Appendix D6: Prognosis of different causes of syncope and effectiveness of treatments

1 Introduction

This appendix is a narrative review of the literature on the prognosis of different causes of syncope, and the effectiveness of treatments.

Syncope is defined as a transient, self-limiting loss of consciousness. Syncope can be subdivided into two main causes: cardiac syncope - caused by problems with the heart itself (including structural heart disease and arrhythmias) – and vascular syncope - caused by problems with the circulation including low blood pressure. The latter category can be subdivided into neurally mediated syncope, including vasovagal syncope and orthostatic hypotension. Another important type of syncope is carotid sinus syncope. In some patients, there are multiple potential causes of syncope which may act together (Chen 2003).

Syncope is important because it may be related to a life-threatening event (e.g. complete heart block or sustained ventricular tachycardia), although at the other end of the scale are patients with benign episodes such as simple,uncomplicated faints (Burn 1995). In addition, major morbidity such as fractures and motor vehicle accidents has been reported in 6% of patients with syncope, and minor injuries such as laceration and bruises in 29% (Brignole 2006b). Recurrent syncope is associated with fractures and soft-tissue injury in 12% of patients (Brignole 2006b).

The primary purpose of the evaluation of people with syncope is to determine whether the person is at increased risk of death (Sorajja 2006). This is particularly important in a person with underlying heart disease in whom syncope can be the precursor to sudden death (Sorajja 2006).

The prognosis of people who have had syncope depends on the underlying cause, and on their age, gender and comorbidities of the patient.

2 Prognosis – general TLoC

2.1 TLoC generally

In a prospective study, 170 patients (mean age 41 years; gender not specified) with TLoC presenting to an emergency department were followed for a mean of 6 months (Martin 1984). The presumed aetiology of the episode was vasovagal syncope in 37%, first seizure in 9%, orthostatic hypotension in 8%, cardiac syncope in 4%, micturition syncope in 2%, hypoglycaemia in 2%, psychogenic non-epileptic seizures in 1% and unknown in the remainder. Two of the seven patients (29%) with cardiac syncope died; 1/13 (8%) patients with orthostatic hypotension died and 1/64 (2%) patients with unknown aetiology died. Recurrence occurred in 4/63 (6%) of the remaining patients with unknown aetiology; 1/15 (7%) with seizures and 1/12 (8%) of the remaining patients with orthostatic hypotension..

2.2 Syncope generally - prognosis

2.2.1 Recurrence and death

In a prospective study of 650 patients who presented to the emergency department with syncope, followed up for 18 months, 15% had at least one episode of recurrence during follow-up, and 9% of patients died (Sarasin 2001).

Data from the Framingham study, in which 822 participants reported syncope (mean age 66 years; 59% female), suggest that patients with any cause of syncope have a high rate of recurrence (multivariable-adjusted hazard ratio 23.2, 95% CI 14.2 to 37.9 compared with the rate of new onset syncope in

patients without a prior history of syncope of 72 per 1,000 patient years) (Soteriades 2002). Over a mean follow up of 8.6 years, these patients had a risk of death that was increased by 31% compared with patients without syncope (Soteriades 2002).

In a prospective study of 499 nursing home residents (mean age 80 years; 71% female), prior syncope was a risk factor for recurrent syncope (risk ratio 11.006; 95% CI 5.775 to 20.975) (Aronow 1997).

In a retrospective study of 1,056 patients aged 65 years or older (mean age around 78 years; 55% female) hospitalised for syncope, the 4-year mortality was around 46% (higher than the 28% expected for this age and gender) (Getchell 2000).

In a retrospective study of 376 patients admitted for syncope to a tertiary referral centre in Israel, mortality data were obtained 30 days and a year after discharge (Shiyovich 2008). The short-term mortality was 1.9% and at 1 year was 8.8%. Discharge diagnoses were vasovagal 26.6% of patients; cardiac syncope 17.3%; neurological 4.3%, metabolic 0.5%; unexplained 47.3% and other 4%. Long-term mortality was higher in patients discharged with a cardiac aetiology than with a non-cardiac aetiology (15.4% versus 7.4%, p=0.04). Long-term mortality rates for cardiac syncope (15.4%), neurological (12.5%) and unknown aetiologies (10.1%) were higher than for the age-adjusted general population of Israel (2.2%); the rate for vasovagal aetiology was not significantly higher (2.5%).

Chapters 3 and 4 discuss the risk factors for death or serious events in people with syncope. Additional information is given below:

In a prospective study involving 176 patients (mean age 54 years, 51% female) presenting to an ED with syncope and followed for a mean of 12 months, 10 patients died during follow up, of whom 9 were over 70 years of age (Eagle 1985). The one-year mortality rate was 16% in those aged 70 years or older compared with 1% in those under 70 years ($p<0.0001$).

502 patients with a first episode of syncope at age 35 or older (evaluated as outpatients or inpatients, presenting to the ED, or experiencing syncope while hospitalised for other reasons) were identified retrospectively and their prognosis examined over a mean follow up of 3.8 years in three age bands: 'middle-aged' (36–60 years, mean 51 years); 'older' (61–75 years, mean 70 years); and 'elderly' (older than 75 years, mean 80 years) (Roussanov 2007). The overall recurrence rate was 26%: it was 29% in the middle-aged patients, 19% in the older patients and 31% in the elderly patients. Overall, there was a mortality rate of 83.4 deaths per 1,000 patient-years, with an all-cause mortality rate of 11.6% at 1 year and 19.3% at 2 years. This was higher than the expected rate (adjusted for age and gender) which is 2.4% at 1 year and 5.0% at 2 years, but not significantly higher than the rate that would be expected after adjusting for age, gender and comorbidities.

In a database study of 1,516 elderly patients diagnosed with syncope, death from all causes was 1% during hospitalisation, 13% one year later and 41% four years later (AHRQ 2000). Individuals aged under 55 years had 91% four-year survival compared with 31% in those aged 85 years or older. People with no other illnesses had better survival than those with several co-existing illnesses (81% versus 23% at four years).

In a study of syncope in older people (aged 60 to 90 years) compared with younger people (aged 15 to 59 years), older people with cardiac syncope had 2-year mortality rate of 38.1% compared with 32.5% in younger people; in patients with non-cardiac syncope, older people had a much higher mortality rate (21.6%) than younger people (4.7%), possibly due to comorbidities (Hauer 2003, Kapoor 1986). In addition, older people with an unknown cause had a mortality rate of 20.4% versus 2.4% in younger people (Hood 2007, Kapoor 1986).

In patients with syncope presenting to the ED, predictors of serious arrhythmia or mortality after 1 year include age over 45 years (odds ratio 3.2, 95% CI 1.3 to 8.1), a history of congestive heart failure (odds ratio 3.1, 95% CI 1.3 to 7.4) or ventricular arrhythmia (odds ratio 4.8, 95% CI 1.7 to 13.9) and an abnormal ECG (odds ratio 3.2, 95% CI 1.6 to 6.4) (Ebell 2006, Martin 1997). The risk of

arrhythmia or death at 1 year was 7.3% in the derivation cohort and 4.4 in the validation cohort for patients with no risk factors, compared with 80.4% and 57.6% for patients with 3 or 4 risk factors (Martin 1997). The risk of death at 1 year was 1.8% and 1.1% for patients with no risk factors compared with 37.0% and 27.3% for patients with 3 or 4 risk factors.

