25 patients with vasovagal syncope (age 60 ± 17 years; 14 women) and a positive tilt test; 7 of whom also had a positive adenosine test (Deharo *et al.*, 2006). There were 30 episodes of recurrent syncope in 12 patients with bradycardia documented in 9 episodes. No correlation was found between bradycardia at the time of recurrent syncope and a cardioinhibitory head-up tilt (HUT) response (p = 1.0) or a positive adenosine test (p = 1.0). Similarly, Brignole *et al* did not demonstrate a correlation between tilt testing and adenosine testing and the mechanism of spontaneous neurally mediated syncope in the 392 subjects enrolled in the 2nd International Study of Syncope of Uncertain Etiology (ISSUE 2) (Brignole *et al.*, 2006a). More than any other data, it is this absence of a correlation between a positive adenosine test and rhythm disturbance at the time of syncope documented on an ILR in these two studies that refute the hypothesis that adenosine testing predicts bradycardia in vasovagal syncope.

1.2.4.9 ***The adenosine test and conducting system disease***

Studies investigating the role of adenosine in unmasking conducting system disease as a cause of syncope have examined both sinus and atrioventricular nodal disease.

In the second part of the study by Brignole *et al*. in which ≥ 6 seconds asystole as was defined as a positive adenosine test (Brignole *et al.*, 1997), nine individuals had spontaneous syncope secondary to sinus arrest and fifteen secondary to AV block. A positive adenosine test was noted in 53% of those with AV block and 0% of those with sinus arrest. The authors postulated that a positive adenosine test in those with unexplained syncope points to paroxysmal AV block as the cause.

Donateo *et al.* prospectively evaluated the mechanism of syncope in 36 patients with unexplained syncope and a positive adenosine test (69 ± 10 years; 22 women) using an implantable loop recorder (Donateo *et al.*, 2003). Syncope recurred in 18 patients (50%) of whom 16 (44%) had an electrocardiographically documented episode. Eleven of these were due to bradycardia (AV block or sinus node disease), 3 were due to tachycardia, and in 2 sinus rhythm was recorded. The authors suggest that the ATP test might be useful in predicting a bradycardic cause of syncope, although they advise caution given the relative heterogeneity of the rhythm disturbance identified on ILR.

In a cohort study of 50 individuals (Parry *et al.*, 2009a) adenosine was 100% sensitive and 86% specific for identifying bradycardia pacing indications (a mixture of sinus node disease, atrioventricular block and cardio-inhibitory carotid sinus syndrome) and a smaller study of 10 patients demonstrated adenosine to be 80% sensitive and 97% specific for sinus node disease (Burnett *et al.*, 1999). This last study is supported by recent work (Fragakis *et al.*, 2012) showing that adenosine testing was comparable to the corrected sinus node recovery time (CSNRT) at electrophysiology study in identifying sinus node disease (94% sensitivity and 84% specificity for adenosine testing versus 74% sensitivity and 100% for CSNRT).

Contrary to these studies reporting a role for adenosine testing to identify a bradycardic cause of syncope, Cheung *et al*. performed adenosine testing in 92 consecutive patients (64 women, age 55 ± 21 years) with unexplained syncope(Cheung *et al.*, 2004). The test was positive in 21 patients (23%). During mean follow-up of 14.3 ± 5.9 months, 14 patients (16%) had recurrent syncope. Three (14%) of them had a positive adenosine test compared to 11 (16%) with a negative adenosine test (p = 1.00); suggesting that a positive adenosine test fails to predict recurrent syncope secondary to bradycardia.

1.2.4.10 *The adenosine test and 'adenosine sensitive syncope'*

As mentioned previously, work by Brignole, comparing adenosine testing and tilt testing in a cohort of 175 individuals with unexplained syncope, introduced the idea of 'adenosine sensitive syncope' (Brignole *et al.*, 2000a). Further recent data from the same group (Brignole *et al.*, 2011) describes a positive adenosine test in 15/18 (83%) of individuals with unexplained syncope that subsequently had spontaneous AV block demonstrated on prolonged monitoring (mean follow-up 4 ± 4 years). An invasive electrophysiology study failed to demonstrate impaired AV conduction in any participants and whilst tilt-testing induced syncope in 7 (41%) participants, AV block was never induced. This prompted the authors to describe 'idiopathic paroxysmal AV block' which adenosine testing seems to unmask with reasonable sensitivity. This continues to be an area of interest for Brignole (Aste and Brignole, 2017; Brignole *et al.*, 2017).

Contrary to these findings, Deharo *et al*. also describe adenosine testing in a group of 15 individuals with a short history of unexplained syncope without prodrome; a group they label as a 'distinct clinical entity'(Deharo *et al.*, 2013). These patients did not have a long period of follow-up with ambulatory monitoring to demonstrate arrhythmia but rather were compared with a control group with typical vasovagal syncope. In comparison to this control group, those in the syncope without prodrome group were older (61±12 versus 46±17 years) and had fewer previous episodes of syncope (median episodes of syncope in lifetime 2 [IQ range 1-2.5] versus 9 [IQ range 4-15] and median time since symptom onset 1 year [IQ range 0-1 year] versus 10.5 years [IQ range 3.3-27 years]). The adenosine test (using asystole of ≥ 6 seconds as the only positive criterion) was positive in 60% versus 43% of the typical vasovagal syncope group (p=0.35). Contrary to Brignole's paper (Brignole *et al.*, 2011), the authors concluded that the adenosine test does not reliably discriminate between this distinct group with unheralded syncope without prodrome and vasovagal syncope. Given that rhythm disturbance was not required to be demonstrated, it is probable that each study is

looking at different populations. Although, in clinical practice, unheralded syncope prompts a search for an arrhythmic aetiology.

1.2.4.11 ***Randomised controlled trials***

It is important now to consider the two randomised controlled trials of pacing therapy in patients with a positive adenosine test. (Flammang *et al.*, 1999a; Flammang *et al.*, 2012). The first was a single centre pilot study; and the second a larger multi-centre trial following on from the findings of the preliminary study.

1.2.4.11.1 ***Pilot study***

The pilot study (Flammang *et al.*, 1999a) involved 20 patients with syncope of presumed vasovagal origin, based on presenting symptoms and the exclusion of all neurological, metabolic and arrhythmic causes, although it is not explained how this was achieved.

Following a positive adenosine test (defined as per that group's original definition of a cardiac pause [from last normally conducted sinus beat pre-adenosine to first normally conducted sinus beat post adenosine] of > 10 seconds) patients were randomised to standard care or to dual chamber pacemaker implantation (DDD). The devices did not have a specific algorithm that paced at a set higher rate in response to abrupt falls in heart rate designed to treat the cardio-inhibitory component of vasovagal syncope as this was not commercially available at the time of enrollment (1988 to 1992). The primary outcome was the recurrence of syncope. Ninety percent of the paced group and 80% of the standard care were women. There were no statistically significant differences between the groups at baseline in age (72.4 ± 9.09 years in paced group vs. 72.2 ± 13.9 years in standard care group) or lifetime number of episodes of syncope prior to enrollment (mean 3.0 ± 1.29 episodes in paced group vs. 2.83 ± 0.98 episodes in standard care group). However, the mean cardiac pause duration between the paced and standard care groups did differ (mean cardiac pause in paced group 21.4 ± 9.3 seconds, range 12 – 39 seconds versus 15.7 ± 3.9 seconds, range 11 – 22 seconds in the standard care group); suggesting that those with more strongly positive adenosine tests were more likely to be paced. This difference was not reported to be significant.

At a mean follow-up of 52 months (range 4 -101 months) there were no recurrences in the paced group versus 6 recurrences of syncope in the standard care group; giving an estimated event-free survival at five years of 100% in the paced group compared to 40 % in the routine care group ($p < 0.02$). Furthermore, two of the standard care group crossed over to the pacing arm following early episodes (months 0 and 1) and were free of syncope recurrence at 20 and 64 months thereafter.

1.2.4.11.2 *Multi-centre randomised controlled trial*

The promising preliminary study prompted the same group to undertake a larger multi-centre randomised controlled trial; this time using 'placebo' pacing rather than standard care as the control arm versus dual chamber pacing (inhibition and triggering in response to sensed atrial and ventricular beats) at 70bpm (DDD). 'Placebo' pacing took the form of AAI (atrial pacing and sensing with inhibition on detection of a sensed atrial beat) at 30bpm; rather than true placebo which would have been pacemaker 'off' (OOO or ODO). It should be noted that the randomisation was only single-blind – the physician enrolling the patient was aware of the pacing allocation. Following the first recurrence of syncope those randomised to AAI at 30bpm were switched to DDD at 70bpm; those randomised to DDD at 70bpm had this maintained but could then have rate-responsive pacing or a rate-drop response algorithm added at the discretion of the enrolling physician.

Between 2000 and 2005, in ten centres throughout France and Belgium, 88 patients with syncope of uncertain aetiology were felt to be eligible. Eight were excluded (3 for not meeting the inclusion criteria and 5 by declining to participate); resulting in 80 randomised patients. Exclusion criteria were exhaustive requiring the absence of a diagnosis following clinical assessment, electrocardiography, echocardiography, ambulatory monitoring and carotid sinus massage plus, if indicated, head-up tilt testing and an electrophysiology study; explaining the length of time required to recruit so small a number across multiple sites. The primary outcome was recurrence of syncope. Patients were followed up every six months and were to self-report episodes of syncope at these visits

The mean age of the total cohort was 75.9 ± 7.7 years and 65 (81%) were women. The mean cardiac pause duration at adenosine testing was 17.8 ± 6.8 seconds; which did not differ between those randomised to AAI or DDD pacing. Over a mean follow-up of 16 months, 27/41 (66%) of the AAI group had a recurrence of syncope compared to 8/39 (21%) of the DDD group; giving Kaplan-Meier estimates of two-year recurrence-free survival of 31% (95% confidence interval 19 – 53) for the AAI group and 77% (95% confidence interval 65 – 93) for the DDD group. The time to first syncope ranged from 7 days to 26 months but this is not stratified by pacing allocation in the paper. Of the 27 patients initially randomised to AAI pacing at 30 bpm that subsequently 'crossed-over' to DDD pacing at 70 bpm following an episode of syncope, there was only one further recurrence. Of the 8 patients in the DDD group that suffered a recurrence, the addition of the rate-response or rate-drop algorithms reduced the severity of symptoms in 3 and there was no further recurrence if syncope in 5. There is no mention as to which algorithms were added in each case.

Clearly, this study is encouraging but it has flaws. It took a long time to recruit, probably due to the extensive exclusion criteria, suggesting the findings may only be applicable to a very small number of individuals with syncope in whom a diagnosis remains elusive despite extensive investigation. The pacing allocation was only single-blind and no attempt was made to determine the integrity of the blind. This is important, as there is precedent in the syncope literature of early observational studies purporting the benefit of pacing therapy being subsequently refuted by adequately blinded trials (Sutton *et al.*, 2000; Connolly *et al.*, 2003; Raviele *et al.*, 2004). Additionally, for those with sinus pauses, either as part of a cardio-inhibitory response or sinus node disease itself, AAI pacing at 30bpm is a potentially sufficient intervention to abort syncope; and thus not really a true 'placebo'.

1.2.4.12 ***Summary***

Thus, there is no clear consensus as to the significance of a positive adenosine test. Indeed, it is a "test looking for a home" (Matthews *et al.*, 2014). The evidence supporting an underlying diagnosis of conducting system disease is the strongest, particularly when one includes 'adenosine sensitive syncope', involving as it does a high proportion

with sudden onset AV block. However, the possibility of cardio-inhibitory neurally mediated syncope cannot be completely discounted.

The absence of a definitive diagnosis in light of a positive adenosine test subsequently hampers the implementation of any management strategy. The most likely therapeutic measure in light of a positive test is permanent pacemaker implantation. Indeed, although flawed, the single large randomised clinical trial assessing pacing therapy in light of a positive adenosine test favours pacemaker implantation.

Strikingly, there are no data at all regarding the significance of negative adenosine test and what the underlying diagnosis in those with unexplained syncope and a negative test.

It is these three principal areas that the randomised placebo-controlled double-blind crossover trial, the core of this thesis, is designed to address.

2 Chapter 2: Aims and Objectives

2.1 Aim

The aim of this single centre randomised double-blind placebo-controlled crossover trial is to determine the efficacy of permanent pacing therapy in the prevention of syncopal episodes in patients with unexplained and a positive adenosine test.

2.2 Objectives

2.2.1 Primary

The primary objective of this study is to assess the effectiveness of permanent pacing in patients with unexplained syncope that have a positive adenosine test through the medium of a randomised, placebo-controlled, crossover trial.

2.2.2 Secondary

The secondary objective of this study is to establish the underlying aetiology of syncopal events in those with a negative adenosine test by inserting an implantable loop recorder (ILR) in this group.

2.3 Outcome measures

In order to determine whether the primary and secondary objectives of this study have been met the following outcome measures will be used:

2.3.1 Primary outcome measure

The primary outcome is syncope burden as measured by the number of syncopal episodes documented by monthly postal patient diaries with telephone reminders to ensure adequate return.

2.3.2 Secondary outcome measures

Secondary outcome measures to assess the primary and secondary measures are:

I. Time to first syncope

II. Number of patients with recurrent syncope

III. Quality of life as measured by

- The condition-specific instrument the Impact of Syncope on Quality of Life questionnaire
- General health-related quality of life measured via the World Health Organisation Quality of Life-BREF (WHOQoL-BREF) and World Health Organisation Quality of Life-Old (WHOQoL-Old) instruments.

IV. ECG diagnosis on ILR following syncopal episode in adenosine negative group

3 Chapter 3: Methods

3.1 Randomised double-blind placebo-controlled cross-over trial

3.1.1 Study design

The design of the study was a randomised double-blind placebo-controlled crossover trial. The flow of participants within the study is outlined in a CONSORT flow diagram (Moher *et al.*, 2001) in **Figure 3.1**.

This was a trial involving intervention. In line with good practice, a TIDieR checklist (Hoffmann *et al.*, 2014) for the trial is shown in **Table 3.1**.

3.1.2 Ethical approval

The study was granted a favourable ethical opinion by the Newcastle and North Tyneside 2 Research Ethics Committee on 4th January 2012.

3.1.3 Study setting

Patients were recruited from the Emergency Department, Assessment Suite (Acute Medical Admissions Unit) or Falls and Syncope Service at the Royal Victoria Infirmary, Newcastle upon Tyne.

The adenosine testing and initial quality of life assessments were conducted in the Falls and Syncope Service at the Royal Victoria Infirmary, Newcastle upon Tyne.

The implantation of permanent pacemakers and implantable loop recorders was undertaken in the Cardiac Catheterisation Laboratories at the Freeman Hospital, Newcastle upon Tyne.

All pacemaker and loop recorder follow-up (either in the department or by remote monitoring) was co-ordinated by the Cardiac Rhythm Management Department at the Freeman Hospital, Newcastle upon Tyne.