In patients with syncope presenting to the ED, the “San Francisco Syncope Rule” was developed and validated to identify patients at risk of serious outcomes (myocardial infarction, significant haemorrhage, pulmonary embolism, arrhythmia, stroke or death) within the next 30 days (Ebell 2006, Quinn 2006). Patients with any one risk factor had a 15.2% risk of serious outcome compared with 0.3% risk for patients with no risk factors.

In a retrospective study of 198 patients who presented to the emergency department with syncope (mean age 44 years; 56% female), followed up for a mean of 11 months, 7.5% had suffered either major morbidity or death related to the cause of the index episode of loss of consciousness (Day 1992). Patients with cardiac causes represented a high risk group for a poor outcome (33%), whereas people who were under age 30 years, or who were under age 70 years and had loss of consciousness due to vasovagal, psychogenic or unknown cause, constituted a low risk group (1%) (Day 1982).

In a prospective study of 146 patients admitted for syncope to an acute care hospital in Chile (mean age 68 years; 58% male), 2% of patients died in hospital and surviving patients were followed up for a mean of 24 months (Dougnac 1991). Recurrence of syncope occurred in around 17% of patients (12% with cardiovascular syncope; 10% with a non-cardiovascular cause and 25% with syncope of unknown origin). Mortality at 24 months was around 18% and was higher among patients aged over 65 years (24% versus 2.3%, $p=0.003$) and for those with cardiovascular syncope than non-cardiovascular cause or syncope of unknown origin (28% versus 20% and 4.2%, respectively; $p<0.008$ for cardiovascular versus unknown; $p<0.004$ for non-cardiovascular versus unknown). Other factors associated with a higher risk of death were hypertension ($p=0.009$), ventricular arrhythmias ($p=0.002$) and stroke ($p=0.02$).

A prospective cohort study followed for 18 months 1,418 patients (mean age 62 years; 56% female) presenting to an ED with syncope (Quinn 2008). The all-cause death rate was 1.4% at 30 days; 4.3% at 6 months and 7.6% at 1 year. Death rates from causes possibly related to syncope were 1.3% at 30 days, 2.3% at 6 months and 3.8% at 1 year. Of the deaths at 1 year, 37% were cardiac related, 36% chronic disease (including cancer, Alzheimer's disease), 9% neurological, 2% pulmonary embolism, 1% accidental and 15% other (including infection, renal, gastrointestinal, pulmonary). The mean age of those who died by one year was 79 years.

3 Cardiac syncope - general

3.1 Overall prognosis for cardiac syncope

In patients presenting with syncope, the presence of certain or suspected heart disease (e.g. coronary artery disease, congestive heart failure, valvular heart disease, obstructive cardiomyopathy, bundle branch block, bifascicular block) is a risk factor for sudden death and overall mortality (Brignole 2006b, Chen 2007, Kapoor 1991).

Numerous studies demonstrate that one-year mortality for patients with a cardiac cause of syncope is significantly higher (18% to 33%, including sudden death 14–24%) than for patients with non-cardiac syncope (0 to 12%, including sudden death 3%) or syncope of undetermined aetiology (3% to 6%, including sudden death 4%) (ACEP 2001, Kapoor 1991, Kapoor 1995, Lewis 1984, McKeon 2006).

In a prospective study of 433 patients with syncope, the 1-year mortality rate after cardiac syncope was around 25% and the 1-year risk of sudden cardiac death 14%, while the rates for non-cardiac or idiopathic syncope were 6–8% and 3%, respectively (Hauer 2003). In another study involving 204 patients with syncope (mean age 56 years; 58% female), 1-year mortality was 30% for cardiac syncope (including sudden death 21%) compared with 12% for non-cardiovascular causes of syncope (including 4% sudden death; p=0.02 for all death compared with cardiac causes) and 6% for syncope of unknown cause

(including sudden death 3%; p<0.0001 for all death compared with cardiac causes) (Kapoor 1983, Lewis 1984).

In a retrospective study of 912 patients presenting to an emergency department with cardiac or non-cardiac causes of syncope, followed for a median of 38 months, the 5-year mortality in patients with a cardiac cause was higher than that for patients with non-cardiac causes (23.1% versus 8.2%, p<0.0001), as was the incidence of cardiac death (17.2% versus 0.9%, p<0.0001) (Suzuki 2004). Cardiac syncope was an independent predictor of overall mortality (relative risk 2.81, 95% CI 1.53 to 5.16) and for cardiac mortality (relative risk 18.74, 95% CI 5.90 to 59.52).

Four predictors of poor outcome on initial presentation in people with syncope are an abnormal ECG (not non-specific ST or T wave changes or sinus tachycardia); prior ventricular arrhythmia (at least 10 premature ventricular contractions an hour or repetitive or multifocal premature ventricular contractions; a history of congestive heart failure; and age above 45 years (Hauer 2003, Martin 1997). The risk of arrhythmia or death at 1 year ranges from 5% for patients with no risk factors to 16% with one risk factor to more than 60% with three or four risk factors. The mortality rate of people with cardiovascular syncope and ejection fractions less than 30% is around 30%, compared with 4% in those with ejection fractions greater than 30% (Kosinski 1993).

Data from the Framingham study, in which 822 participants reported syncope, suggest that people with a documented cardiac cause of syncope have a high rate of recurrence (multivariable-adjusted hazard ratio 30.0, 95% CI 14.9 to 60.3 compared with the rate of new onset syncope in people without a prior history of syncope of 72 per 1,000 patient years) (Soteriades 2002). Over a mean follow up time of 8.6 years, these people also had twice the rate of death of people without syncope (Soteriades 2002).

In a prospective study of 650 patients who presented to the emergency department with syncope, followed for 18 months, 9% with cardiac syncope

had at least one episode of recurrence during follow-up, and 26% of patients died (including 7% sudden death) (Sarasin 2001).

Sudden cardiac death in young athletes occurs in around 1 per 100,000, while sudden death in older people undergoing exertional activity is around 1 in 15,000 (McKeon 2006).

502 patients with a first episode of syncope at age 35 or older (evaluated as outpatients or inpatients, presenting to the emergency department, or experiencing syncope while hospitalised for other reasons) were identified retrospectively and their prognosis examined over a mean follow-up period of 3.8 years (Roussanov 2007). Sudden cardiac death on follow-up was more common in the cardiac syncope group (31%) compared with neurogenic (11%), vasovagal (10%), orthostatic (12%) and unexplained (9%) groups.

Individuals with positive electrophysiological tests are at higher risk of death (62% versus 22% at 48 months in one study; 61% versus 15% at 3 years in another) and sudden death (50% versus 10% at 48 months; 48% versus 9% at 3 years) than those with negative electrophysiological tests (Benditt 1992, Kapoor 1991).

3.2 Cardiac syncope with structural heart disease

Syncope is an ominous sign in the setting of structural heart disease, with a 5-year mortality rate of 50% (Kanjwal 2005).

The prognosis of 86 patients with syncope and structural heart disease but negative electrophysiological study (mean age 61 years; 57% male; 66 with coronary heart disease, 11 dilated cardiomyopathy, 9 other; mean ejection fraction 44%) was retrospectively evaluated (Seidl 1995). During a follow-up period of 21 months, the rate of recurrence of syncope was 12%; the rate of mortality was 15%; and the rate of sudden cardiac death was 5%. Left ventricular dysfunction was independently associated with an increased risk of death.

In people with syncope and structural heart disease, syncope is due to ventricular tachycardia in around a third of patients, and, if left untreated,

these people have a 10–20% annual risk of sudden death due to cardiac arrest (Hadjkoutis 2004). Those who have inducible tachycardia on electrophysiological testing have a poor prognosis (30% mortality at 3 years) while patients who are non-inducible have a better survival rate (10% mortality at 3 years).

3.2.1 Aortic stenosis - prognosis

Angina pectoris, syncope or near syncope, and congestive heart failure are three classical manifestations of severe aortic stenosis (Aronow 2007). In patients with severe aortic stenosis who do not undergo surgery, the average survival rate is 3 years after onset of angina or syncope, and 1.5 to 2 years after onset of congestive heart failure (Aronow 2007).

3.2.2 Hypertrophic cardiomyopathy - prognosis

One in 500 people has hypertrophic cardiomyopathy, a genetically determined myocardial disease (Coughlin 2006). Recurrent syncope is a relatively frequent symptom, occurring in as many as 25% of patients (Lim 2002). The prognosis for these patients is variable (Coughlin 2006). Community-based series have suggested an overall yearly mortality in hypertrophic cardiomyopathy of 1.5% per year, including sudden cardiac death 0.6–1% per year, while the incidence of sudden cardiac death in referral populations may be as high as 4–6% per year (Cotga 2006, Strickberger 2006). The risk factors for sudden cardiac death in this population are (Cotga 2006):

- prior cardiac arrest: people with prior cardiac arrest treated with conventional medical therapy and/or surgery have a seven-year mortality rate of around 33% (Cotga 2006).
- ventricular fibrillation or symptomatic ventricular tachycardia;
- unexplained syncope, particularly if recurrent, exertional or in the young
- massive left ventricular hypertrophy (maximum left ventricular thickness 30mm or above from echocardiogram or MRI)
- sudden death due to hypertrophic cardiomyopathy in the family (particularly a first-degree relative or sudden cardiac death in a family member aged 40 years or younger)

- non-sustained ventricular tachycardia on 24 or 48 hour ECG, defined as three or more beats of non-sustained ventricular tachycardia at 120 beats per minute or more, especially if frequent, repetitive or prolonged:
- an abnormal blood pressure response with exercise (a fall or sustained failure to rise by at least 20mmHg during exercise or recovery, in patients under 40 years of age)
- left ventricular outflow obstruction and a resting peak instantaneous outflow tract gradient above 30mmHg.

In a cohort study of 202 patients with a mean age of 41 at diagnosis of hypertrophic cardiomyopathy, followed for a mean of 10 years, the annual mortality rate for cardiovascular disease was 0.6% and that due to sudden cardiac death was 0.1%; the cumulative survival rates were 97% at five years; 95% at ten years and 92% at 15 years (Cecchi 1995).

In a study of 96 patients with hypertrophic cardiomyopathy (median age 53 years; 66% male), followed for a median of 20 months, 8 reached an endpoint (cardiac arrest, documented sustained ventricular tachycardia, implantable cardioverter defibrillator discharge or death) (Efthimiadis 2007). The variables that were predictive of adverse clinical outcome included family history of premature sudden death ($p=0.03$), syncope ($p<0.01$), and maximum wall thickness of 3cm or above ($p=0.02$).

In a referral centre registry study of 368 patients (mean age 37 years; 65% male) with hypertrophic cardiomyopathy, followed for a mean of 3.6 years, 9.8% died including 6% sudden deaths (Elliott 2000). Five risk factors were considered: non-sustained ventricular tachycardia, syncope, exercise blood pressure response, family history of sudden death and left ventricular wall thickness. Overall, the 6-year sudden-death-free survival rate was 91%; this was 95% for patients with no risk factors; 93% for one risk factor; 82% for two risk factors; and 36% for three risk factors.

In a study of 214 patients (mean age 37 years; range 3 to 76 years; 52% female) in a tertiary care centre, the cumulative survival rates were 94.5% at 5 years; 91% at 10 years and 87.9% at 15 years; the annual mortality rate was

1% (Arteaga 2005). Only New York Heart Association functional class III/IV and maximal ventricular wall thickness above 30mm were associated with hypertrophic cardiomyopathy-related cardiac death.

In a study of 95 patients diagnosed as having hypertrophic cardiomyopathy at age 65 years or older, 75% of patients were symptomatic (chest pain 49%, dyspnoea 47%, syncope 17%) (Fay 1990). The median follow up period was 4.2 years. The survival rates at 1 and 5 years were 95% and 75% (not significantly different from an age-matched control group). Patients presenting with New York Heart Association functional class III dyspnoea had a 1-year mortality rate of 36% (higher than controls, $p<0.003$). Of the echocardiographic variables, indexed left atrial size was related to reduced survival ($p<0.008$).

3.2.3 Advanced heart failure due to non-ischaemic cardiomyopathy – prognosis and treatment

In a retrospective study involving 147 patients (mean age 48 years; 60% male) with syncope and heart failure due to non-ischaemic cardiomyopathy (those with sustained VT or cardiac arrest were excluded), outcomes were compared for the 25 in whom ICD implantation was attempted (1 of whom had a pre-existing permanent pacemaker) and 122 managed with conventional medical therapy (those with AF or frequent non-sustained VT received amiodarone; 10 had a pre-existing pacemaker) (Foranow 2000). After a mean follow-up of 22 +/-26 months, there were 2 deaths (none sudden) in patients with an implantable cardioverter defibrillator (8%) and 31 deaths (18 sudden) in patients on conventional therapy (25%). The hazard ratio for death in those with ICD compared with conventional treatment was 0.46 (95% CI 0.22-0.98). The actuarial 2-year survival was higher with ICD (84.9% versus 66.9%, $p=0.04$). At 2 years, the actuarial rate of sudden-death-free survival was 100% in the ICD group compared with 78.3% with conventional treatment, $p=0.05$. There was no significant difference in the rate of non-sudden cardiac death (9.8% in the conventional group versus 8.0% in ICD patients).

In another study of people with syncope and advanced heart failure, mostly due to non-ischaemic cardiomyopathy, the 1-year risk of sudden death was 45% regardless of the aetiology of syncope (Strickberger 2006).

3.2.4 Dilated cardiomyopathy - prognosis

50% of people with dilated cardiomyopathy die within 5 years of diagnosis, and half of these are sudden deaths (Fruhwald 1996). In a study of 23 people with dilated cardiomyopathy and syncope and 201 people without a history of syncope, followed for a mean of around 2.5 years, 26% in the syncope group and 20% in the no syncope group died (not significantly different). However, sudden deaths comprised 83% of deaths in the syncope group compared with 32% in the no syncope group ($p<0.025$).

3.2.5 Arrhythmogenic right ventricular dysplasia/cardiomyopathy - prognosis

In a study of 130 patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy (mean age at onset of symptoms 32 years; 77% men; 32**% had syncope**), followed for a mean of 8.1 years, 24 deaths were recorded giving an overall mortality rate of 18.5% and an annual mortality rate of 2.3% (Hulot 2004). Syncope predicted cardiovascular death in univariate analysis (odds ratio 3.51, $p=0.01$) but not in multivariate analysis.