Repeat quality of life assessments were conducted at crossover and end of study visits at the Cardiac Rhythm Management Department at the Freeman Hospital, Newcastle upon Tyne.

Item Number	Item	Explanation
1	Brief name: *Provide the name or a phrase that describes the intervention*	ADEPT-ILR
2	Why: *Describe any rationale, theory, or goal of the elements essential to the intervention*	Adenosine testing may unmask a need for a pacemaker implant
3	What materials: *Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)*	Nil
4	Procedures: *Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities*	Adenosine testing Pacemaker implantation Loop recorder implantation (ILR)
5	Who provided: *For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given*	Adenosine testing – Cardiology Specialist Registrar or Consultant Geriatrician Pacemaker and ILR implantation – Cardiology Specialist Registrar or Consultant Cardiologist
6	How: *Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group*	Face-to-face; individual
7	Where: *Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant feature*	Adenosine Testing – Falls and Syncope Service (specialist out-patient facility within a hospital) Pacemaker and ILR implantation – Cardiac Catheter Laboratory (specialist in-patient theatre like facility)
8	When and how much: *Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose*	Adenosine Testing – once Pacemaker and ILR implantation – once
9	Tailoring: *If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how*	No tailoring
10	Modifications: *If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)*	No modifications
11	How well – planned: *If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them*	No formal adherence assessed
12	How well – actual: *If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned*	See Chapter 4

Table 3.1. TIDieR checklist for ADEPT-ILR

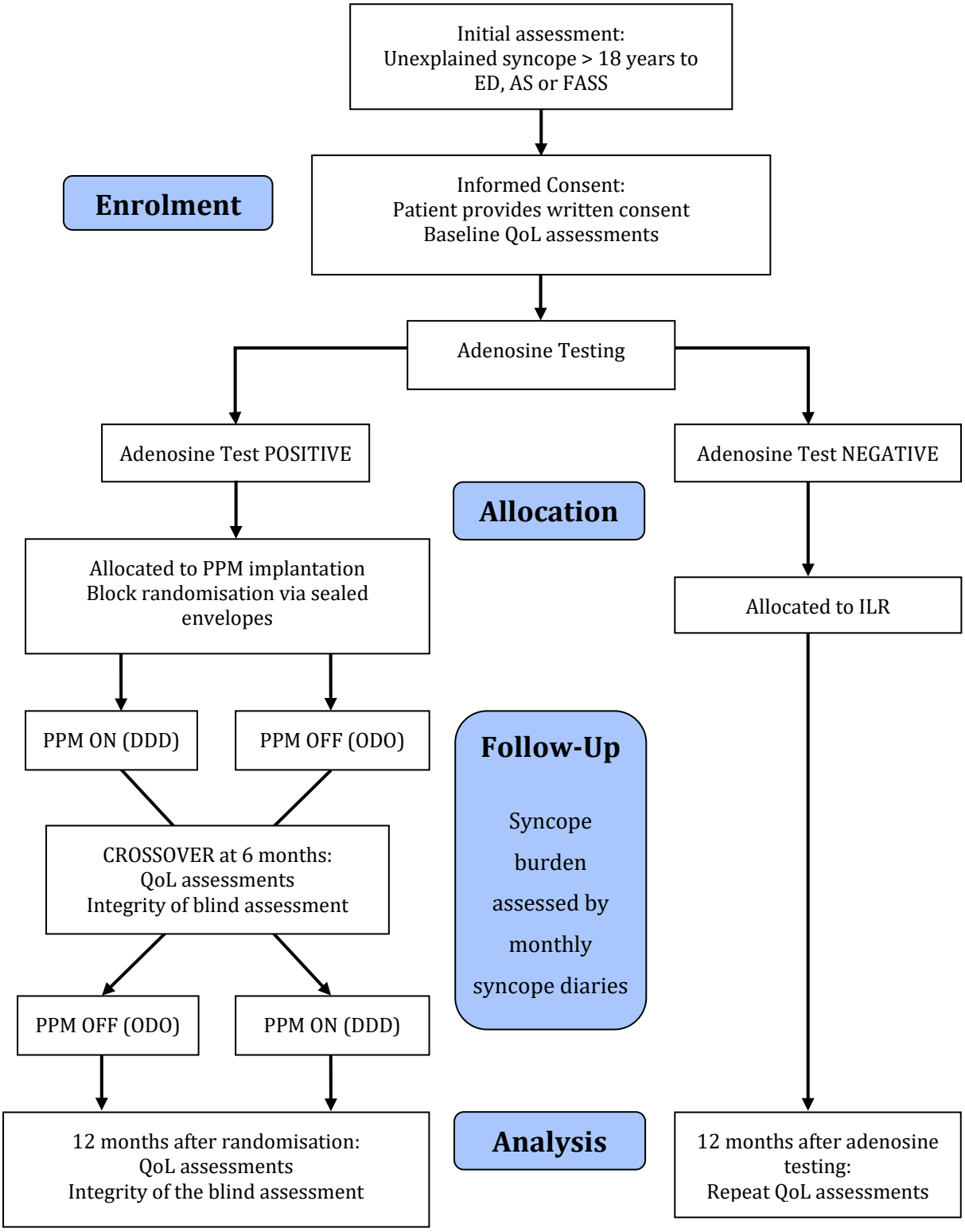

Figure 3.1. CONSORT study flow diagram

ED = Emergency Department; AS = Assessment Suite; FASS = Falls and Sycnope Service; QoL = Quality of Life; PPM = permanent pacemaker; ILR = implantable loop recorder.

3.1.4 Recruitment

Initially participants were identified on presentation with syncope to the Emergency Department (ED) or Assessment Suite by either:

- The usual healthcare team and referred to the research fellow; or
- The research fellow directly on frequent visits to the Emergency Department and Assessment Suite throughout Monday to Friday (9am to 5pm)

Two months into the recruitment period, it was apparent that the number of potential participants coming through the ED and Assessment Suite was lower than expected. This prompted a search for other potential avenues of recruitment.

In discussion with the Falls and Syncope Service (FASS) at the Royal Victoria Infirmary it was noted that there was a significant number of patients being referred directly by their general practitioner (GP) to FASS following an acute syncopal event rather than being referred to the Assessment Suite. This was a peculiarity of being based in Newcastle and having the presence of an internationally renowned service on the doorstep. We felt that we were missing a proportion of the population of interest by not including such individuals.

As such, a formal application was submitted to amend the recruitment criteria to include persons ≥ 40 years referred to FASS by their GP as a result of a contact specifically initiated because of syncope. This was granted approval by the Newcastle and North Tyneside 2 Research Ethics Committee on 18th April 2012.

The case notes of potential participants were reviewed. Provided the inclusion criteria were met, and no exclusion criteria identified, potential participants were approached to discuss involvement in the study.

Following this initial discussion, should potential participants have expressed an interest they were provided with a patient information sheet and given the opportunity to ask questions. They were given a minimum of 24 hours to review the patient information sheet and were then contacted by telephone to confirm a desire to be

involved in the study and to arrange attendance at the Falls and Syncope Service for the initial study visit.

A screening log was kept to:

- Document the details of subjects invited to participate;
- Document a reason for not participating if one was identified or provided; and
- To ensure potential participants were only approached once.

3.1.5 Inclusion criteria

The inclusion criteria for the study were:

- ≥ 1 episode of syncope;
- Provision of written informed consent for participation in the study prior to any study specific procedures;
- Age ≥ 40 years; and
- No cause of syncope clearly identified on clinical history and examination, lying and standing blood pressure measurements and standard 12 lead ECG.

3.1.6 Exclusion criteria

The exclusion criteria for the study were:

- Active asthma or chronic obstructive pulmonary disease on regular therapy;
- Severe coronary disease (myocardial infarction within 3 months, known coronary stenosis >70%, NYHA heart failure or angina symptoms Class III or IV);
- Known severe cerebrovascular disease or known significant internal carotid artery stenosis (>70%);
- Prolonged corrected QT interval;
- Known accessory pathway that had not been ablated;

- Pregnancy or lactation;
- Use of dipyridamole or any rate-limiting medication that could not be safely discontinued;
- Hypertrophic cardiomyopathy;
- Cardiac transplantation;
- Concurrent participation in another investigational study or trial;
- Inability to give informed consent as assessed by the Mental Capacity Act 2005 and using the Mini Mental State Examination; and
- Cause of syncope established from initial clinical history and examination, lying and standing blood pressure and 12-lead ECG

3.1.7 Consent

Participants had to have capacity to consent to involvement in the study as assessed by the Mental Capacity Act 2005. Screening for the presence of cognitive impairment was undertaken using the Mini Mental State Examination (MMSE). A MMSE score of < 24/30 was accepted as demonstrating cognitive impairment and participants were excluded from the study should this be the case. Those taking part provided written informed consent prior to randomisation and prior to study specific procedures/investigations. The original signed consent form was retained in the participant Case Report Form.

3.1.8 Power calculation

3.1.8.1 *Original power calculation*

The only previous randomised controlled trial involving the use of the adenosine test and subsequent pacemaker implantation in patients with syncope demonstrated a 65.9% syncope recurrence rate in AAI pacing (placebo) versus 20.5% in DDD subjects (active) with a positive adenosine test (Flammang *et al.*, 2012). More conservative recurrence rates of 65% (ODO) and 25% (DDD) were assumed for purposes of the power calculation. The study was a crossover design; half the patients received ODO pacing (placebo) followed by DDD pacing (active); the other half received DDD pacing

followed by ODO pacing. Complete data on two groups of 36 patients would have 90% power to detect a 40% difference in recurrence rates assuming a type 1 error rate of 5%. The crossover design, however, only a single group of 36 patients would be required. Assuming a 20% loss to follow-up, this meant recruiting 44 patients.

The number of ED attendances in the Newcastle Upon Tyne NHS Hospitals Trust during 2009 was 65,844, of whom 15,479 were >55 years of age (Mr Bas Sen, personal communication). Assuming a rate of 1% of attendances due to syncope, this would mean 1550 potentially eligible patients. In our group's pilot study of adenosine testing (Parry et al., 2009a) only 50 of the 264 potential participants (19%) were included in the study. Using an inclusion rate of 20% of those screened, this would involve screening around 300 patients.

The first consecutive 36 patients who tested adenosine negative would undergo ILR insertion. A sample of 36 patients would enable an estimate of the proportion of false negatives (those with a negative adenosine test who subsequently have a bradycardia episode resulting in syncope) with a 95% confidence interval of plus or minus 10% (assuming a rate of no more than 25%).

3.1.8.2 ***Revised power calculation***

Even following the widening of the inclusion criteria to include those presenting to the Falls and Syncope Service, study enrolment continued to prove challenging. In order to ensure timely study completion the power calculation was revised. A reduction in power from 90% to 80% (widely utilised in clinical studies) meant complete data on two groups of 28 patients would have 90% power to detect a 40% difference in recurrence rates assuming a type 1 error rate of 5%. Assuming a 20% loss to follow-up, this meant recruiting 34 patients. Accordingly, a formal application was submitted for this reduction in sample size. This was approved by the Newcastle and North Tyneside 2 Research Ethics Committee on 20th September 2013.

3.1.9 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23. Chi-square analysis or Fisher's Exact Test were used to compare binary baseline data, while the Mann-Whitney U Test or an independent T-Test was used for continuous baseline data. Negative binomial regression was used to compare the numbers of syncopal episodes in the six month period with the pacemaker on compared to six months period with the pacemaker off, using the log of variation between patients and periods as fixed effects, and the log of the number of days at risk as an offset. Paired T-tests were used to compare parametric data from the pacemaker on and off periods collected from the quality of life questionnaires. For non-parametric quality of life data, results were logarithmically transformed and a paired T-test was performed. If data were unsuitable for transformation, then the Wilcoxon Sign Rank Test was used. Finally, the unpaired non-parametric quality of life data from the implantable loop recorder (ILR) patient group was compared with pacemaker on or pacemaker off periods using the Mann-Whitney U test.

3.1.10 Study schedule

The study schedule of events is outlined in **Table 3.**

3.1.11 Baseline visit

The baseline visit was conducted in the Falls and Syncope Service and consisted of the following:

- Screening for cognitive impairment using the Mini Mental State Examination and confirmation of capacity to consent to involvement in the study;
- Informed consent;
- Clinical examination incorporating postural blood pressure and 12-lead ECG (if these had been undertaken at the time of screening they were not repeated);
- Quality of life assessment using these instruments:
    - Impact of Syncope on Quality of Life
    - WHOQoL-BREF

    - WHOQoL-Old instruments.
    - EQ-5D; and
- Adenosine Testing

Activities	First Visit	Every Week	Following clinical event	Week 4	Week 6	3 months	6 months	9 months	12 months
Informed Consent	X								
Medical History	X								
Physical Exam	X								
12 lead ECG	X								
Drug history review	X								
Adenosine Test	X								
QOL questionnaire	X						X *(PPM only)*		X
PPM implant	X								
Hospital PPM Follow-up					X		X		X
Telephone calls and postal diary		X							
ILR implant	X								
Remote monitoring in ILR group			X	X		X	X	X	
Cross-over							X		
Final assessment									X

Table 3.2. Study schedule of events

3.1.12 Adenosine testing

Adenosine testing was performed in accordance with European Society of Cardiology guidance (Task Force for the *et al.*, 2009). Following counselling regarding expected symptoms during the test (which might specifically include transient flushing, wheezing, breathlessness, chest discomfort, nausea, pre-syncope and syncope) a 20mg intravenous bolus of adenosine was delivered via an 18G cannula in a large upper limb vein (most commonly in the antecubital fossa). This was followed immediately by a 20ml flush of 0.9% saline.

Continuous ECG and blood pressure monitoring (Task Force Monitor, CN Systems, Graz, Austria) was in-situ. Advanced cardiac life support equipment (including a defibrillator with external non-invasive pacing), high flow oxygen and salbutamol nebulisers was immediately available.

A positive test was defined as per European Society of Cardiology guidelines:

- Ventricular asystole (from the last normally conducted QRS complex to the next QRS complex) ≥ 6 seconds; or
- 2nd or 3rd degree AV block ≥ 10 seconds.

Prior to the administration of adenosine participants were given instruction concerning a "cough" command. This was to encourage them to forcefully cough in the event of pre-syncopal symptoms in association with a positive test to transiently increase cardiac output with the aim of aborting syncope (Criley *et al.*, 1976; Jafary, 2008).

3.1.13 Cardiac implantable device insertion

Following adenosine testing, patients who were adenosine test positive were listed for permanent pacemaker implantation, and those who were adenosine test negative were listed for ILR insertion.

3.1.13.1 ***Permanent Pacemaker Implantation***

The implant procedure was undertaken in the Cardiac Catheterisation Laboratory at the Freeman Hospital, Newcastle upon Tyne. Participants provided informed consent for the procedure following appropriate counselling regarding the procedure itself and associated risks. The following specific procedural risks were quoted:

- Pneumothorax 2%;
- Lead displacement 2%;
- Infection 1%; and
- Haematoma requiring evacuation 1%.