3.2.6 Prognostic factors for sudden death

The key points in the history of young athletes associated with sudden death are:

- syncope (especially on exertion), which may indicate hypertrophic cardiomyopathy, aberrant origin of the left or right coronary artery, aortic stenosis or dysrhythmias;
- chest pain on exertion (hypertrophic cardiomyopathy, aberrant origin of the left or right coronary artery, aortic stenosis or premature atherosclerotic coronary artery disease);
- palpitations (hypertrophic cardiomyopathy, aberrant origin of the left or right coronary artery, dysrhythmias);

- hypertension or hypercholesterolaemia (premature atherosclerotic coronary artery disease);
- a family history of premature death or cardiovascular events (hypertrophic cardiomyopathy, premature atherosclerotic coronary artery disease, Marfan syndrome with aortic aneurysm);
- family history of dyslipidaemia (premature atherosclerotic coronary artery disease); or
- personal or family history of TLoC (long QT syndrome) (Del Rosario 1996).

Also, recent viral prodromal symptoms may indicate infection with Coxsackie B virus leading to myocarditis and dilated cardiomyopathy (Del Rosario 1996).

85% of people with Marfan syndrome have family members with the disorder (Del Rosario 1996). Patients are typically tall with disproportionately long limbs, they may have kyphoscoliosis, anterior thorax deformities and ectopia lentis (Del Rosario 1996). Cardiovascular abnormalities (e.g. mitral valve prolapse, aortic root dilatation) are present by the third or fourth decade (Del Rosario 1996).

Between 5 and 24% of sudden deaths from cardiac causes in young people are attributed to mitral valve prolapse (Del Rosario 1996). Risk factors for sudden death in such patients include a family history of sudden death; a prolonged QT interval; the presence of complex ventricular tachyarrhythmia, prior syncope and resting ECG abnormalities (Del Rosario 1996).

3.2.7 Myocardial infarction prognosis

In a prospective study of 130 people with syncope, myocardial infarction and bundle branch block, followed for a mean of 4.7 years, 12 patients died suddenly and 12 died from heart failure (Brembilla-Perrot 2001). In multivariate analysis, QRS duration predicted total cardiac mortality ($p=0.02$) and induction of ventricular tachycardia predicted total cardiac mortality ($p=0.033$) and sudden death ($p=0.04$).

In 230 people who had had a myocardial infarction, in whom programmed ventricular stimulation was performed, cardiac mortality was 9% over a follow-up period of 4 years (Brembilla-Perrot 2005). Syncope was more frequent among people who died (48% versus 19% in those who did not die, $p<0.01$), and left ventricular ejection fraction below 40% was also a risk factor for total cardiac mortality (odds ratio 3.109, 95%CI 1.36 to 7.09) and arrhythmic death (odds ratio 9.34, 95% CI 1.18 to 75.02).

3.2.8 Acute coronary syndrome prognosis

In a prospective observational study of 20,881 patients presenting to hospital with acute coronary syndrome, 1,763 had an atypical presentation (i.e. without chest pain), of whom 335 had syncope or presyncope as the main presenting feature (Brieger 2004). After adjusting for potentially confounding variables, an increased hospital mortality rate was noted in syncope patients with atypical compared with typical presentations (odds ratio 2.0, 95% CI 1.4 to 2.9).

3.2.9 Amyloidosis prognosis

In a study of 26 patients (mean age 55 years; 77% male) with primary amyloidosis and one or more episodes of syncope, 23 patients died during follow-up (of up to 55 months); the median survival was 2 months for people with syncope associated with stress (physical exertion or intense emotion; 7/8 patients had sudden death) and 13 months for those with syncope due to postural changes, cardiac arrhythmia, conduction disturbance, micturition or a combination of postural and vasovagal mechanisms (4/25 had sudden death).

3.3 Cardiac syncope – arrhythmic cause

3.3.1 General prognosis

Some people with cardiac syncope have an arrhythmic cause. The prognosis for arrhythmic causes generally is as follows:

In a prospective study of 90 people (mean age around 50 years; 51% female) in whom non-arrhythmic causes of syncope had been ruled out and who were followed for a mean of 20 months, those with a negative electrophysiological study had a recurrence rate of 21%, with no deaths, whilst those with a positive electrophysiological study (93% treated, either with a pacemaker or antiarrhythmic drugs) had a recurrence rate of 6.5% and a mortality rate of 6.5% (Lewis 1984).

Certain arrhythmias detected on prolonged ECG monitoring in patients with syncope have been related to mortality and sudden death on follow up (Kapoor 1991). The finding of frequent or repetitive ventricular ectopy in patients with syncope was an independent predictor of mortality and sudden death (Kapoor 1991). Patients with frequent or repetitive premature ventricular contractions had a 3.7-fold increased risk of mortality (and 14.9=fold risk of sudden death) after adjustment for the effect of underlying comorbidities (Kapoor 1991). Sinus pauses have also been suggested as having a 3.3-fold increased risk of mortality in patients with syncope (Kapoor 1991).

3.3.2 Sinus node disease (sick sinus syndrome)

3.3.2.1 Prognosis

Sinus node disease covers a range of disorders from the usually benign sinus bradycardia to sinus arrest or bradycardia-tachycardia syndrome). Such disorders may be treated with a pacemaker, and they have a generally good prognosis, so pacemaker implantation is usually indicated for symptomatic rather than prognostic benefit.

Sinus pauses have a 3.3-fold increased risk of mortality in patients with syncope (Kapoor 1991).

3.3.2.2 Treatment

The European Society of Cardiology guidelines from 2007 (Task Force 2007) recommend pacing for:

- Sinus node disease with symptomatic bradycardia with or without bradycardia-dependent tachycardia. Symptom–rhythm correlation must have been spontaneously occurring or drug-induced where alternative drug therapy is lacking.
- Syncope with sinus node disease, either spontaneously occurring or induced at electrophysiological study
- Sinus node disease with symptomatic chronotropic incompetence (spontaneously occurring or drug-induced where alternative drug therapy is lacking).

This was based a consensus of expert opinion or small studies, retrospective studies, and registries.

3.3.3 Atrio-ventricular (AV) block

AV block may be treated with a pacemaker with or without drug therapy, or not treated. Advanced AV block (Mobitz II or complete) has a poor prognosis with a clear risk of sudden death. Pacing restores life expectancy to normal for the age.

AV block is classified as:

- 1st degree
- 2nd degree
- Type I or Wenckebach or Mobitz I
- Type II or Mobitz II
- 3rd degree or complete AV block

3.3.3.1 Complete heart block - prognosis

A retrospective cohort study assessed 204 people with complete heart block (134 constant; 70 transient; mean age 68 years; **44 people (22%) initially consulted for syncope**; 102 for other cardiac symptoms; 9 for a low heart rate; 49 consulted for other non-cardiac diseases) (Johansson 1966). The authors estimated the incidence of complete heart block in their population (Malmo, Sweden) was 6.3 per 100,000 population per year. The aetiology of the complete heart block was reported as myocardial infarction, non-acute coronary heart disease, hypertension, rheumatic heart disease, digitalis intoxication, 'miscellaneous' (e.g. myocarditis, sepsis) or 'unknown'. A subset of 193 patients (diagnosed after 1950) was used for a 'prognostic study' by these authors. Overall, of these 193 patients (with syncope and no syncope), 62 (32%) had died within 4 weeks of diagnosis of complete heart block; this increased to 85 (44%) within 6 months; and 97 (50%) at 1 year (i.e. 96 [50%] still alive at 1 year). One-year mortality in people aged 80 years or more was 78% compared with 43% in those aged 59 years or younger. The excess 1-year mortality compared to the age-matched population was 41% in those aged 59 or younger; 42% at ages 60-69 years; 38% at 70-79 years; and 56% at ages 80 years or more. Among the patients where a cause of death was known, this was thought to be due to the complete heart block with or without syncope in a third of patients (the other causes were other cardiac disease or non-cardiac disease). **Among the patients with syncope**, the 1-year survival rate was 45% compared with 58% among patients without syncope.

3.3.3.2 Complete heart block - treatment

The Johansson (1966) retrospective study (in which only 22% patients had syncope) reported there was no significant difference in 1-year survival between the patients who had or had not been treated medically (e.g. with atropine, ephedrine or isopropylnoradrenaline). Pacemakers were implanted in 48 of the patients, of whom 36 had a follow-up time of 6 months or more (17% died at 6 months and there were no further deaths by 1 year); 19% of these patients died overall (maximum follow up 4.5 years). The authors suggested that the poor prognosis of patients with complete heart block (50% dead in one year) and the evidence that the prognosis in people with complete

heart block is improved with a pacemaker (although there is an operative mortality) is an argument for having wide indications for pacing in people with complete heart block.

In a series of 36 patients with complete heart block treated with a pacemaker, of whom **30 (83%) had a history of syncope**, over a mean follow-up period of 12 months after pacemaker insertion (37 months after onset of syncope), 17% had died (Gadboys 1964). The authors compared their results with another published study of patients with syncope and complete heart block treated medically, 50% of whom had died at 42 months after the onset of syncope. The authors suggest that this rate (14% per year) was similar to their mortality rate of 17% at 1 year.

In a study of 44 patients treated with a pacemaker for heart block (**42 had prior syncope (95%)** and 2 had a pacemaker for congestive cardiac failure), 3 died during hospitalisation (due to coronary thrombosis), 1 during hospitalisation (due to MI), and 6 additional patients died (minimum follow up 13 months: 2 cerebral emboli, at 3 and 9 months after surgery; uraemia and congestive heart failure in 2, at 1 month and 31 months after surgery; 1 suicide at 12 months; and 1 sudden death of unknown cause at 9 months) (Donmoyer 1967). Survival rates were calculated as: 1 year: 81%; 2 years: 78%; 3 years: 72%. All patients had relief of syncope with pacemaker, except 9 who had return of syncope and 19 who had pre-syncope when their pacemaker malfunctioned (e.g. battery failure). The authors compared their results to other published studies of similar patients treated medically, in whom there was a 35% hospital mortality and an additional 15% mortality within 1 year (i.e. total mortality 50% at 1 year with medical treatment versus around 80% at 2 years in this study with pacing).

3.3.3.3 2nd degree block - prognosis

In an observational study of 214 patients with 2nd degree AV block (77 type I block, mean age 69 years; 86 patients with type II block, mean age 74 years; 51 with 2:1 or 3:1 block), five-year survival was 57%, 61% and 53%, respectively (Connelly 1996). In the Mobitz type I group, the 5-year survival rate was 42% for the unpaced patients ($p<0.01$).

A prospective study assessed 147 patients with chronic Mobitz type I block (Shaw 2004). Of these, **30 had syncope, 11 pre-syncope and 4 both (31%, i.e. indirect evidence)**; 23 had cardiac symptoms (e.g. palpitation, breathlessness, chest pain) but not TLoC; 58 had a coincidental discovery of Mobitz type I block (e.g. prior to surgery [93% of these patients had no symptoms of bradycardia]). Survival curves were compared with an age- and sex-matched population, and all unpaced patients had a worse survival than population norms (20% at 10 years versus 50% at 10 years in the unpaced general population).

3.3.3.4 2nd degree block - treatment

For 2nd degree type I block, pacing improves survival in older patients and can improve symptoms:

In a prospective study of 56 people with 2nd degree AV block, 19 had no evidence of heart disease (of whom **6 (32%) had syncope**) and 37 had organic heart disease (of whom **7 (19%) had syncope**) (Strasberg 1981). At a mean follow-up of 1395 days for the no heart disease group, **5 of the 6 patients with syncope** remained asymptomatic without a pacemaker, and one who had a pacemaker for recurrent syncope (at day 220 of the study) had syncopal symptoms alleviated by the pacemaker. Two patients died during follow-up (of pneumonia and MI). In the heart disease group, 10 had pacemakers (2 for syncope) and after a mean follow up of 1347 days, **neither of the 2 patients with pacemakers for syncope** had recurrence, although one of these two patients died with congestive failure.

In an observational study of 214 patients with 2nd degree AV block (77 type I block, mean age 69 years; 86 patients with type II block, mean age 74 years; 51 with 2:1 or 3:1 block), five-year survival was 57%, 61% and 53%, respectively (Connelly 1996). In each group, symptomatic patients were paced, and more paced patients than unpaced patients survived. In the Mobitz type I group, the 5-year survival rate for the paced patients was 78%, and was similar to that for an age- and sex-matched healthy population. This high survival rate compared with 42% for the unpaced patients ($p<0.01$). After age and sex matching, survival in the paced population was still significantly

greater at 5 years (P < 0.015) despite the fact that the unpaced patients had been largely asymptomatic. The authors suggested pacing for patients with chronic Mobitz type I block, especially older people with structural heart disease.

A prospective study assessed 147 patients with chronic Mobitz type I block. Of these, **30 had syncope, 11 pre-syncope and 4 both (31%);** 23 had cardiac symptoms (e.g. palpitation, breathlessness, chest pain) but not TLoC. A total of 90 pacemakers were implanted for incapacitating symptoms (syncope/pre-syncope or cardiac) or the development of higher degree block (74 pacemakers); in the last part of the study, older patients were offered a pacemaker prophylactically if there were no contraindications (16 prophylactic pacemakers) (Shaw 2004). The results were not given separately for people with syncope, however, symptomatic bradycardia did not persist in any patient after pacing. The patients with syncope or cardiac symptoms (of whom 81% received a pacemaker) had a survival rate of around 45-50% at 10 years. Survival curves were compared with an age- and sex-matched population, and all unpaced patients had a worse survival than population norms (20% at 10 years versus 50% at 10 years in the unpaced general population). None of the patients in the first age cohort (20–44 years), with or without a pacemaker, died within 14 years, but in the second (45–64 years) and third cohorts (65–79 years) the difference in survival between patients with and those without a pacemaker was highly significant (p=0.001 and p=0.003, respectively). In the fourth cohort (> 80 years) patients with a pacemaker had a better five year survival than those without (46% versus 33%), but the difference was not significant. The authors suggest that the data are compatible with the proposition that Mobitz I in people aged younger than 45 years is, per se, an indication for pacing to improve both survival and quality of life (the latter being a major factor in very old people). Younger people manage well unpaced, although even here the condition is not always benign.

3.3.3.5 Bifascicular block - treatment

In a study of 13 patients with syncope and bifascicular block (mean age 62 years) who had an electrophysiological study, 4 of the 5 patients with an HV

interval 70msec or more or inducible infranodal block were treated with permanent pacemakers; 4 of 4 with VT received antiarrhythmic therapy and 3 of 4 with non-diagnostic studies received no therapy (1 received a pacemaker) (Ezri 1983). During a mean follow up of 19 months, all but 3 patients were free of syncope (1 later diagnosed with basilar migraine; 1 not taking their medication; 1 sudden death). The authors stated that it was difficult to determine whether treatment based on the results of the electrophysiological testing definitely altered the clinical course in these patients; the evidence suggests that it may be helpful, although the patient number was small.