Prior to the procedure patients were given pre-medication in the form of 1g oral paracetamol and 1g oral flucloxacillin (or an appropriate alternative if penicillin allergic). Following the procedure the participants completed a 2 day course of 500mg oral flucloxacillin four times a day (or an appropriate alternative if penicillin allergic). The procedure was undertaken under local anaesthetic. The device implanted was a Medtronic Adapta (Medtronic, Minneapolis, USA) dual chamber rate responsive pacemaker

Participants remained in hospital overnight following implantation. The next day the function of the pacemaker was checked and a chest X-ray undertaken to assess the presence of implant related complications. Having established that the device was functioning appropriately and no complications were present, the participants were randomised by the cardiac physiologist undertaking the device check to one of two pacing modes:

I. DDD ± R (dual chamber pacing); or
II. ODO (placebo).

Following randomisation the patients were discharged with a plan to be reviewed in Cardiac Rhythm Management in four to six weeks.

3.1.13.2 *Implantable loop recorder implantation*

Those with a negative adenosine test received an implantable loop recorder. This small device (the approximate size of a USB stick) was implanted subcutaneously below the left clavicle under local anaesthetic in a similar manner to a permanent pacemaker. The device implanted was a Medtronic Reveal XT (Medtronic, Minneapolis, USA). The procedural risks associated with the loop recorder are less than for a pacemaker. The following specific risks were quoted:

- Infection <1%; and
- Haematoma requiring evacuation <1%

As with pacemaker implantation, the same antibiotic regime was provided. Participants were discharged on the same day of implant; following checking of the function of the device and after education regarding appropriate use of the device activator from the Cardiac Rhythm Management Department. Follow-up was arranged at four weeks either by attending the department or remote monitoring. Remote monitoring is a service that allows the function of the implanted device to be checked remotely and securely via the internet. Technology set up in the participants' home via a telephone landline makes this possible.

3.1.14 Randomisation and Blinding

Assignment to either DDD ± R (active) pacing or ODO mode (placebo) occurred following routine device checks on the day after pacemaker implantation and was blinded to both the participant and investigators (double-blind).

Randomisation was performed by the use of sealed envelopes in blocks of 10 to ensure balanced allocation.

A code-break file was kept in the site file in Cardiac Rhythm Management at the Freeman Hospital to be utilised in the event of a clinical requirement to know the pacing allocation.

At the six-month cross-over and final visits, the integrity of the blind was assessed by asking both the participants and investigator: "Do you think you had your pacemaker

switched “on” or “off” in the last six months? Why do you think this?” The investigator recorded their answer separately prior to asking the participant to avoid bias.

At the end of the study, participants were told the order of their allocation but the investigators remained blinded until conclusion of the study.

3.1.15 Six month visit

The six month visit was conducted at Cardiac Rhythm Management at the Freeman Hospital and consisted of the following:

- Repeat quality of life assessment using these instruments:
    - Impact of Syncope on Quality of Life
    - WHOQoL-BREF
    - WHOQoL-Old instruments.
    - EQ-5D;
- Cross-over to the alterative pacing mode; and
- Integrity of the blind assessment

3.1.16 Twelve month visit

The twelve month visit served as the end of study visit and was conducted at Cardiac Rhythm Management at the Freeman Hospital. It involved the following:

- Repeat quality of life assessment using these instruments:
    - Impact of Syncope on Quality of Life
    - WHOQoL-BREF
    - WHOQoL-Old instruments.
    - EQ-5D; and

- Integrity of the blind assessment in those with a pacemaker in situ

3.1.17 Data collection

Assessments and data collection adhered to the study schedule of events (**Table 3.**).

Slippage of 2 weeks was permitted for the 6 week, 6 month and 12 month reviews.

Primary and secondary measures related to syncope were collected via monthly postage-paid syncope diaries with telephone prompting to ensure contemporaneous return.

Data collected on paper (Case Report Forms) were stored in a locked office at the Royal Victoria Infirmary and also at the Freeman Hospital for device follow-up and randomisation specific data. Data were entered electronically onto a secure study specific password-protected database held on the Newcastle upon Tyne Hospitals NHS Foundation Trust secure network. All data were handled, computerised and stored in accordance with the Data Protection Act 1998.

3.1.18 Safety evaluation

3.1.18.1 ***Definitions***

The following definitions were used with regards to safety:

Adverse event:

Any untoward medical occurrence in a subject to whom a study intervention or procedure was administered, including occurrences which are not necessarily caused by or related to that intervention. An adverse event, therefore, did not necessarily have a causal relationship with the treatment. In this context, "treatment" means all interventions administered during the course of the study. Medical conditions present before starting the study were only considered adverse events if they worsened after study commencement.

Related adverse event**:**

An adverse event resulting from any study procedure. All adverse events judged by the investigators as having reasonable causal relationship to a study procedure qualified as 'related adverse events'. The expression "reasonable causal relationship" conveyed that there was evidence or argument to suggest a causal relationship.

Causality**:**

The assignment of the causality was made by the investigators using the definitions in the table **Table 3.**. All adverse events judged as having a reasonable suspected causal relationship to a study procedure were considered to be related adverse events.

Unexpected Adverse Event**:**

Any adverse event that was not listed in the study protocol (**Table 3.4**) as an expected occurrence.

Serious Adverse Event (SAE):

An untoward occurrence (whether expected or not) that:

- Resulted in death;
- Was life-threatening (referring to an event in which the subject was at risk of death at the time of the event; not to an event which hypothetically might have caused death if it were more severe);
- Required hospitalisation, or prolongation of existing hospitalisation;
- Resulted in persistent or significant disability or incapacity; or
- Was otherwise considered medically significant by the investigator

Medical judgement was exercised in deciding whether an adverse event was serious in other situations. Important medical events that were not immediately life-threatening or did not result in death or hospitalisation but jeopardised the patient or required intervention to prevent one of the other outcomes listed in the definition above, were considered serious.

Severity of adverse events:

The severity of adverse events was graded on a three-point scale:

- Mild: Discomfort noticed, but no disruption of normal daily activities;
- Moderate: Discomfort sufficient to reduce or affect normal daily activities; and
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 3.3 Definitions related to causality

Procedure	Adverse event		
	Common & well understood	Less common and with unpleasant side effects	Rare events
Adenosine testing	• Shortness of breath • Chest discomfort • Flushing • Anxiety • Wheezing • Presyncope • Syncope	• Loss of consciousness	• Transient atrial tachyarrhythmia • Theoretical but never documented stroke and myocardial infarction due to occult critical cerebrovascular or coronary artery stenosis
Pacemaker implantation	• Localised discomfort and bruising post-procedure	• Lead displacement (up to 5%) • Haematoma requiring evacuation (1%) • Infection (1%) • Pacemaker erosion (<1%)	•
Local Anaesthetic	• Pain at site of injection (during or immediately following injection)	• None	• Haematoma • Allergic reaction
Implantable loop recorder insertion	• Localised discomfort and bruising post-procedure	• Haematoma requiring evacuation (1%) • Infection (1%)	• Erosion

Table 3.4 Expected adverse events during study

3.1.18.2 ***Recording and reporting of adverse events***

All adverse events were reported using the mechanisms outlined below.

Adverse event:

All non-serious adverse events during study participation were recorded on the study Case Report Form.

Serious adverse events:

All serious adverse events were recorded by the investigators and reported to the Regional Ethics Committee within 15 days of becoming aware of the event unless urgent safety measures were required, in which case initial notification by telephone was made followed by notice in writing. Serious adverse events were reported using the National Research Ethics Service Report of Serious Events Form (Version 3, April 2007).

3.1.19 Research Governance

3.1.19.1 *Withdrawal of participants*

Participants had the right to withdraw from the study at any time for any reason, without the need to provide a reason for doing so. The right to withdraw patients from the study intervention if it was judged to be in the patient's best interests was preserved. It was understood by all participants that an excessive rate of withdrawals would make the study difficult to interpret. Therefore, unnecessary withdrawal of patients was avoided if possible. In the event of a withdrawal, all efforts were made to report the reason for withdrawal.

There were two withdrawal options:

I. Withdrawing completely (i.e. withdrawal from both the study treatment and provision of follow-up data); and
II. Withdrawing partially (i.e. withdrawal from study treatment [including a request to move to another treatment arm] but continuing to provide follow-up data by attending for visits and completing questionnaires/syncope diaries).

Consent was sought from participants choosing option 1 to retain data collected up to the point of withdrawal. Participants were asked if they would be happy for the reason for the decision to withdraw to be recorded.

3.1.19.2 *Trial management*

The trial was managed the Trial Management Group (TMG) comprising:

Dr Steve Parry	Principal Investigator
Dr Iain Matthews	Co-investigator
Dr Chris Plummer	Co-investigator

An independent data monitoring and ethics committee (IDMC) comprising two Cardiologists not connected to the trial (Dr Neil Sulke, Consultant Cardiologist, Eastbourne [Chair] and Dr Michael Norton, Consultant Community Cardiologist, Sunderland) and a statistician not connected to the trial (Dr Elaine Stamp, Newcastle University) undertook independent review to monitor efficacy and safety endpoints following one year of recruitment. Initial rates of recruitment were used to project total recruitment to ensure sufficient participants to power the trial. Also, the IDMC were allowed access to unblinded study data in order to make a decision as to continue or halt recruitment of the trial on the basis of this outcome data. If the study were to be prematurely discontinued, active participants were informed and no further participant data was collected.

3.2 Audit of presentation with transient loss of consciousness to the Emergency Department

3.2.1 Background

During the course of running the clinical trial that is the core of this thesis it became apparent that recruitment was slower than anticipated. As previously outlined, this was addressed by opening-up recruitment to include referrals with unexplained syncope from the community to the Falls and Syncope Service.

Given the lower than planned number of presentations with syncope to acute medical services, it became important to characterise the nature and volume of presentations with syncope to acute medical services. This was to ensure that we were not missing a significant number of presentations with syncope. Therefore, an audit into the diagnosis and management of transient loss of consciousness presenting to the ED was performed.

3.2.2 Audit setting

This was a retrospective case series review of presentations with transient loss of consciousness to the ED throughout the month of October 2012

3.2.3 Audit standard

The audit standard was the 'Diagnosis and management of transient loss of consciousness (blackouts) in adults and young people' clinical guideline published in 2010 by the National Institute of Clinical Excellence (CG 109) (Westby *et al.*, 2010).

3.2.4 Case identification

The ED admissions database was searched to identify all presentations with transient loss of consciousness (TLoC) in adults ≥ 16 years of age during October 2012. The presenting complaint entry in the admission database is free text therefore a broad-based search of terms which might incorporate TLoC was conducted. The terms searched for were:

- Syncope;
- Collapse;
- Collapse with uncertain cause;
- Vasovagal;
- Faint;
- Fit;
- Seizure; or
- Epilepsy

The clinical records of the attendance (the ED 'card' and/or hospital admission notes) were reviewed and should the presentation be deemed to be with TLoC then they were included in the audit.

3.2.5 Exclusion criteria

Exclusion criteria were if the presentation was with a different complaint but had been misclassified as TLoC or if there had been a loss of consciousness but this was not transient.

3.2.6 Inclusion criteria

Cases were included if in the opinion of the case record reviewer the presentation was with TLoC. As per the audit standard, this specifically meant a diagnosis of syncope, seizure (epilepsy) or psychogenic TLoC.

3.2.7 Data collection

The initial assessment, diagnosis and onward referral decision for each presentation was assessed using NICE CG 109 as the standard of practice. An adapted version of the template data collection tool produced in NICE CG109 was used to collect data. The admission documentation was reviewed to determine whether all areas of clinical questioning and examination as described in the clinical guideline were recorded.

Discharge diagnosis forms a key component of practice outlined in the guideline. Therefore, the ED discharge diagnosis, either to home or to a hospital admission, was assessed and categorised using the following definitions:

Arrhythmia

Evidence of a bradycardia or tachycardia on 12 lead ECG or ambulatory telemetry sufficient to merit specific therapy; or evidence of conducting system disease on 12 lead ECG insufficient to merit therapy but in the context of a strong clinical suspicion of arrhythmia.

Vasovagal syncope

A typical history of situational or reflex syncope; or a compatible clinical history incorporating the '3 Ps' – provoking factors, upright posture and clinical prodrome.

Orthostatic hypotension

A fall of 20mmHg in the systolic blood pressure or 10 mmHg in the diastolic blood pressure within 3 minutes of standing.

Post prandial syncope

Syncope within 120 minutes after eating a meal in the absence of another clear cause.

Cough syncope

Syncope during or immediately following a bout of coughing.

Epilepsy

Witnessed description of a tonic-clonic seizure or, in the absence of a witness, the presence of 2 or more of the following features: a bitten tongue, head-turning to one side during TLoC; no memory of abnormal behaviour surrounding event; unusual posturing; prolonged limb-jerking; confusion following the event; or prodromal *deja* or *jamais* vu.

Unexplained syncope

None of the other previously outlined diagnosis could be attributed.

No diagnosis

No diagnosis was offered by the attending ED doctor.

4 Chapter 4: Results

4.1 Audit of presentation with transient loss of consciousness to the Emergency Department

4.1.1 Presentation with transient loss of consciousness

During October 2012, there were 9759 attendances at the Emergency Department of the Royal Victoria Infirmary by patients over 16 years of age. Two hundred and fifty seven were coded on discharge or admission to hospital as one of:

- Syncope;
- Vasovagal;
- Faint;
- Collapse;
- Collapse of unknown cause;
- Epilepsy;
- Fit; or
- Seizure

Seventeen patients (7%) left the ED prior to being assessed by a doctor. The clinical records of the episode were unable to be located for 21 patients (8%). This left 219 records to be analysed.

Of these 219, ninety-one patients had a primary presentation with transient loss of consciousness (TLoC); representing 0.95% of all ED attendances over the age of 16 years.

4.1.2 Age and sex

The mean age at presentation was 51 ± 24 years with peaks around age 20 years, age 60 years and age 80 years (**Figure 4.1**). Fifty six (62%) were female and 35 (38%) were male.