In a study of 93 patients with bifascicular block and unexplained syncope, electrophysiological abnormalities were detected in 45 patients (36 distal conduction disease, sick sinus syndrome in 6, carotid sinus hypersensitivity in 2, and sustained VT 1; mean age 75 years) (Twidale 1988). Of these EPS positive patients, 42 had a pacemaker only; 1 had antiarrhythmic drugs only, and 2 had both (treated EPS positive = group 1). Of the EPS negative patients (mean age 71 years), 8 were treated empirically with pacemaker (group 2) and 40 had no specific therapy (group 3). At a mean follow up of 39 months, recurrence occurred in 4% in group 1, 0% group 2 and 25% of group 3. Mortality was 47% (including 5 sudden deaths), 25% (no sudden deaths) and 35% (2 sudden deaths), respectively. The authors concluded that treatment improved symptoms but not survival in patients with chronic bifascicular block and syncope.

3.3.4 Ventricular tachycardia (VT)

3.3.4.1 Prognosis

In a registry study, 598 patients with ventricular tachycardia and syncope were followed for a mean of 16 months; 21.2% died and the two-year survival rate was 76% (Anderson 1999).

In a retrospective study, 32 patients with clinically documented sustained ventricular tachycardia (22 (69%) of whom had syncope or near syncope; mean age 66 years) and 22 patients with syncope (17) or near syncope (5)

plus inducible sustained ventricular tachycardia on electrophysiological testing (mean age 69 years) were followed for a median of 46 months and 34 months, respectively (Andrews 1999). Nearly **40% of syncope patients** had spontaneous recurrence of syncope (in spite of implantable cardiac defibrillator therapy). The 36-month actuarial survival rates were 89% and 60% respectively (p=0.06). In contrast, patients with negative electrophysiological testing were reported to have a very low incidence of sudden death (1% per year) (Andrews 1999).

In a study of 104 patients (mean age 61 years, 78% male) with sustained symptomatic (44% palpitations, congestive heart failure, lightheadedness; **15% syncope (i.e. indirect evidence)**; 15% in hospital cardiac arrest; 26% out of hospital cardiac arrest) ventricular tachycardia or ventricular fibrillation treated with amiodarone, 25 had fatal or non-fatal cardiac arrest after a mean of 7.3 months of therapy (Dicarlo 1985). Multivariate analysis indicated that risk factors for cardiac arrest were ejection fraction below 40% ($p<0.03$); syncope or cardiac arrest before amiodarone therapy ($p<0.01$) and ventricular tachycardia on pre-discharge ambulatory ECG ($p<0.01$). The survival rate among patients with none of these factors was 98% at 6 months and 95% at 18 months. Patients with all three factors had survival rates of 38% at 6 months and 24% at 18 months. Patients with any 1 or 2 factors had intermediate survival rates.

3.3.4.2 Treatment:

The Antiarrhythmics Versus Implantable Defibrillators (AVID) study was a large randomised secondary prevention trial in people with life-threatening ventricular arrhythmias (trial-eligible arrhythmias were VF cardiac arrest, syncopal VT or symptomatic VT, i.e. **not all had syncope**) (Anderson 1999). ICD therapy was associated with 39%, 27% and 31% reductions in mortality at 1, 2 and 3 years, respectively, compared with antiarrhythmic drug therapy (mainly empirical amiodarone).

In parallel with the RCT, the AVID investigators maintained a registry of patients, randomised or not, with any ventricular arrhythmia or unexplained syncope who could be considered for either of the treatment strategies.

Reasons for non-randomisation included patient, family or physician refusal; treatment predetermined by referring physician and previous amiodarone use. 1509 patients were eligible for the trial but not randomised, and differences between these patients and those randomised were small; around 50% were discharged with ICD and 50% with antiarrhythmic drugs. 2-year survival was around 75.7% **for the 241 patients with VT and syncope**, and 84.1% for the 158 patients with unexplained syncope. However, patients were not compared by treatment group.

3.3.5 Complex ventricular arrhythmias

3.3.5.1 Prognosis

In a prospective study, 148 elderly patients (mean age 82 years; 68% female) who had 24-hour ambulatory ECGs were followed for a mean of 32 months (Aronow 1992). Recurrent syncope occurred in 82% of patients with complex ventricular arrhythmias compared with 54% with no significant arrhythmia ($p<0.001$).

3.3.5.2 Treatment

In a retrospective study of 421 patients who had received an **implantable cardioverter-defibrillator** for cardiac arrest, ventricular tachycardia or both symptoms, followed for a mean of 26 months, **14.7% had syncope** (Bansch 1999). The actuarial survival rate free of syncope was 90% at 12 months, 85% at 24 months and 81% at 36 months after implantation; once patients had a ventricular tachycardia, syncope during ventricular tachycardia and a high ventricular tachycardia rate were the strongest predictors of future syncope.

3.3.6 Supra-ventricular tachycardia (SVT)

There are many different types of SVT, but atrial fibrillation is the one most likely to be associated with TLoC. SVT may be treated with drugs, ablation (e.g. for atrial fibrillation), or nothing.

In addition, the patient may experience problems due to a malfunction of an existing pacemaker or due to an arrhythmia (e.g. Torsade de Pointes) induced

by medication (which requires the responsible drug to be stopped, and, for Torsade de Pointes, correcting potassium and/or magnesium depletion). Wolff-Parkinson-White (WPW) syndrome, which may present with syncope during exercise, is likely to be treated with catheter ablation (Christopher 2007).

3.3.6.1 Prognosis of Wolff-Parkinson-White syndrome

In a study of 101 patients with Wolff-Parkinson-White syndrome, 36 (had syncope and 65 did not (Auricchio 1991). 22 patients had a history of aborted sudden death (28% of those with a history of syncope and 18% of those without such a history), and this was predicted by the shortest RR interval during atrial fibrillation being 250ms or less (sensitivity 91%, specificity 36%).

In another study of 518 patients with Wolff-Parkinson-White syndrome (mean age 35 years, 59% male), of whom **71 (14%) had syncope**, electrophysiological study was carried out (Brembilla-Perrot 2008). Patients with syncope had a higher rate of inducible atrioventricual re-entrant tachycardia (53.5% versus 10% in patients with no symptoms), atrial fibrillation (31% versus 18.5%) and high-risk forms (rapid conduction over an accessory pathway and atrial fibrillation or antidromic tachycardia; 25% versus 8%), which may indicate a higher risk for sudden death.

3.3.7 Bradyarrhythmias

In a retrospective study of 243 patients (mean age 75 years; 53% female) admitted to the emergency department of a general hospital with symptomatic bradyarrhythmia (**54% had syncope**), 4.5% of patients had ventricular fibrillation or Torsades de Pointes (Diaz-Castro 2004). In multivariate analysis, therapy with diuretics (p=0.04) and/or amiodarone (p=0.02) and long QTc on admission (p=0.008) were significant predictors of developing these outcomes. A QTc above 460ms had a sensitivity of 80%, specificity 76%, negative predictive value 98.8%).

3.3.7.1 Long QT syndrome - prognosis:

Inherited cardiac ion channel abnormalities such as long QT syndrome can cause syncope and sudden death (Coughlin 2006). 40% of patients with long

QT syndrome remain asymptomatic but 5–10% present with sudden death (Nemec 2003). Estimates of the mortality rate in untreated patients with long QT syndrome include 1–2% per year to 50% at 10 years (Johnson 2001, Khan 2002). Individuals treated with beta-blockers still have a 10% incidence of sudden cardiac death at 5 years; pacemaker implantation may reduce cardiac events by a further 50% (Johnson 2001). The lifetime risk of syncope, aborted or actual sudden death in patients with long QT syndrome is 5% if the QTc is below 440ms; 20% if it is 460–500ms; and 50% if it is above 500ms (Strickberger 2006). Syncope is considered an ominous sign in patients with long QT syndrome (Coughlin 2006, Khan 2002).