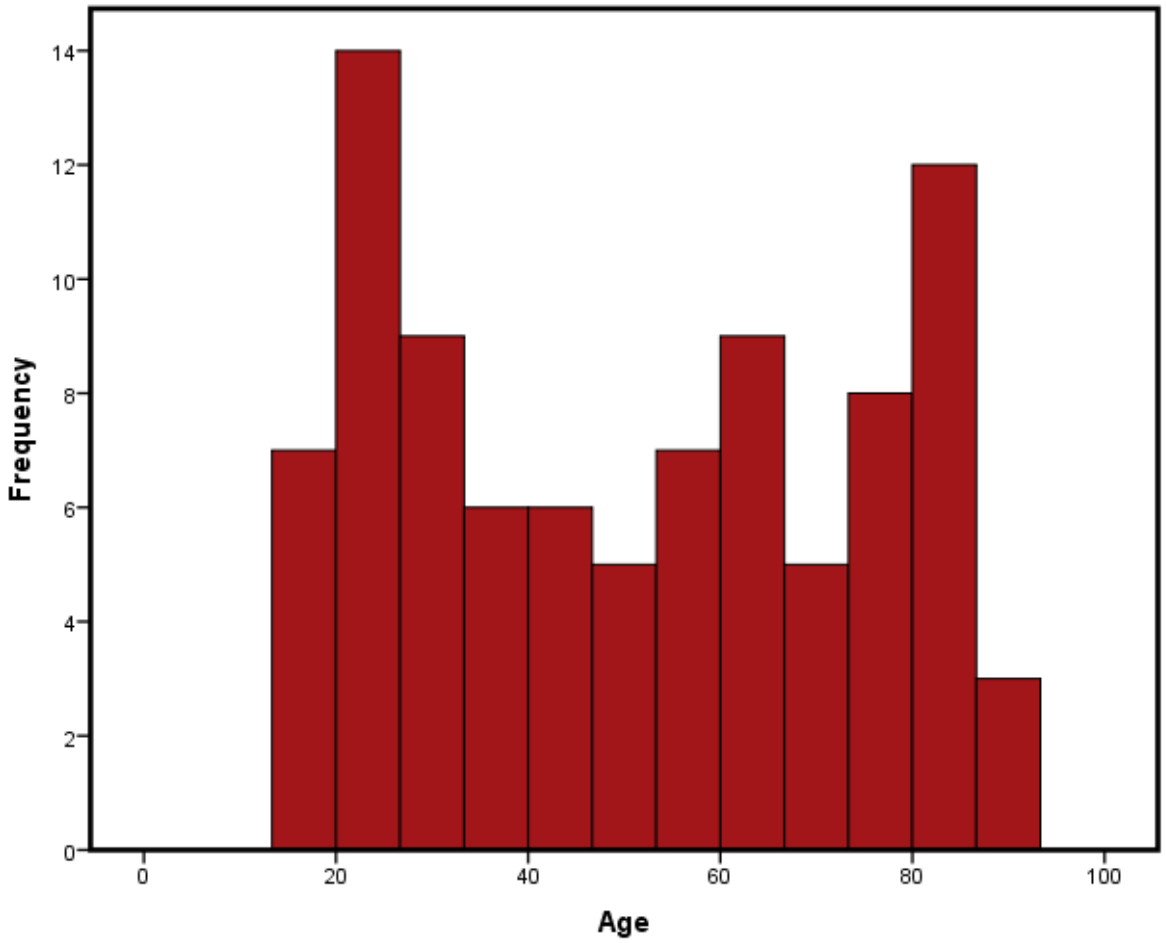

Figure 4.1 Age distribution of patients presenting to the Emergency Department with transient loss of consciousness in October 2012

4.1.3 Diagnosis on discharge

The breakdown of diagnoses on discharge from ED is shown in **Figure 4.2**. The most common diagnosis was vasovagal syncope (n=56, 62%). Epilepsy accounted for a small proportion of attendances (n=7, 8%). There were small numbers with an arrhythmia (n=5, 5%); situational syncope, either cough or post-prandial (n=6, 6%); orthostatic hypotension (n=3, 3%); and unexplained syncope (n=3, 3%). No diagnosis was offered in 6 patients (7%). Those labelled other (n=5, 5%) describe transient loss of consciousness clearly related to an alternative medical problem (night terror, n=1; leaking abdominal aortic aneurysm, n=1; seizure secondary to acute alcohol

withdrawal, n=1; urinary tract infection n=1; and a non-epileptic/psychogenic seizure, n=1).

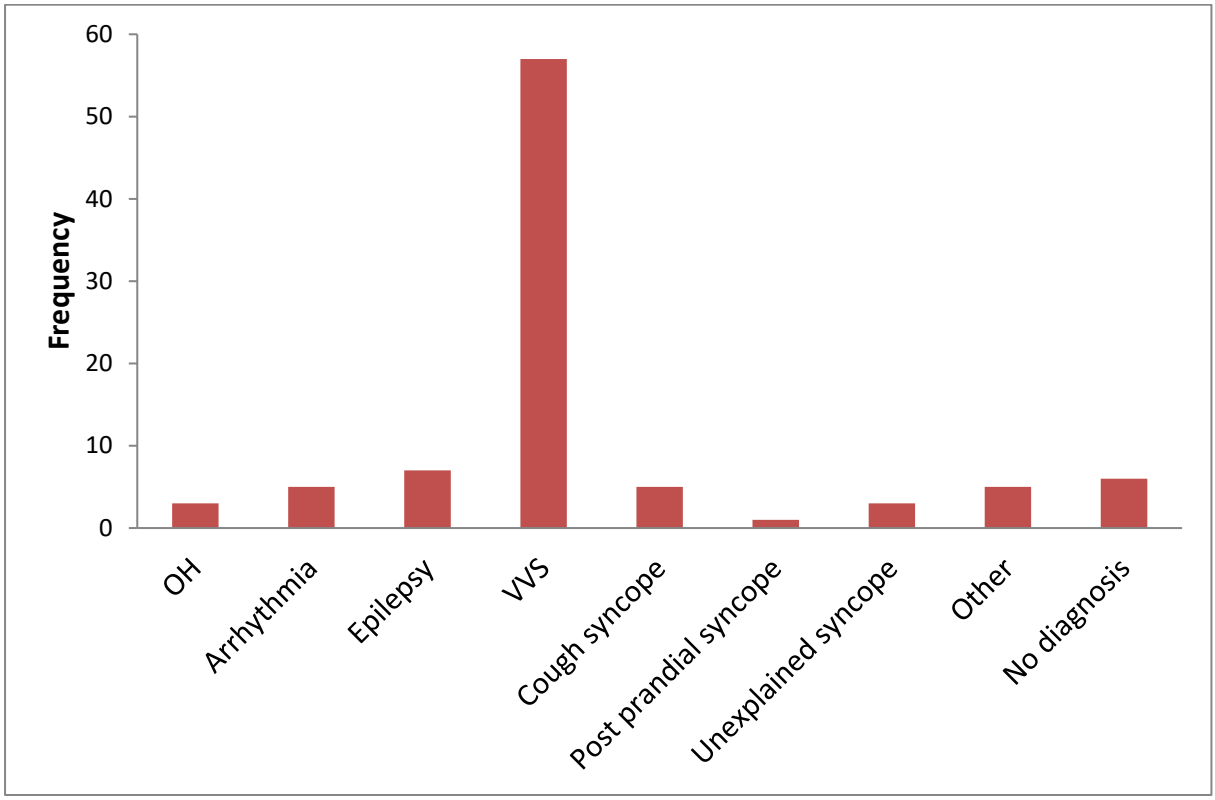

Figure 4.2 Diagnosis category on discharge from the Emergency Department

OH = orthostatic hypotension; VVS = vasovagal syncope.

4.1.4 Performance of initial assessment against audit standard

Performance of the initial assessment, incorporating history taking and clinical examination, were assessed against the NICE CG 109 standard. Table 4.1 documents the completion rate of each individual component of the audit standard in initial assessment.

With regards to the history taking aspect of the initial assessment, no aspects were done well (completion rate > 90%). Several aspects were performed moderately well (completion rate >60%):

- Enquiring about the entirety of the event (before, during and after) as recalled by the patient was completed in 76 cases (84%);

- Ascertaining the detailed circumstances of the event that was done in 69 cases (76%); specifically with posture at the time of syncope documented in 55 cases (60%); the presence or absence of prodromal symptoms documented in 72 cases (79%); and the duration of loss of consciousness enquired about in 55 cases (60%); and
- Current potential culprit documentation was documented in 69 cases (76%)

Several aspects of the initial assessment were performed notably poorly:

- The documented presence or absence of a witness to the clinical event and an attempt to contact this witness should one have been present was completed in 20 cases (22%);
- Enquiring about any prior history of transient loss of consciousness was completed in only 23 cases (25%);
- A family history of sudden cardiac death under the age of 50 years was explored in only 3 cases (3%);
- The recording of driving status was completed in only 4 cases (4%); and
- Not a single person discharged from the ED was documented as having been provided with a copy of their 12 lead ECG.

On the whole, the clinical examination component of the initial assessment initial assessment was well conducted. Aspects done particularly well included:

- Vital signs (pulse rate, blood pressure, resting oxygen saturation and temperature) were recorded in 85 cases (93%);
- Full examination of the cardiovascular system was completed in 88 cases (97%) and neurological system in 84 cases (92%); and
- A 12 lead ECG was undertaken in 78 cases (86%) and reported in 73 cases (94%) in which one was available.

The only significant criterion of the clinical examination component of the standard not done well was the performance of postural blood pressure that was only undertaken in 22 cases (24%).

4.1.5 Discharge and Follow-Up from the Emergency Department

Sixty-five patients (71%) were discharged from the Emergency Department. Follow-up was arranged in 11 (16%), the majority of which (6 cases, 55%) was with a Neurologist in the first fit clinic. These were all cases in which a diagnosis of epilepsy was suspected.

On detailed review of the clinical records, it was felt that follow-up would have been appropriate in an additional 15 cases discharged with no plans to do so. The reasons and proposed destination for follow-up were:

- Recurrent vasovagal syncope (n=4), Falls and Syncope Service;
- Demonstrable orthostatic hypotension (n=3), Falls and Syncope Service;
- Conducting system disease on a 12 lead ECG (n=4), Falls and Syncope Service;
- Clinical suspicion of epilepsy (n=2), Neurology;
- Unheralded syncope (n=1), Falls and Syncope Service; and
- Syncope whilst sitting (n=1), Falls and Syncope Service.

Parameter	Performed (%)
History	
Entirety of History	76 (84%)
Witness present*	20 (22%)
Circumstances of TLOC	69 (76%)
Posture	55 (60%)
Prodrome	72 (79%)
Appearance during TLOC†	10 (50%)
Limb-jerking during TLOC†	11 (55%)
Tongue biting	73 (80%)
Injury	61 (67%)
Duration of TLOC	55 (60%)
Confusion post TLOC	37 (41%)
Limb weakness post TLOC	4 (4%)
Previous episodes	23 (25%)
Family history of SCD < 50 years	3 (3%)
Culprit medication	69 (76%)
Driving status documented	4 (4%)

Initial Assessment	
Vital signs	85 (93%)
Lying and standing blood pressure	22 (24%)
Cardiovascular examination	88 (97%)
Neurological examination	84 (92%)
12 lead ECG	78 (86%)
Reporting of 12 lead ECG‡	73 (94%)
Copy of 12 lead ECG§	0 (0%)

Table 4.1 Performance of individual components of initial assessment against NICE CG 109 standard

TLOC = transient loss of consciousness; DSC – sudden cardiac death; ECG = electrocardiogram.

*Witness present and attempt made to contact witness †Only applicable when a witness present ‡Only applicable when ECG performed §Only applicable in those discharged from ED.

4.2 Randomised double-blind placebo-controlled cross-over trial

4.2.1 Trial recruitment and progression

Trial recruitment commenced on 13th February 2012. The last participant was recruited on 17th November 2015. The CONSORT flow diagram (Moher *et al.*, 2001) outlines the progress of patients throughout the trial **(Figure 4.3).**

In total, 323 patients were screened. Two hundred and seventy-one patients were excluded. Detailed reasons for exclusion are given in **Table 4.2**. The most common reason for exclusion was for the patient to decline participation in the trial after receipt of the patient information sheet and following a minimum of twenty-four hours of

deliberation (n=121, 45%). The second most frequent reason for exclusion was cognitive impairment of sufficient severity to affect the capacity to give informed consent (n=31, 11%).

Fifty-two patients gave their informed consent to participate in the trial and went on to have adenosine testing. There were 35 positive adenosine tests (67%) and 17 negative adenosine tests (33%). Baseline characteristics of the two groups are shown in **Figure 4.4** and discussed later.

Of the 52 included participants, 6 (12%) were recruited directly from the Emergency Department, 11 (21%) from the Assessment Suite (Acute Medical Admissions Unit) and 35 (67%) via the Falls and Syncope Service.

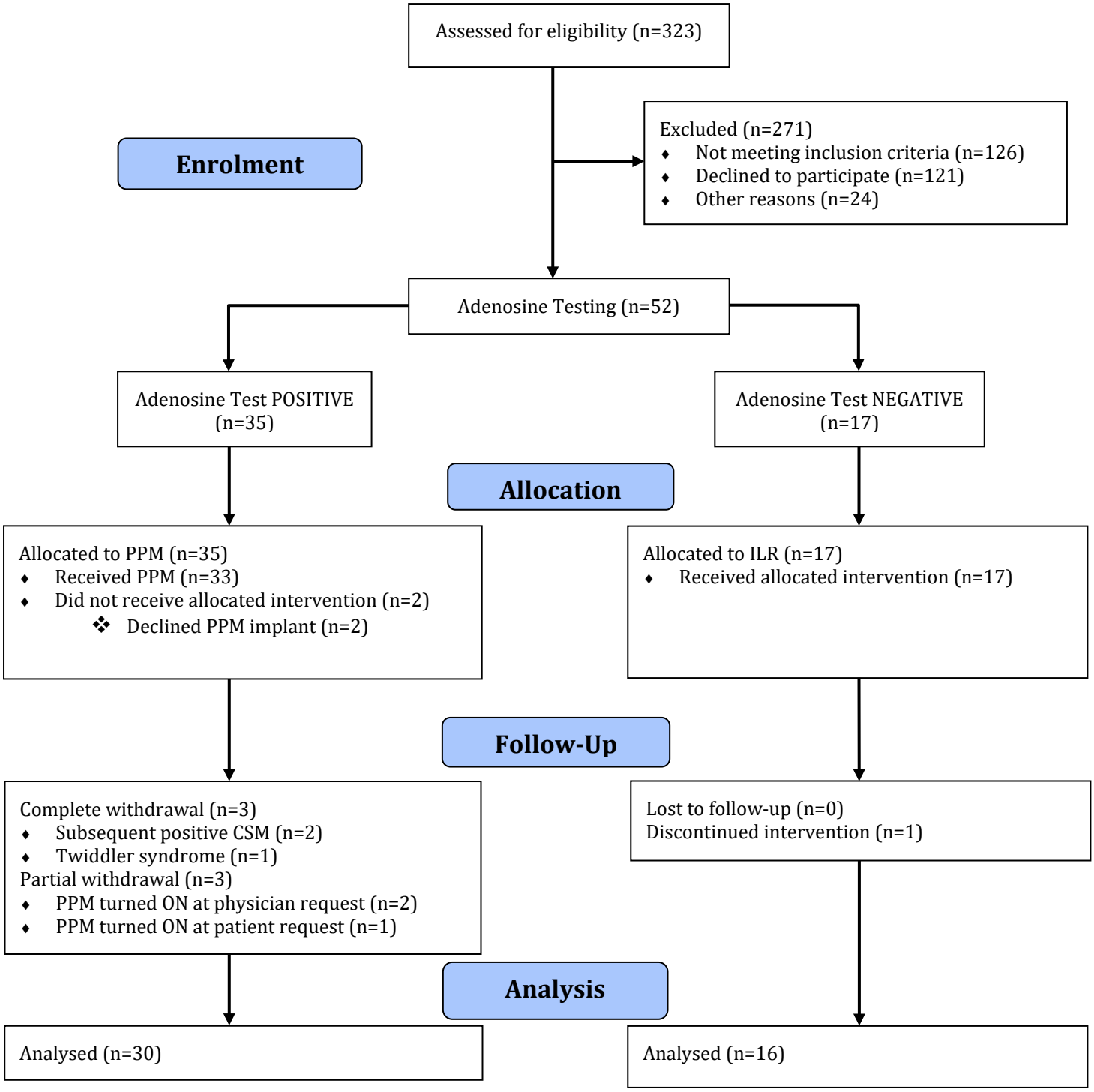

Figure 4.3 CONSORT Flow diagram outlining the progression of participants throughout the ADEPT ILR trial.

PPM = permanent pacemaker; ILR = implantable loop recorder.

Reason for Exclusion	Number (%)
Address not local	6 (2%)
Aortic stenosis	1 (<1%)
Accessory pathway on 12 lead ECG	1 (<1%)
Asthma	8 (3%)
Cardiac implantable electronic device in-situ already*	8 (3%)
Chronic obstructive pulmonary disease	23 (9%)
Clinical decision to implant permanent pacemaker	3 (1%)
Cognitive impairment	31 (11%)
Declined to participate	121 (45%)
Denies syncope	5 (2%)
Epilepsy or high clinical suspicion of epilepsy	4 (2%)
Ischaemic heart disease†	2 (1%)
Not possible to contact patient after initial screening	18 (7%)
Not a presentation with syncope	10 (4%)
Orthostatic hypotension	10 (4%)
Prolonged QT interval	1 (<1%)

Severe LVSD – high clinical suspicion of ventricular arrhythmia	4 (2%)
Sinus node disease	1 (<1%)
Symptomatic congestive cardiac failure	2 (1%)
Vasovagal syncope	12 (4%)
Total	**271 (100%)**

Table 4.2 Reasons for exclusion in the ADEPT-ILR trial

LVSD = left ventricular systolic dysfunction

*Either implantable loop recorder, permament pacemaker or implantable cardioverter-defibrillator; †myocardial infarction within the last three months or known severe coronary disease

4.2.2 Baseline clinical characteristics

Fifty-two patients gave informed consent to participate in the trial and went on to have adenosine testing. There were 35 positive adenosine tests (67%) and 17 negative adenosine tests (33%). Baseline characteristics of the two groups (**Figure 4.4**.) were well-matched with the only statistically significant difference between the groups being a numerically lower mean supine systolic blood pressure in the adenosine positive group (130.3±15 vs. 141.9 ± 25.4 mmHg, p=0.042). The adenosine positive group was slightly older but this did not reach statistical significance (65.1 ± 11.4 years vs. 59 ± 12.0 years, p=0.083).

There were no significant differences in co-morbid conditions that might point to either a diagnosis of arrhythmic or neurally mediated syncope: hypertension 14 (40%) vs. 4 (24%), p=0.242; ischaemic heart disease 8 (23%) vs. 1 (6%), p=0.241 and vasovagal syncope 2 (6%) vs. 1 (6%), p=1.000.

Similarly, there were no significant differences in prescribed drug therapy that might be a contributory factor in the diagnosis of syncope: beta-blockers 5 (14%) vs. 2 (12%); calcium-blockers 5 (14%) vs. 2 (12%); loop diuretics 4 (11%) vs. 2 (12%); thiazide diuretics 4 (11%) vs. 1 (6%); angiotensin receptor blockers 3 (9%) vs. 2 (12%); selective serotonin reuptake inhibitors 6 (17%) vs. 3 (18%), all p=1.000; angiotensin converting enzyme inhibitors 9 (26%) vs. 1 (6%), p=0.137 and tricyclic antidepressants 8 (23%) vs. 2 (12%), p=0.467.

There were no significant differences in the baseline 12 lead electrocardiographic data of the two groups.

Baseline Characteristics			
	Adenosine Positive (N=35)	**Adenosine Negative (N=17)**	**Probability**
Age, Mean years (SD)	65.1 (11.4)	59 (12.0)	p=0.083
Sex N (%)			
Female	18 (51)	6 (35)	p=0.274
Male	17 (49)	11 (65)	
Co-morbidities N (%)			
Hypertension	14 (40)	4 (24)	p=0.242
Ischaemic Heart Disease	8 (23)	1 (6)	p=0.241
Cerebrovascular Disease	7 (20)	2 (12)	p=0.700
Diabetes mellitus	6 (17)	1 (6)	p=0.404
Vasovagal syncope	2 (6)	1 (6)	p=1.000
Depression	10 (29)	5 (29)	p=1.000
Other	13 (37)	7 (41)	p=0.774
Medications N (%)			
Beta-blocker	5 (14)	2 (12)	p=1.000
Calcium-blocker	5 (14)	2 (12)	p=1.000
Loop diuretic	4 (11)	2 (12)	p=1.000
Thiazide diuretic	4 (11)	1 (6)	p=1.000
Angiotensin converting enzyme inhibitor	9 (26)	1 (6)	p=0.137
Angiotensin receptor blocker	3 (9)	2 (12)	p=1.000
Selective serotonin reuptake inhibitor	6 (17)	3 (18)	p=1.000
Tricyclic	8 (23)	2 (12)	p=0.467
Other	14 (40)	9 (53)	p=0.378
Evaluation, Mean (SD)			
Syncopal episodes in last 12 months Mean (SD)	4.2 (4.7)	5.2 (5.8)	p=0.936
Mean Lying SBP (mm Hg)	130.3 (15)	141.9 (25.4)	*p=0.042*
Mean Lying DBP (mm Hg)	78.0 (16.2)	86.2 (8.7)	p=0.059
Mean Stand SBP (mm Hg)	134.5 (18.7)	141.4 (25.5)	p=0.730
Mean Stand DBP (mm Hg)	89.7 (17.1)	85.9 (23.3)	p=0.871
ECG			
Sinus rhythm, N (%)	35 (100)	17 (100)	
Atrial fibrillation, N (%)	0 (0)	0 (0)	
First degree atrioventricular block, N	4 (11)	1 (6)	p=1.000
Mean PR interval, milliseconds (SD)	169.3 (25.7)	164.1 (26)	p=0.494
Right axis deviation, N (%)	0 (0)	0 (0)	
Left axis deviation, N (%)	7 (20)	0 (0)	p=0.081
Right bundle branch block, N (%)	0 (0)	0 (0)	
Left bundle branch block, N (%)	0 (0)	0 (0)	
Mean QTc, milliseconds (SD)	439.6 (23.4)	434.6 (24.1)	p=0.494
Mean QRS, milliseconds duration (SD)	91.6 (12.9)	90.9 (11.3)	p=0.913

Table 4.3. Baseline characteristics of the patient population

SBP=systolic blood pressure, DBP=diastolic blood pressure, AV=atrioventricular.

4.2.3 Adenosine testing

Fifty-two patients had adenosine testing. There were 35 positive adenosine tests (67%) and 17 negative adenosine tests (33%). The mean cardiac pause and duration of atrioventricular block in the adenosine positive group was 5.6 ± 2.8 seconds and 17.2 ± 4.4 seconds compared to 2.5 ± 1.5 seconds and 6.2 ± 2.7 seconds in the adenosine negative groups ($p<0.001$ for both). Adenosine testing was well tolerated, and none of the participants experienced syncope, largely because of the prolonged asystole cough command that aborted more prolonged asystole in 18 of the 35 adenosine positive individuals (51%). There were no significant differences in the symptom profile following the administration of adenosine (**Table 4.4**).

Adenosine Testing N=52			
	Adenosine Positive (N=35)	**Adenosine Negative (N=17)**	**Probability**
Adenosine			
Mean ventricular asystole, seconds (SD)	5.6 (2.8)	2.5 (1.5)	*p<0.001*
Mean AV block duration, seconds (SD)	17.2 (4.4)	6.2 (2.7)	*p<0.001*
Symptoms with Adenosine			
Shortness of breath, N (%)	10 (29)	4 (24)	p=1.000
Pre-syncope/Dizzy, N (%)	4 (11)	3 (18)	p=0.670
Chest tightness, N (%)	10 (29)	5 (29)	p=0.950
"Unwell", N (%)	18 (51)	5 (29)	p=0.134
Flushing, N (%)	22 (63)	10 (59)	p=0.779
Other, N (%)	11 (31)	9 (53)	p=0.135
Similar to syncopal episodes, N (%)	6 (17)	2 (12)	p=1.000

Table 4.4. Clinical response to adenosine testing.

AV=atrioventricular.

Adenosine Test Positive			
Criterion for positivity	> 6 secs asystole	> 10 seconds AV block	> 6 secs asystole AND 10 secs AV block
N (%)	0 (0)	18 (51)	17 (49)

Table 4.5. Breakdown of positive adenosine tests

AV = atrioventricular

In the adenosine positive group there was an even split with regards to the criteria used to determine whether the test was positive **(Table 4.5)**. In 18 cases (51%) only more than 10 seconds of atrioventricular block was present whilst in 17 cases (49%) both 10 seconds of atrioventricular block and 6 seconds of asystole occurred. In no cases was there 6 seconds of asystole without 10 seconds of atrioventricular block.

4.2.4 Treatment withdrawals and complications

4.2.4.1 *Withdrawals*

Eight out of the thirty-five patients that tested adenosine positive withdrew from the study. The reasons for withdrawal are summarised in **Table 4.6**.

Reason for withdrawal	N=
Complete withdrawal	
Declined permanent pacemaker following positive adenosine test	2
Carotid sinus syndrome found during routine care requiring pacemaker in active DDD mode	2
Twiddler syndrome	1
Partial withdrawal	
Bradycardia requiring pacemaker in active DDD mode	2
Patient request	1

Table 4.6. Breakdown of reasons for withdrawal from ADEPT-ILR

There were three partial withdrawals (withdrawal from study treatment but continuing to provide follow-up data by attending for visits and completing quality of life

questionnaires/returning syncope diaries) and six complete withdrawals. No data was available from the complete withdrawals but the data from the partial withdrawals is included in the analysis.

The patient who developed Twiddler syndrome was discovered during a routine check following the pacemaker implant when both the atrial and ventricular leads were non-functional. A chest radiograph demonstrated both leads to be wrapped around the device within the pre-pectoral pocket with both tips in the superior vena cava. The individual admitted to a constant desire to "scratch the device from (his) chest". The device was explanted without complication at the patients' request.

One patient in the adenosine negative loop recorder group developed oesophageal cancer during the course of the study and withdrew. This was towards the end of the twelve-month observation period and there had been no further syncopal episodes.

4.2.4.2 *Complications*

There were two complications of a permanent pacemaker implantation in the adenosine positive group in the form of a ventricular lead displacement and an iatrogenic pneumothorax. The ventricular lead displacement was identified during a routine check six weeks post implant and repositioned without incident. There had been no episodes of syncope during this six-week period and the patient went on to complete the study.

The pneumothorax required an internal chest drain and an unplanned in-patient stay but the patient went on to complete the study.

There were no complications in the adenosine negative implantable loop recorder group.

4.2.5 Cumulative syncope burden

Of the twenty-seven patients that completed the study, twenty-three did not suffer syncope in either six-month period. Two patients had syncopal episodes in both periods, two were syncopal only when the pacemaker was turned off and two were syncopal only when the pacemaker was turned on. **Table 4.7** shows the mean number

of syncopal episodes for each pacing period. A mean of 0.4 fewer syncopal episodes per patient were recorded during the six-month period with the pacemaker turned on compared to the six-month period with pacemaker turned off (mean of 1.2 versus 1.6 falls respectively). Moreover, the relative risk of syncope with the pacemaker turned off compared with the pacemaker turned on was 2.1 (95% confidence interval 1.0-4.4). p=0.048).

Excluding the 3 patients who partially withdrew from the study (due to the demonstration of bradycardia requiring a DDD pacemaker in active mode in 2 cases and a request to have the device active in DDD mode regardless of the blinded allocation) in keeping with strict "intention to treat" principles finds a persisting and greater increased relative risk of syncope with the pacemaker turned off (relative risk 4.9 95% CI 1.7 to 13.8, p=0.003).

Number of Syncopal Episodes (Mean, SD)			Number of days (Mean, SD)	
Pacemaker off	**Pacemaker on**	**Total**	**Pacemaker off**	**Pacemaker on**
1.6 (5.2)	1.2 (4.5)	2.9 (9.4)	183.1 (13.0)	186.8 (14.9)

Table 4.7 Mean number of syncopal episodes and days at risk for patients during pacemaker on and off periods

4.2.6 Time to first syncope and number of patients with recurrent syncope

There were 9 patients in both the adenosine positive and negative groups that had recurrent syncope (53% of the adenosine negative group and 30% of the adenosine positive group). The mean and median time to first syncope in the adenosine positive group was 56 days and 24 days and in the adenosine negative group 92 days and 100 days **(Table 4.8).**

	Adenosine Positive	Adenosine Negative
Recurrent Syncope (n)	9 (30%)	9 (53%)
Time to first syncope (days)		
Mean	56	92
Median	24	110

Table 4.8 Recurrent syncope and time to first syncope in the adenosine positive and negative groups

4.2.7 Quality of life

All patients in the trial completed the baseline quality of life questionnaires (ISQL= Impact of Syncope on Quality of Life, WHOQOL-OLD= World Health Organisation Quality of Life-Old; WHOQOL-BREF= the World Health Organisation Quality of Life-BREF). All participants in the adenosine positive group returned the six-month and twelve-month quality of life questionnaires. Four patients from the ILR group did not return their ISQL or WHOQOL- OLD questionnaire and three patients did not complete their WHOQOL-BREF questionnaire at 12 months.

Using the ISQL questionnaire, quality of life improved in both the adenosine positive and adenosine negative groups from baseline indicated by a lower score at the end of the study period. Little difference was seen between the pacemaker on and off periods (**Table 4.9**). The score for quality of life statistically decreased compared to baseline for the ILR group by a mean of 10.1 according to the ISQL questionnaire ($p=0.017$). Similarly, a reduction in the mean score compared to baseline by 10.5 in pacemaker on period and 11.2 in pacemaker off period was also observed (both $p<0.001$). No statistically significant differences, however, were seen amongst pacemaker on, pacemaker off and ILR groups for quality of life from the ISQL questionnaire (**Table 4.9**).

Lack of statistical difference was seen between baseline scores compared to scores after pacemaker on or off periods for the WHOQOL- BREF or OLD questionnaires. Out of the WHOQOL-BREF questionnaire, only the social relationship domain was observed to have any statistically significant differences, with a reduction in mean score of 2.8 seen between baseline and ILR treatment (p=0.005). Additionally, patients from the pacemaker on and pacemaker off periods had statistically higher mean scores by a mean of 2.4 and 2.0 respectively than the ILR group for social relationship domain by the end of the study (p=0.003 and p=0.008 respectively, **Table 4.9**).