In a study of 54 patients from different families in a Chinese national registry (mean age 29 years; 74% female), followed up for a mean of 25 months, sudden cardiac death occurred in 3 patients: 1/32 on antiadrenergic therapy died (3.1%) compared with 2/22 (9.1%) on no therapy ($p<0.05$) (Li 2004).

In an international long QT syndrome registry, risk factors for aborted cardiac arrest or sudden cardiac death included gender (males had a higher risk before around age 14 and females thereafter); a baseline QTc interval of 500ms or above; and a history of syncope (Goldenberg 2008). The 5-year rates of aborted cardiac arrest or sudden cardiac death were 0.5% in patients with QTc below 500ms and no prior syncope; 3% in those with QTc of 500ms or more and/or prior syncope; and 14% in those with prior cardiopulmonary resuscitation or spontaneous Torsades de Pointes.

In a study of a subset of 2,759 patients from the international long QT syndrome registry, aged between 41 and 75 years, patients were categorised by QTc into affected (QTc 470ms or above); borderline (QTc 440 to 469ms) and unaffected (QTc below 440ms) (Goldenberg 2008b). The cumulative probability of a fatal or near-fatal event (first occurrence of aborted cardiac arrest or death due to any cause between ages 41 and 75 years) was higher in the affected group than the borderline or unaffected groups (28% versus 20% and 21% respectively, $p=0.02$). The differences were significant among women (26% versus 16% and 12%, $p=0.001$) but not among men (29% versus 26% and 27%). Within the affected group, **a recent history of**

syncope (within 2 years) predicted an event in the younger age group (hazard ratio compared with no syncope or syncope more than 10 years ago 9.92 for age 41-60 years, p<0.001; 2.13 for age 61-75 years, p=0.3) and a history of syncope 2–10 years ago also predicted an event in both age groups (hazard ratio compared with no syncope or syncope more than 10 years ago 2.76 for age 41-60 years, p=0.005; 2.96 for age 61-75 years, p=0.01).

3.3.7.2 Brugada syndrome - prognosis

The Brugada syndrome is characterised by an ECG pattern of right bundle branch block and persistent ST elevation in patients suffering from aborted sudden death without demonstrable structural heart disease; some patients have syncope (Brugada 1997). It can be inherited and predominantly affects males (Corrado 1999).

Sudden death is reported in 8–30% of patients over 2 years (Coughlin 2006, McKeon 2006). Patients with prior history of aborted sudden death or ventricular fibrillation have the highest risk of aborted sudden death or sudden cardiac death (Ito 2008).

In a study of 63 patients with Brugada syndrome (mean age 38 years; 90% male) followed for a mean of 34 months, mortality was 31% among 13 patients on no treatment; 26% among 15 patients on drug therapy (beta-blockers and/or amiodarone) and 0% among 35 patients who had an implantable defibrillator; all mortality was due to sudden death (Brugada 1998).

In another study from the same investigators, 252 patients with Brugada syndrome (mean age 42 years; 78% male), 116 (46%) of whom had had syncope or aborted sudden death, were followed for a mean of 34 months (Brugada 2001). **Among the patients with syncope**, inducibility of a sustained ventricular arrhythmia on programmed ventricular stimulation predicted an arrhythmic event (ventricular fibrillation or sudden death) on follow up with a sensitivity of 92%, specificity of 41%, positive predictive value of 29% and negative predictive value of 95%.

In a further study from the same investigators of 334 patients with Brugada syndrome (mean age around 42 years; 76% male), three groups were identified: Group A patients had resuscitated cardiac arrest; **Group B presented with syncope**; and Group C were asymptomatic (Brugada 2002). During 54 months of follow-up in Group A, 62% had a new arrhythmic event (sudden cardiac death or documented ventricular fibrillation); during 26 months **in Group B**, 19% had an event and during 27 months in Group C, 8% had a first event. In all groups, inducibility of ventricular arrhythmias on electrophysiological testing was predictive of subsequent events.
In symptomatic patients, the recurrence rates were 13.7% per mean follow up year in Group A and 8.8% in **Group B**. In asymptomatic patients (Group C), a spontaneously abnormal ECG was a marker of arrhythmic events (14% of patients with an abnormal ECG had an event compared with 0% of those with a normal ECG).

A subsequent publication from the same investigators described 547 patients with Brugada syndrome (mean age 41 years; 75% male), including **124 (23%) patients with at least one episode of syncope** (Brugada 2003, i.e. indirect evidence). During a mean follow-up period of 24 months, 8% of patients suffered a sudden death or documented ventricular fibrillation. Multivariate analysis identified inducibility of ventricular arrhythmias on electrophysiological testing and a history of syncope as predictors of events. It should be noted that there may be overlap between the cohorts of patients described in these papers from the same research group. Overall, the clinical outcome of affected patients appears to be poor unless they receive an implantable cardioverter defibrillator (Corrado 1999).

In a study of 212 patients with Brugada syndrome (mean age 45 years; 72% male), 58% were asymptomatic; 31% had one or more episodes of syncope and 11% had to be resuscitated due to ventricular fibrillation (Eckhardt 2005). During a mean follow-up period of 40 months, 17% with aborted sudden death and 6% **with a prior syncope** had a recurrent arrhythmic event, whereas only 1 of 123 asymptomatic individuals (0.8%) had a first arrhythmic event.

3.3.7.3 Inducible ventricular flutter - prognosis

In a study of 73 patients with inducible ventricular flutter on electrophysiological testing but without rapid spontaneous ventricular tachycardia, followed up for 3.5 years, there were 13 deaths from cardiac causes (mortality 18%) (Brembilla-Perrot 1993). The actuarial probability of survival without cardiac death was 90% at one year; 85% at two years; and 74% at five years. **Patients with syncope** had a significantly poorer prognosis than those without ($p<0.01$). Two groups of patients were identified: the first, who had a normal 24-hour Holter monitor, had an excellent outcome. The second, who had couplets or salvos of extrasystoles on Holter monitoring, the risk of cardiac mortality was high (35%), and in this group, a history of syncope and decreased left ventricular ejection fraction increased the risk of mortality.

4 Neurally mediated syncope

4.1 Prognosis and treatment of neurally mediated syncope in general

4.1.1 Recurrence

The natural history of neurally mediated syncope shows that even severely symptomatic patients may remain asymptomatic for long periods due to an unpredictable recurrence rate, although the rate is usually reported as around 30% per year (Brignole 2006).

Recurrence rates of 24–46% per year have been reported in the placebo arms of drug and pacemaker trials (Brignole 2006). For example, in a randomised placebo-controlled trial of drug therapy (atenolol, dihydroergotamine, domperidone, cafedrine, with or without compression stockings) in 30 patients with neurally-mediated syncope, syncope recurred in 27% of the placebo group (and 20% on treatment) over a mean follow up of 10 months (Brignole 1992).