From the WHOQOL-OLD questionnaire, pacemaker on and pacemaker off groups had statistically greater scores than the ILR group for past, present and future activities domain by mean increases in score of 13.6 (p=0.043) and 14.7 (p=0.029) respectively. This was similar to the intimacy domain, where patients from the pacemaker on period had a higher mean score by a mean of 26.8 compared to those from the ILR group (p=0.016), and patients from the pacemaker off period had a mean score that was higher by 27.2 compared to ILR group (p=0.009). Moreover, the mean total score for the pacemaker off period from the WHOQOL-OLD questionnaire was statistically higher than the ILR group total mean score by a mean of 9.2 (p=0.031), while no other statistical differences were observed (**Table 4.9**).

Questionnaire	Mean Score (SD)				
	Adenosine Positive			Adenosine Negative	
	Baseline	**Pacemaker on**	**Pacemaker off**	**Baseline**	**12 months**
ISQL	37.2 (13.4)	26.7 (13.0)***	26.0 (13.2)***	38.2 (14.2)	28.1 (18.1)*
WHOQOL-BREF					
Total	91.5 (14.5)	93.9 (14.6)	94.7 (14.4)	92.0 (14.6)	85.8 (18.5)
Physical health	12.7 (3.8)	13.0 (3.3)	13.3 (3.6)	12.5 (4.0)	12.3 (4.2)
Psychological health	14.5 (2.4)	15.0 (2.6)	15.1 (2.9)	14.6 (3.0)	13.7 (3.9)
Social relationship	11.4 (2.4)	11.8 (1.8)$^{++}$	11.4 (2.1)$^{++}$	12.2 (1.0)	9.4 (2.3)**
Environment	16.4 (2.2)	16.6 (2.3)	16.7 (2.3)	16.4 (1.9)	15.0 (2.6)
WHOQOL -OLD					
Total	93.2 (10.8)	94.1 (11.6)	95.5 (11.6)$^{+}$	92.7 (11.0)	86.3 (13.3)
Sensory Abilities	77.1 (21.7)	76.4 (22.1)	78.0 (22.0)	79.8 (16.8)	74.5 (25.2)
Autonomy	72.5 (18.0)	72.0 (18.9)	74.1 (16.1)	71.6 (16.5)	61.1 (23.7)
Past, present and future activities	72.7 (18.2)	72.7 (16.5)$^{+}$	73.8 (16.6)$^{+}$	67.3 (17.7)	59.1 (23.9)
Social participation	61.1 (21.2)	65.5 (16.2)	66.0 (20.5)	57.2 (19.1)	57.2 (19.1)
Death and Dying	72.7 (24.4)	71.1 (21.5)	73.8 (24.8)	82.7 (21.1)	83.7 (19.4)
Intimacy	76.6 (26.4)	80.6 (20.6)$^{+}$	81.0 (21.4)$^{++}$	70.7 (28.0)	53.8 (36.3)

Table 4.9. Quality of life reported from the ISQL, WHOQOL-OLD and WHOQOL-BREF questionnaires for baseline, six months with pacemaker on or off periods, or ILR treatment.

N=27 in the pacemaker periods, N=13 in the ILR group for ISQL and WHOQOL- OLD, N=14 for WHOQOL-BREF

*** $p<0.001$, **$p<0.01$ and *$p<0.05$ versus baseline for pacemaker periods or ILR treatment, $^{++}p<0.01$ and $^{+}p<0.05$ for pacemaker periods versus ILR treatment

ILR=implantable loop recorder; ISQL= Impact of Syncope on Quality of Life, WHOQOL-OLD= World Health Organisation Quality of Life-Old; WHOQOL-BREF= the World Health Organisation Quality of Life-BREF.

4.2.8 Results of those with a negative adenosine test and ILR insertion

Seventeen patients tested adenosine negative and underwent a loop recorder implant. One patient was diagnosed with epilepsy following a syncopal episode associated with typical seizure artefact on the loop recorder with no concurrent underlying rhythm disturbance. One patient had sinus arrest demonstrated on the loop recorder and went on to have a permanent pacemaker implantation, giving a negative predictive value of the adenosine test for identifying a bradycardia pacing indication of 0.94 (95% CI 0.69 – 1.00) or 94%. Two patients from this group received a clinical diagnosis of vasovagal syncope (VVS) as part of routine clinical care although they did not have any recorded syncopal episodes during the study period.

5 Chapter 5: Discussion

Transient loss of consciousness (TLoC) is a common symptom, accounting for around 1% of attendances at emergency departments (Brignole *et al.*, 2018). Whilst around two thirds of cases are rapidly diagnosed as having a neurally mediated origin, a substantial minority remain unexplained after the initial evaluation and require further investigation. The investigation pathway varies between centres, but can be costly and time consuming, often involving ever more invasive tests including an implantable loop recorder and an electrophysiological study, particularly in non-UK health systems. The adenosine test, first described in 1994 (Brignole *et al.*, 1994) was developed to compliment these investigations; and is safe, cheap, easy to administer and interpret and can be performed at the bedside with appropriate ECG monitoring (Parry *et al.*, 2006; Matthews *et al.*, 2014). However, despite the inclusion of around 1500 patients in a number of clinical studies on adenosine testing, several of which suggest symptom improvement with permanent pacing following a positive test, the test has never gained traction because of an often contradictory evidence base.

This study was an attempt to help clarify the role of adenosine testing in the investigation of unexplained syncope, through the medium of a double blind, placebo-controlled cross-over study of permanent pacing in syncopal patients with a positive adenosine test. Uniquely, an implantable loop recorder arm for those testing negative was included, to explore any rhythm problems that a negative adenosine test may have missed.

In this section, I will first describe the audit of presentations with TLOC to emergency services and relate this to the second part of the discussion on the main subject of this thesis, the randomised controlled trial.

5.1 Audit of presentation with transient loss of consciousness

5.1.1 Presentation with transient loss of consciousness

Transient loss of consciousness (TLoC) accounted for 0.95% of all attendances in a large, city centre Emergency Department. This is in keeping with the remarkably

consistent figure of around 1% presenting with syncope to either individual hospitals or a regional or city network of hospitals across Europe in the published literature (Sarasin *et al.*, 2001; Blanc *et al.*, 2002; Disertori *et al.*, 2003; Olde Nordkamp *et al.*, 2009; Baron-Esquivias *et al.*, 2010).

5.1.2 Age and Sex

The mean age of presentation was 51 ± 24 years. This is lower than the figure of around 60 years of age a range contemporary studies across Europe (Sarasin *et al.*, 2001; Blanc *et al.*, 2002; Disertori *et al.*, 2003; Baron-Esquivias *et al.*, 2010), although, interestingly, closer to the other published study focusing on a city centre Emergency Department in the Netherlands that reported a mean age of 46 (IQ range 30-65) years (Olde Nordkamp et al., 2009). City centre populations tend to be younger and this is the most probable reason. There were three peaks of presentation by age – around 20 years, 60 years and a final peak at 80 years. This is a trend observed elsewhere particularly when population level trends are examined (Soteriades *et al.*, 2002; Vanbrabant *et al.*, 2011; Ruwald *et al.*, 2012). Sixty two percent of attendees were women. Once again, this is very much in keeping with contemporary published data (Soteriades *et al.*, 2002; Ganzeboom *et al.*, 2006; Vanbrabant *et al.*, 2011).

5.1.3 Diagnosis on discharge

The most common diagnosis on discharge was vasovagal syncope (62%). This is in keeping with published literature (Sutton, 2013). In contrast, there was a markedly lower rate of orthostatic hypotension than might be expected (3% vs. 15%) (Sutton, 2013) most probably reflecting the younger age profile. Orthostatic hypotension becomes more common with increasing age.

Unexplained syncope accounted for only 3% of presentations, considerably smaller than rates of 14-54% in published series (Ammirati *et al.*, 2000; Sarasin *et al.*, 2001; Blanc *et al.*, 2002; Disertori *et al.*, 2003; Farwell and Sulke, 2004) and only 29% of attendances were admitted, smaller than rates of 46-76% in published series (Ammirati *et al.*, 2000; Blanc *et al.*, 2002; Kenny *et al.*, 2002; Disertori *et al.*, 2003; Farwell and Sulke, 2004). This reflects dedicated TLoC specific educational content provided in the ED to embed

key principles of diagnosis and onward referral pathways. Additionally, the presence of an adjacent established syncope service is likely to result in a trickle-down effect regarding TLoC awareness. The availability of a dedicated syncope service has previously been shown to be associated with reduced length of inpatient stay for patients with syncope compared with peer hospitals (Kenny, 2003).

5.1.4 Performance of initial assessment against audit standard

Overall, initial assessment was performed poorly with no aspect having a completion rate >90%. The most obvious targets for service improvement to meet National Institute of Clinical Excellence Clinical Guideline 109 are the areas with completion rates well less than 50%, notably the documentation of driving status, measurement of postural blood pressure, provision of copies of the 12 lead ECG on discharge and improving onward referral.

Possible solutions, proposed to the clinical team in the emergency Department were:

- Mandatory documentation of driving status on registration in the department;
- Mandatory postural blood pressure measurements on all those presenting with a fall or collapse regardless of reported loss of consciousness
- Departmental policy to provide patients with an additional copy of the 12 lead ECG regardless of diagnosis
- Improved awareness of the dedicated onward referral pathways for epilepsy and syncope in the form of visual aids in the department or the initiation of a 'flagging' system on the departmental database at the conclusion of the clinical episode.

5.2 Randomised double blind placebo controlled trial

5.2.1 Trial recruitment and progression

Fifty-two participants out of 323 individuals screened were included in the trial. This gives an inclusion rate of 16%. The only other randomised controlled clinical trial in the

field did not report any screening data and thus it is difficult to draw comparisons regarding recruitment rate (Flammang *et al.*, 2012). Interestingly, this number is similar to the 19% inclusion rate achieved in pilot work by our group involving the adenosine test and assessing its reliability in identifying bradycardia-pacing indications (Parry *et al.*, 2009a). In that trial, all participants were already set to receive a bradycardia pacemaker on clinical grounds and were consenting to an adenosine test only. The slightly lower rate of 16% in this study perhaps reflects the greater commitment required on behalf of the participants – consenting to receive both an adenosine test and either a permanent pacemaker (which would only deliver therapy for a six-month period) or an implantable loop recorder.

It was originally intended that it take 18 months to recruit to time and target. In reality, it took much longer. Recognising the slow recruitment prompted an amendment to the inclusion criteria to approach people referred directly to the Falls and Syncope service via primary care or following an attendance at the Emergency Department with syncope. This proved to be very successful with ultimately 67% of participants recruited via this route versus 12% via the Emergency Department and 21% via the Assessment Suite.

Despite what was felt to be slow recruitment, it should be noted that over the 45-month recruitment period a mean of 1.15 patients were included per month. This compares favourably with a recent large meta-analysis of 151 randomised controlled trials undertaken in the United Kingdom between 2004-2016 that found a median of 0.92 patients recruited per centre per month (Walters *et al.*, 2017).

Lastly, to put recruitment in context, in the other randomised controlled trial of pacing therapy in those with positive adenosine test it took the Flammang group 5 years to recruit 80 patients in 10 centres albeit with more extensive testing to explore a diagnosis (echocardiography, ambulatory monitoring, carotid sinus massage and an optional head-up tilt test) (Flammang *et al.*, 2012). The lack of screening data reported makes it difficult to draw comparisons with the present study regarding recruitment rate. We took a deliberately reductionist view compared to the Flammang approach. The intention was to pragmatically include patients with unexplained syncope on initial

evaluation per the ESC and NICE TLOC guidance rather than exhaustively investigate, though we did not interfere with our patients' clinical course following recruitment to the study.

The most common reason for exclusion was to decline to participate (45%). Although detailed data was not recorded on the reason to decline, as the primary recruiting agent for the trial, I can comment that individuals tended not to be bothered at the thought of an adenosine test, even involving as it does some unpleasant side effects; but were more concerned at the thought a pacemaker implantation procedure that they may not need. The second most common reason (11%) was cognitive impairment. This patient group tends to be older and frailer and accordingly may have a higher likelihood of cardiac causes of syncope. Further study is much needed in this vulnerable cohort.

5.2.2 Baseline clinical characteristics

Both the adenosine positive and negative groups were well-matched at baseline with the only significant difference being a lower lying systolic blood pressure in the adenosine positive group. It is difficult to postulate a reason for this and equally to attribute clinical significance. There was no difference in the standing systolic blood pressure of both groups indicating that orthostatic hypotension was not an issue; nor was there a difference in the prescription rates of anti-hypertensive therapy that might have been an explanation. The cohort were highly symptomatic with a mean of around 5 unexplained syncopal episodes in the last 12 months (4.2 episodes adenosine positive vs. 5.2 episodes adenosine negative, p=0.936) and a range from 1-24 episodes.

One might argue that the non-significant trend towards the adenosine positive group being older and having more evidence of conducting system disease in the form of left axis deviation suggests that this group would be more likely to require a pacemaker for bradycardia. There is perhaps a role for the adenosine test in those presenting with syncope in the presence of conducting system disease insufficient to merit a pacemaker by current international guidance.

The mean age in the trial was ten years younger than that in the Flammang study (65.1 ± 11.4 years in the adenosine positive group vs 75.9 ± 7.7 years)(Flammang *et al.*,

2012). As previously mentioned, there was no adenosine negative group. Older patients have higher rates of syncope (Task Force for the *et al.*, 2009) and a higher incidence of conducting system disease requiring permanent pacemaker implantation (Greenspon *et al.*, 2012). This might explain the high event rate (66% recurrence rate in the atrial pacing and sensing with inhibition arm) in the Flammang paper.

5.2.3 Adenosine testing

All adenosine tests were conducted without complication. There were no significant differences in the side effect profile of both groups suggesting that dosing was equal across the study i.e. there is nothing to suggest the inadvertent administration of a smaller dose to the adenosine negative group accounting for the negative result.

We used adenosine rather than ATP in this trial because adenosine was readily available locally and because of the lack of evidence of superiority of one over the other in this setting (Parry *et al.*, 2006; Fragakis *et al.*, 2015). The guidance from the European Society of Cardiology at the time was that either were appropriate (Task Force for the *et al.*, 2009) and there has been nothing in the literature in the interim to support the use of one over the other. A mean duration of AV block of 17.2 ± 4.4 seconds in the adenosine positive group and 6.2 ± 2.7 seconds in the adenosine negative group suggests adequate action upon the conducting system of the AV node by adenosine and supports its use along with ATP in the clinical setting.

All patients with a positive test had more than 10 seconds of atrioventricular block but only in 17 cases (49%) was there more than 6 seconds of ventricular asystole in addition to the 10 seconds of atrioventricular block. In no cases did more than 6 seconds of ventricular asystole occur in isolation. Thus, in this data set, the role of 6 seconds of ventricular asystole proposed as a positive criterion by Brignole (Brignole *et al.*, 1997) and accepted by the European Society of Cardiology (Task Force for the *et al.*, 2009) is called into question.

At the outset of this trial, the most recent iteration of the European Society of Cardiology guidelines on syncope dated from 2009 (Task Force for the *et al.*, 2009). These guidelines made a level IIB recommendation on the use of the adenosine test in

unexplained syncope (evidence or general agreement suggesting the test was not useful/effective in select patients for cardiac pacing owing to a lack of correlation with spontaneous syncope based on large non-randomised studies). A new and updated version of the guidance was published in 2018 (Brignole *et al.*, 2018). This removes any recommendation for adenosine testing despite acknowledging the randomised controlled trial suggesting benefit, again citing the lack of correlation between atrioventricular block on adenosine testing and ECG findings documented by ILR during spontaneous syncope (Brignole *et al.*, 2006a; Deharo *et al.*, 2006; Flammang *et al.*, 2012). The published results of this study ought to re-ignite interest in the adenosine test.

Syncope secondary to idiopathic AV block has been a recent focus of research interest (Brignole *et al.*, 2011; Deharo *et al.*, 2013; Brignole *et al.*, 2017). A new categorisation of syncope secondary to paroxysmal AV block has been proposed (Aste and Brignole, 2017):

I. *Intrinsic paroxysmal AV block* secondary to intrinsic disease of the AV conduction system amenable to pacing therapy
II. *Extrinsic vagal paroxysmal AV block* secondary to the effect of the parasympathetic nervous system on the cardiac conduction system as seen with reflex syncope
III. *Extrinsic idiopathic paroxysmal AV block* associated with low levels of endogenous adenosine, a frequently positive adenosine test and amenable to pacing therapy

None of the participants in this study had known paroxysmal AV block. They had unexplained syncope and were selected early in the syncope journey (prior to exhaustive investigation) on the premise that adenosine testing would identify those that would benefit from a permanent pacemaker to treat underlying paroxysmal sinus node or AV conducting system disease. It is possible that the adenosine test selected those falling into the extrinsic idiopathic paroxysmal AV block category but there is overlap between the three areas in clinical practice and given the absence of prior demonstrable AV block this is not possible to prove. Whether it matters or not is

perhaps moot as in this study there was definite benefit from pacing in those with a positive adenosine test without the need for exhaustive investigation to fit them into one of the categories. These categories have yet to gain widespread acceptance in the literature and time will tell whether they become established.

5.2.4 Treatment withdrawals

The size of the treatment effect in the prior randomised controlled trial in this area (Flammang *et al.*, 2012) meant that our revised power calculation for this study required complete data on two sets of 28 individuals. In reality, the crossover design of the trial meant that this was a single set of 28 individuals. Assuming a 20% loss to follow-up, this meant a recruitment target of 34 individuals with a positive adenosine test. We successfully recruited 35 with complete syncope diary data on 30. The trial is thus adequately powered to answer the question asked.

In this study, there were eight withdrawals in the adenosine positive arm. The withdrawal of two individuals following the development of a definite pacing indication (carotid sinus syndrome) and two individuals in whom there was documented bradycardia after episodes of syncope (and thus the pacemaker was switched on at physician discretion) may well have had an impact on the cumulative syncope burden (primary outcome of the trial). It was possible to conduct an analysis with the inclusion of the two individuals in whom the pacemaker was switched on (syncope diary data was available) with the primary outcome of cumulative syncope burden remaining reduced in pacemaker on arm; but not possible to include those who developed carotid sinus syndrome as data was not available. The premise of this study was that the adenosine test would unmask those with unexplained syncope likely to benefit from a permanent pacemaker. As such, the subsequent requirement for a pacemaker in four individuals in the adenosine positive arm supports the idea that a positive adenosine test unmasks bradycardia pacing indications as previously suggested (Parry *et al.*, 2009a).

Lastly, there was one withdrawal in the adenosine negative loop recorder arm. The individual developed an oesophageal malignancy late in the study period and withdrew.

There had been no syncopal episodes up to this point. As such, this withdrawal had little impact on the significance of a negative adenosine test.

5.2.5 Cumulative syncope burden

The primary outcome of the trial was positive with a mean of 0.4 fewer syncopal episodes per patient recorded during the six-month period with the pacemaker turned on compared to the six-month period with pacemaker turned off (1.2 vs. 1.6 episodes) and a higher relative risk of syncope with the pacemaker turned off compared with the pacemaker turned on (RR 2.1, 95% CI 1.0 to 4.48, p=0.048). The relative risk of syncope with the pacemaker off increased further if the three partial withdrawals were excluded (RR 4.9 95% CI 1.7 to 13.8, p=0.003). As such, permanent pacemaker implantation following a positive adenosine test in those with unexplained syncope should be considered.

However, the event rate in the trial was low with the majority of patients having no syncopal episodes at all in either period (23/27, 85%). This was despite the trial cohort being highly symptomatic with a mean of around 5 unexplained syncopal episodes in the last 12 months (4.2 episodes adenosine positive vs. 5.2 episodes adenosine negative, p=0.936) and a range from 1-24 episodes. Increasing the duration of observation in each arm (a further six months) may well have resulted in a higher event rate but was not part of the trial protocol and was not possible in the middle of the trial.

As outlined extensively in the introduction of this thesis, there remains keen debate in the literature as to the diagnosis evinced by a positive adenosine test. This uncertainty points to why it has not gained widespread clinical acceptance and lacks support in international clinical guidance. This trial suggests a modest benefit from permanent pacemaker implantation but does not answer as to what the pacemaker is treating – conducting system disease or cardio-inhibitory vasovagal syncope? A higher event rate and a more impressive reduction in the cumulative syncope burden may have rendered this question moot – would there be the need to be exactly certain providing the test clearly pointed to the pacemaker having irrevocable benefit? As it is, there remains a degree of doubt.

5.2.6 Time to first syncope and number of patients with recurrent syncope

The time to first syncope in the adenosine positive arm was shorter than the adenosine negative arm (mean 56 days vs. 92 days and median 24 days vs. 110 days). This is likely to reflect untreated underlying bradycardia during the pacemaker off period of the adenosine positive arm. The percentage of patients with recurrent syncope in the adenosine negative arm was higher (53% vs. 30%) again probably reflecting the intervention of the active DDD pacemaker in the adenosine positive group.

5.2.7 Quality of life

Using the well-validated (Rose *et al.*, 2009) syncope specific Impact of Syncope on the Quality of Life questionnaire, quality of life in both the adenosine positive and negative arms improved throughout the duration of the study. An improvement in quality of life simply by being involved in clinical research is well recognised (Verheggen *et al.*, 1998). However, there were no statistically significant differences seen amongst the pacemaker on, pacemaker off and implantable loop recorder groups. Similarly, there was no statistical difference seen between baseline scores compared to scores after pacemaker on or off periods for the WHOQOL- BREF or OLD questionnaires.

At the end of the trial, the social domain of the WHOQOL-BREF questionnaire was significantly lower in the adenosine negative versus the adenosine positive arm. The social domain concerns personal relationships, practical social support and sexual relationships. This suggests a better network of support and improved inter-personal relationships in this group. This is mirrored in the similarly focused WHOQOL-OLD questionnaire intimacy domain where patients in the adenosine negative arm had a significantly lower score that both the pacemaker on and off periods of the adenosine positive arm.

In the past, present and future domain of the WHOQOL-OLD questionnaire that focuses on the physical impact of ill-health, the adenosine negative group had a lower score than both the adenosine positive pacemaker on and off groups at the end of the trial.

Lastly, it is worth noting that there were reduced events in the placebo pacing group fitting with other data in the field presented by Prof Robert Sheldon and colleagues and highlighting the complexity of studying syncope in clinical trials (Ng *et al.*, 2019).

Overall, the quality of life data suggests an improved quality of life from being in the trial but no significant impact upon the quality of life from pacing therapy in the adenosine positive group. Given the low event rate it is perhaps not surprising that pacing therapy did not improve quality of life. It is more difficult to explain the improved social, intimacy and past present and future domains of the WHOQOL-BREF and WHOQOL-OLD questionnaires; perhaps the establishment of a diagnosis in 4/16 (25%) of this group was involved but, in the absence of comparative quality of life data on an individual basis, this is speculative.

5.2.8 Results of those with negative adenosine test and implantable loop recorder

This is the first study in the syncope literature to include data on those with a negative as well as a positive adenosine test. Only one patient in the adenosine negative arm developed a bradycardia pacing indication identified on an implantable loop recorder (sinus node disease). It is not possible to calculate the sensitivity and specificity of the adenosine test due to the nature of the intervention in the adenosine positive arm - pacemakers do not store data on bradycardic episodes but either treat them or ignore them depending on the programming; and, thus, true or false positive events cannot be classified. However, the negative predictive value of the adenosine test for identifying a bradycardia pacing indication was 94% (95% CI 0.69 – 1.00) suggesting that there is no role for a pacemaker in those with a negative test. However, the upper limit of the 95% confidence interval just reached 1.00 meaning this is suggested rather than definitive.

Two patients went on to receive a clinical diagnosis of vasovagal syncope as part of routine clinical care. No rhythm disturbance was demonstrable by loop recorder and they did not have any further episodes of syncope.

There was one other confirmed clinical diagnosis as a cause of syncope – epilepsy – made following a witnessed syncopal episode associated with typical seizure artefact on

the loop recorder and no disturbance to the underlying cardiac rhythm. The use of a loop recorder in supporting a diagnosis of generalised tonic-clonic epilepsy is well established (Ho *et al.*, 2006).

In summary, a study design including loop recorder implantation in those with a negative adenosine test and unexplained syncope lends weight to the notion that a positive adenosine test unmasks the need for permanent pacing treatment, given the dearth of cardiac rhythm disturbance in this group.

5.2.9 Study Limitations

This study has a number of limitations. It is a single centre study undertaken in the environment of an established internationally renowned syncope service. Single centre studies are recognised to show larger intervention effects than multicentre trials (Bafeta *et al.*, 2012) and there is evidence to show improved outcomes with a dedicated syncope service (Kenny *et al.*, 2002). That said there is benefit from pacing therapy in those with positive adenosine test in a multicentre setting (Flammang *et al.*, 2012) and widespread experience of adenosine testing suggesting these results are generalizable.

There was a low rate of unexplained syncope in the presenting population according to the audit of presentations to the Emergency Department with transient loss of consciousness (3%). This would suggest a small role for adenosine testing. However, the much higher published rates of unexplained syncope actually suggest a potentially much larger part to play.

The partial withdrawals in this study in combination with the crossover nature of its design made analysis difficult. Ideally, there would have been two parallel groups but given the issues with recruitment subsequently encountered, it is doubtful whether the study would have completed to time and target had this been the case.

It would have been additionally beneficial to be able to have calculated a sensitivity and specificity of a positive adenosine test but the nature of the pacing intervention made this impossible.

6 Conclusion

The ADEnosine testing to determine the need for Pacing Therapy with the additional use of an Implantable Loop Recorder (ADEPT-ILR) study shows that permanent pacing reduces the syncope burden in patients with unexplained syncope and a positive adenosine test.

It is also the first study ever to document the natural history of those with unexplained syncope and a negative adenosine test. The high negative predictive value of the adenosine test for a bradycardia pacing indication suggests the adenosine test does unmask the need for pacemaker implantation in the unexplained syncope population without the need for exhaustive investigation.

As such, a clinical strategy of an adenosine test early in the unexplained syncope journey followed by permanent pacing in those with positive test and loop recorder implantation in those with a negative test merits consideration.

Lastly, all patients with a positive test had more than 10 seconds of atrioventricular block. In half of the positive tests there was more than 6 seconds of ventricular asystole in addition to the 10 seconds of atrioventricular block. In no cases did more than 6 seconds of ventricular asystole occur in isolation. This suggests that the positive criterion of more than 6 seconds of ventricular asystole currently adopted by the European Society of Cardiology ought to be reviewed.

7 Appendices

7.1 Appendix A Patient Information Sheet

Adenosine Testing to Determine the need for a Pacing Therapy in Unexplained Blackouts (ADEPT-ILR study)

Patient Information Sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask the team if there is anything that is not clear or if you would like more information. You will have at least 24hrs to decide whether or not you wish to take part.

Thank you for reading this information sheet.

What is the purpose of the study?
Diagnosing the causes of blackouts can take many months, using tests that can be lengthy and uncomfortable. A new test, lasting a few minutes, using a drug called adenosine has been used in a number of hospitals across the world to help uncover the cause of blackouts. Unfortunately, there is no consensus view on what condition the test is diagnosing and because of this there is uncertainty on the best way to treat both those who have a positive test and a negative test. In this year-long study we hope to find out whether or not the adenosine test can identify those with blackouts who could be treated with the implantation of a pacemaker.

Why have I been chosen?
You have been chosen because you have had a blackout. After a physical examination, blood pressure measurements lying down and standing up and an electrocardiogram (ECG; recording of the heart rate and rhythm) it is not clear what caused your blackout. We hope the adenosine test will help diagnose the cause of your blackout without further extensive investigation. We hope that a total of 180 patients like you will participate in the study, 90 who will receive a pacemaker and a further 90 who will receive an implantable loop recorder (a device implanted under the skin that records heart rate and ECG for up to 3 years).

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What is the adenosine test?
Adenosine is a natural chemical messenger in the body, and the drug form of adenosine has been used for more than twenty years in the treatment of very fast heart rhythms and during electrical tests of heart function. It will be given directly into a vein at a dose of 20mg.

What are the side effects of this test?

Adenosine injection can cause side effects, but these last only from a few seconds to one minute at most (the drug is made inactive by your body in less than 10 seconds). These effects can include flushing, light-headedness, a sensation of difficulty in breathing, nausea and chest pressure. Less commonly people can have sweating, nervousness, blurred vision, a metallic taste or a burning sensation and a fast heart rate for a few minutes. On very rare occasions people may blackout for a very short time during the test. These side effects are only found at the time of injection.

What will happen to me if I take part?

Firstly, you will be asked to come to the Royal Victoria Infirmary for one visit lasting around one hour. Travel expenses will be paid. The drug adenosine will then be injected into a cannula (small plastic tube) placed in a vein in your arm whilst you are on a heart monitor.

Following the administration of adenosine, the doctor will be looking at the heart monitor to assess the effect of the adenosine on your heart rhythm. A positive test is defined as a temporary block of the electrical connection between the top and bottom chambers of the heart for more than 10 seconds or the temporary halting of the heart's own pacemaker activity for greater than 6 seconds. The test is negative should neither of these two things happen.

If the test is positive you will be asked to consent to the implantation of a permanent pacemaker. This is a device which sits under the skin below the left collar-bone in the hollow of the shoulder and connects to the heart through two leads which travel in the vein that leads back to the heart from the arm. The pacemaker is designed to detect slow heart rates/rhythms and treat them by stimulating the heart to beat. The implantation of the pacemaker requires an operation under local anaesthetic lasting around one hour, which will be done at Freeman Hospital.

This pacemaker will then be turned "on" (capable of treating slow heart rates) or turned "off" (capable only of monitoring slow heart rates). Neither you nor the researcher will know whether or not your pacemaker is turned "on" or "off". After six months, those who have had the pacemaker turned "off" will have it turned "on" and vice versa. Again, neither you nor the researcher will know in which mode the pacemaker is working. The reason that neither you nor the researcher will be aware of whether the pacemaker is "on" or "off" is to ensure that nobody can accidentally influence whether pacing affects you having further blackouts. If during the course of the study we find that you need a pacemaker regardless of the study, the pacemaker will be switched on to ensure you get the appropriate treatment you need.

You will be asked to report any blackouts that happen over the course of the year by completing a diary that will be sent to you by post every week (a pre-paid envelope will accompany the diary so you can return it by post without any cost to yourself). Should a blackout happen we will arrange for you to come to the Freeman Hospital so that we can check the heart rate/rhythm recorded by the pacemaker.

Should the adenosine test be negative you will asked to consent to the implantation of a loop recorder. This is a small device that sits under the skin below the left collar-bone like a pacemaker but does not have the leads that travel to the heart. It continuously monitors the heart rate/rhythm but cannot treat any slow heart rates. It is implanted under local anaesthetic and takes around twenty minutes. Like the pacemaker group, you will be asked to report any blackouts that happen over the course of the year by completing and returning a diary by pre-paid post. Should a blackout happen we are able to interrogate the recorder without you having to visit the hospital using technology called Remote Monitoring installed in your home (this would be discussed with you at the time of the implantation of the loop recorder) or by you coming to the hospital.

What do I have to do?

If you are taking drugs called beta-blockers, digoxin, verapamil or diltiazem you will be asked to stop these for 5 days before the Royal Victoria Infirmary visit. You will only be asked to do this if it is safe for you to do so, that is if you take these drugs for high blood pressure and not chest pain. There are no other restrictions whatsoever.

Depending on the result of the adenosine test, we will arrange for you to come to the Freeman Hospital to have either a pacemaker or loop recorder implanted. If you have a pacemaker put in we will arrange a follow-up visit to the pacemaker department at six weeks and then six months (to have the pacemaker switched “on” or “off” depending on what the setting was previously). Any other follow-up will be dictated by any blackouts you might have (as indicated previously). At the end of the study period (one year) we will arrange for you to attend the pacemaker clinic where regardless of the current setting all pacemakers will be turned “on”.

Should you suffer a blackout we will check to see whether this was due to a slow heart rate/rhythm. Should this be the case and you are in the group with the pacemaker turned “off” at the time we will turn the pacemaker “on” to ensure you have appropriate treatment.

If you have loop recorder put in, the device will be looked at by Remote Monitoring or by you coming to the hospital at four weeks, three months, then every three months until the end of the study at one year. If you suffer a blackout and your loop recorder ECG shows the need for a pacemaker or any other treatment we will ensure that this happens as would happen in routine clinical care.

What are the risks associated with the implantation of a pacemaker or loop recorder?
The implantation of a permanent pacemaker is a well-tolerated and generally safe procedure but there are risks attached. The most serious potential risk is a puncture of the lung (pneumothorax) that occurs in 2% of cases but is readily treatable. The other most common risk (2% of cases) is displacement of one of the leads within the heart requiring another procedure to reposition it. Other important risks are those of infection and haematoma (collection of blood) formation around the pacemaker requiring a further procedure that occurs in 1% of cases. A general anaesthetic is not required for the procedure. The implantation of a loop recorder is more straightforward than a pacemaker and is very safe with less than 1% chance of bleeding/infection. There is no risk of a pneumothorax or lead displacement.

Once the pacemaker or loop recorder is implanted, it is important to keep the wound area dry for the first few days. We ask you to try to avoid using the left arm for strenuous activity for a period of six weeks. Electrical equipment used at home such as hairdryers, electric shavers and microwaves are safe to use with a pacemaker. If you drive, you need to inform the DVLA that you have had a pacemaker fitted and you are unable to drive for one week following the procedure (if you have a normal licence). Mobile phones are safe to use with a pacemaker but they should be kept more than 15cm (6 inches) away from the pacemaker and used with the ear on the opposite side. Airport security systems rarely cause problems with pacemakers but you need to tell the security staff that you have a pacemaker fitted and they should either search you by hand or with a hand-held metal detector. In some countries you might still need to go through the security system and should this happen it is important to move through the gate quickly. This is also true for security systems used in shops. Magnetic devices or fields can interfere with your pacemaker (including MRI scans). Should there be any concern regarding this then you should discuss it with the pacing department (should you need an MRI scan then the doctor requesting this test should discuss it with the pacemaker department and with the research team).

What are the possible benefits of taking part?
We think that the adenosine test will allow the early identification of those with blackouts who would benefit from the implantation of a pacemaker and save them the need for lengthy and often uncomfortable further investigation as would currently be the case. Avoidance of such investigation is obviously a benefit to you and should our thinking be correct then this study may help future patients with blackouts in a similar way. Similarly, implantable loop recorders are sometimes recommended to help investigate patients with blackouts after a long series of investigations. If you are in the implantable loop recorder part of the study, you will have this device in place early to monitor your heart rate/rhythm during symptoms.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research

doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

What if something goes wrong?
If you are harmed by taking part in this research project there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it, unless this is to communicate with your GP or other healthcare professionals, and then only with your consent.

Will my GP and/or other healthcare professionals involved in my care be informed of my participation in the study?
Your GP and/or hospital consultants will be informed by letter of your participation, with your consent.

What will happen to the results of the research study?
The results of the study will be published in medical journals and presented at national and international medical conferences. Dissemination of the results to other patients, relatives and healthcare professionals will be facilitated through STARS (Syncope Trust and Reflex Anoxic Seizures patient support group), though you would never be personally identified in any way.

Who is funding the research?
The research is being funded by the British Heart Foundation and by Medtronic Inc, a pacemaker company who is supplying some of the devices.

Who has reviewed the study?
The study has been reviewed by the Newcastle & North Tyneside 2 Local Research Ethics Committee and by the British Heart Foundation Clinical Research Training Fellowships Committee.

What happens if I lose the ability to consent to continue in the study when I am already involved in the research?
If this happens, the data gathered prior to your losing the ability to consent will be retained and used per your original consent, but from that point onwards, you will be withdrawn from the study. Your usual clinical care will not be affected in any way.

What will happen at the end of the study?
If you received a pacemaker, it will stay in place, though if the study proves negative (that is pacemakers did not help prevent blackouts in adenosine test positive patients),
you will be given the option to have the pacemaker taken out, again under local anaesthetic. If you received an implantable loop recorder, it will stay in place for up to three years, or until a diagnosis is made for your blackouts. It will then be taken out under local anaesthetic.

Contact details for further information

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Thank you for considering participating in this study.

7.2 Appendix B Patient Consent Form

Adenosine Testing to DEtermine the need for a Pacing Therapy in Unexplained Blackouts (ADEPT-ILR study)

Patient Informed Consent

	Initial box
1. I understand that my participation is voluntary	☐
2. I understand that I am free to refuse to participate in the proposed study at any time, without giving a reason, without medical care or legal rights being affected	☐
3. I understand that I am free to withdraw from the proposed study at any time, without giving a reason, without medical care or legal rights being affected	☐
4. I understand that anonomysed data collected during the study prior to the withdrawal will be used in the analysis and communicated in publications	☐
5. I confirm that I have read and understand the information presented for the study and have had the opportunity to ask questions	☐
6. I agree to participate in the proposed study and comply with the procedures related to it.	☐
7. I give my permission to have my general practitioner informed of my involvement in the study	☐

8. I give my permission to have sections of my medical notes inspected by those undertaking the study and appropriate regulatory authorities ☐

Name of Patient	Signature	Date
Name of Investigator taking consent	Signature	Date

Contact for further information

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7.3 Appendix C Impact of Syncope on Quality of Life questionnaire

The Impact of Syncope on Quality of Life Questionnaire

INSTRUCTIONS (Please read carefully): The purpose of this survey is to identify difficulties that you may be experiencing because of your fainting. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

As a result of your fainting, how often during the last month have you been:

	All of the time	*Most of the time*	*A good part of the time*	*Some of the time*	*A little of the time*	*None of the time*
Tired and worn out?						
Frustrated?						
Worried about your fainting?						
Frightened that you will faint?						

How often in the last month has your fainting

	All of the time	*Most of the time*	*A good part of the time*	*Some of the time*	*A little of the time*	*None of the time*
Interfered with performing vigorous physical activity?						

Think back over the last month and indicate how much you agree with the following statements:

	Strongly Agree	*Agree somewhat*	*Neither agree nor disagree*	*Disagree*	*Strongly disagree*
No one understands the effect that fainting has on my life					
Because of my fainting, I accomplish less that I would like.					
My fainting leaves me feeling confused					

As a result of your fainting, how often during the last month have you:

	All of the time	*Most of the time*	*A good part of the time*	*Some of the time*	*A little of the time*	*None of the time*
Avoided driving a vehicle?						
Avoided standing for long periods of time in case you faint?						
Avoided being in warm or hot environments in case you faint?						
Been limited in the kind of work you can do?						

7.4 Appendix D WHO QUALITY OF LIFE BREF questionnaire

THE WORLD HEALTH ORGANIZATION

QUALITY OF LIFE (WHOQOL) -BREF

The World Health Organization Quality of Life (WHOQOL)-BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5

6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always

26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

7.5 Appendix E WHO QUALITY OF LIFE OLD questionnaire

WHOQOL OLD QUESTIONNAIRE

Instructions

This questionnaire asks for your thoughts and feelings about certain aspects of your quality of life and addresses issues that may be important to you as an older member of
society.

Please answer all the questions. If you are unsure about which response to give to a question, please choose the one that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life in the last two weeks.

For example, thinking about the last two weeks, a question might ask:

How much do you worry about what the future might hold?

Not at all 1	A little 2	A moderate amount 3	Very much 4	An extreme amount 5

You should circle the number that best fits how much you have worried about the future over the last two weeks. So you would circle the number 4 if you worried about your

future "Very much", or circle number 1 if you have worried "Not at all" about your future. Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

Thank you for your help

The following questions ask about how much you have experienced certain things in the last two weeks, for example, freedom of choice and feelings of control in your life. If you have experienced these things an extreme amount circle the number next to "An extreme amount". If you have not experienced these things at all, circle the number next to "Not at all". You should circle one of the numbers in between if you wish to indicate your answer lies somewhere between "Not at all" and "Extremely". Questions refer to the last two weeks.

1. (F25.1) To what extent do impairments to your senses (e.g. hearing, vision, taste, smell, touch) affect your daily life?

Not at all 1	A little 2	A moderate amount 3	Very much 4	An extreme amount 5

2. (F25.3) To what extent does loss of for example, hearing, vision, taste,

smell or touch affect your ability to participate in activities?

Not at all 1	A little 2	A moderate amount 3	Very much 4	An extreme amount 5

3. (F26.1) How much freedom do you have to make your own decisions?

Not at all 1	A little 2	A moderate amount 3	Very much 4	An extreme amount 5

4. (F26.2) To what extent do you feel in control of your future?

Not at all 1	Slightly 2	Moderately 3	Very 4	Extremely 5

5. (F26.4) How much do you feel that the people around you are respectful

of your freedom?

Not at all	Slightly	Moderately	Very	Extremely
1	2	3	4	5

6. (F29.2) How concerned are you about the way in which you will die?

Not at all	A little	A moderate amount	Very much	An extreme amount
1	2	3	4	5

7. (F29.3) How much are you afraid of not being able to control your death?

Not at all	Slightly	Moderately	Very	Extremely
1	2	3	4	5

8. (F29.4) How scared are you of dying?

Not at all	Slightly	Moderately	Very	Extremely
1	2	3	4	5

9. (F29.5) How much do you fear being in pain before you die?

Not at all	A little	A moderate amount	Very much	An extreme amount
1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last two weeks, for example getting out as much as you would like to. If you have been able to do these things completely, circle the number next to "Completely". If you have not been able to do these things at all, circle the number next to "Not at all". You should circle one of the numbers in between if you wish to indicate your answer lies somewhere between "Not at all" and "Completely". Questions refer to the last two weeks.

10. (F25.4) To what extent do problems with your sensory functioning (e.g. hearing, vision, taste, smell, touch) affect your ability to interact with others?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

11. (F26.3) To what extent are you able to do the things you'd like to do?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

12. (F27.3) To what extent are you satisfied with your opportunities to continue achieving in life?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

13. (F27.4) How much do you feel that you have received the recognition you deserve in life?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

14. (F28.4) To what extent do you feel that you have enough to do each day?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

The following questions ask you to say how satisfied, happy or good you have felt about various aspects of your life over the last two weeks . For example, about your participation in community life or your achievements in life. Decide

how satisfied or dissatisfied you are with each aspect of your life and circle the number that best fits how you feel about this.

Questions refer to the last two weeks

15. (F27.5) How satisfied are you with what you have achieved in life?

Very dissatisfied 1	Dissatisfied 2	Neither satisfied nor dissatisfied 3	Satisfied 4	Very satisfied 5

16. (F28.1) How satisfied are you with the way you use your time?

Very dissatisfied 1	Dissatisfied 2	Neither satisfied nor dissatisfied 3	Satisfied 4	Very satisfied 5

17. (F28.2) How satisfied are you with your level of activity?

Very dissatisfied 1	Dissatisfied 2	Neither satisfied nor dissatisfied 3	Satisfied 4	Very satisfied 5

18. (F28.7) How satisfied are you with your opportunity to participate in community activities?

Very dissatisfied 1	Dissatisfied 2	Neither satisfied nor dissatisfied 3	Satisfied 4	Very satisfied 5

19. (F27.1) How happy are you with the things you are able to look forward to?

Very unhappy	Unhappy	Neither happy nor unhappy	Happy	Very happy
1	2	3	4	5

20. (F25.2) How would you rate your sensory functioning (e.g. hearing, vision, taste, smell, touch)?

Very poor	Poor	Neither poor nor good	Good	Very good
1	2	3	4	5

The following questions refer to any intimate relationships that you may have. Please consider these questions with reference to a close partner or other close person with whom you can share intimacy more than with any other person in your life

21. (F30.2) To what extent do you feel a sense of companionship in your life?

Not at all	A little	A moderate amount	Very much	An extreme amount
1	2	3	4	5

22. (F30.3) To what extent do you experience love in your life?

Not at all	A little	A moderate amount	Very much	An extreme amount
1	2	3	4	5

23. (F30.4) To what extent do you have opportunities to love?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

24. (F30.7) To what extent do you have opportunities to be loved?

Not at all	A little	Moderately	Mostly	Completely
1	2	3	4	5

Do you have any comments about the questionnaire?

THANK YOU FOR YOUR HELP

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