Recurrence rates were reported in six additional studies, and appeared to depend on the number of previous episodes. Across studies, the recurrence

rate in the absence of treatment (with the number of episodes given in brackets), was reported to be:

- 3 months: 17% (Brignole 2006 (≥ 3 episodes))
- 6 months: 24% (Brignole 2006 (≥ 3 episodes))
- 12 months: 18% to 37% (Aerts 2005 (1 episode =18%); Aerts 2005 (≥ 2 episodes = 37%); Brignole 2006 (≥ 3 episodes = 33%)
- 16-17 months: 18% to 36% (Brignole 1992c; depending on presence of asystole, number of episodes not stated)
- 18 months: 17% (Sarasin 2001 (episodes not stated))
- 24 months: 49% (Brignole 2006 (≥ 3 episodes))
- 28 months: 33% (Aydin 2007, episodes not stated)
- 30 months: 25 to 44% (Baron-Esquivias 2004; (≥ 5 episodes = 44% and <5 = 25%))
- 40 months: 40% (Brignole 1992c; all with asystole on tilt test)

Further details of these studies are given below.

In a prospective observational study, 392 patients (mean age 66 years; 45% male) with three or more clinically severe syncopal episodes in the last two years who had suspected neurally mediated syncope (syncope excluding cardiac causes, orthostatic hypotension, subclavian steal syndrome, carotid sinus hypersensitivity and non-syncopal loss of consciousness) had an implantable event recorder (IER) fitted (Phase I of the study) (Brignole 2006). The recurrence rates of syncope were 17% at 3 months; 24% at 6 months; 33% at 12 months and 49% at 24 months.

In another study, 474 athletes reported that they had had a syncopal spell in the last 5 years (Colivicchi 2004). This was unrelated to exercise in 86.7% or post-exertional in 12.0%, all of which had the typical features of neurally-mediated fainting. The remaining 6 athletes had syncope on exertion (4 exercise-induced neurally-mediated syncope; 1 hypertrophic cardiomyopathy and 1 right ventricular outflow tract tachycardia). All athletes were followed for a mean of 6.4 years and the recurrence rate was around 20 per 1000 subject-years. No other adverse event was noted during follow up.

In another study of 28 patients with syncope and an asystolic response on tilt testing (mean age 58 years; 61% male) and 28 patients with a positive but not asystolic response (mean age 55 years; 50% male), syncope recurred in 18% in the asystolic group over a mean follow up of 17 months, and in 36% in the non-asystolic group over 16 months (not significantly different); the actuarial rates of absence of syncope at 40 months were 60% and 62%, respectively (Brignole 1992c).

In a study of 334 patients with vasovagal syncope and an abnormal head-up tilt test (mean age 44 years; 52% female) followed up for 30 months, 30% had recurrence of syncope (44% among patients with 5 or more previous episodes compared with 25% in those with fewer than 5 previous episodes, p=0.001) (Baron-Esquivias 2004).

In another study (Bastos 2006) of 37 patients with refractory recurrent neurally-mediated syncope (mean age 31 years; 51% female) who had had a positive tilt test and who became asymptomatic with a negative tilt test on therapy (beta-blockers and/or fludrocortisone), treatment was discontinued and the patients were followed for a mean of 21 months. In this time, 59% of patients had a recurrence, and this was more likely if the tilt test became positive again after interrupting therapy (p=0.0002); if the patient was female (68% of patients with a recurrence were female compared with 27% of those without recurrence, p=0.0131) or if the patient had had a higher number of previous episodes of syncope (mean 4.5 for patients with recurrence versus 3.5 for those without, p=0.0248).

In a cohort study involving 58 patients who had asystole on tilt test (mean age 35 years; 59% male) followed up for 41 months, 21% had syncopal recurrence (Baron-Esquivias 2002). This was compared with a control group of 118 patients with a vasovagal response on head-up tilt test but without asystole (mean age 29 years; 52% male), who were followed for 52 months and had a recurrence rate of 28.8% (not significantly different). The recurrence of syncope was not dependent on the presence of asystole, but compared to patients free of recurrences, those with recurrence had suffered more syncopes prior to head-up tilt test (4.5 versus 3, p=0.002). Taking the

patients with and without asystole together, 2/8 patients treated with pacemakers (25%), 18/62 treated with drug therapy (29%) and 26/106 (25%) who received only advice had recurrences.

4.1.2 Effect of therapy on recurrence rate

One study (Brignole 2006) investigated the recurrence rate of 103 patients with suspected neurally mediated syncope following treatment. 103 patients who had a syncope documented by the IER were followed up again. Of these, 53 patients received specific therapy based on the IER findings (47 a pacemaker because of asystole; 6 anti-tachyarrhythmia therapy) and the remaining 50 patients did not receive specific therapy (including 13 who did not receive a pacemaker despite documentation of asystole or bradycardia and one who did not receive anti-arrhythmic therapy despite a tachyarrhythmia; 7 did receive empirical drug therapy). The recurrence rate was reduced by specific therapy (10% at 12 months, i.e. lower than in these same patients in the previous 12 months [33%] and lower than in the patients without specific therapy [41%]).

4.1.3 Death - prognosis

Data from the Framingham study, in which 822 participants reported syncope, suggest that people with vasovagal syncope do not have an increased risk of death compared to participants without syncope (Soteriades 2002). A second study (Aerts 2005) in 131 people with suspected vasovagal syncope undergoing a tilt test found no deaths.

4.2 Vasovagal syncope

4.2.1 Prognosis

Data from the Framingham study, in which 822 participants reported syncope, suggest that patients with vasovagal syncope do not have an increased risk of death (Soteriades 2002).

In a tertiary referral unit cohort of 418 patients with vasovagal syndrome (median age 60 years at first presentation; 67% female) of whom **69% reported syncope at presentation** and followed for a median of 5 years,

35% were asymptomatic at 5 years regardless of treatment received (Ross 2008). In the **subgroup of patients with syncope only** (i.e. not reporting pre-syncope or falls), 60% were symptom-free at follow-up.

In a prospective study of 650 people who presented to the emergency department with syncope, followed for 18 months, 17% with vasovagal syncope had at least one episode of recurrence during follow-up (Sarasin 2001).

In 131 patients with suspected vasovagal syncope (mean age 53 years; 53% male) undergoing a tilt test, recurrence one year later was ascertained using a questionnaire (Aerts 2005). Overall, 29% of patients had at least one recurrence (44% of the females and 16% of the males, $p<0.001$); and having had two or more prior syncopes was also predictive of recurrence (37% versus 18% among patients with only one syncope, $p=0.027$). Recurrence rates were not predicted by passive tilt testing, but were 34% with a positive nitrate-stimulated tilt test and 13% with a negative test ($p=0.031$). There were no deaths in this study.

In another study involving 68 people (mean age 52 years; 54% male) with recurrent vasovagal syncope, neither tilt table test (including sublingual nitroglycerine if necessary) nor postural blood pressure test result nor their combination had any predictive value for the person's risk of syncope recurrence (Aydin 2007). After a follow up of around 830 days, recurrent syncope occurred in around 33% of people (15/46 for whom data available) and two people (42%) died.

In a study of 101 people with vasovagal syncope who received no drug therapy and were followed for up to 3 years, the probability of remaining free of recurrence was 72% at one year; 62% at two years and 51% at three years (Fenton 2000). The risk for syncope increased with the frequency of previous episodes (e.g. probability of being syncope-free at 2 years was 26% for a patient with 17 episodes in the previous 6 months compared with 82% for a patient with only 2 episodes in that time).

In a study involving 195 people with syncope and 121 with pre-syncope, an infusion of ATP 20mg provoked a cardiac pause greater than 10s in 41%, who were treated with pacemakers, and a pause of 10s or less in 59%, who were followed without pacemaker (but with or without drug treatment) for up a mean of 50 months (Flammang 1997). Among long-pause patients with pacemakers, symptoms recurred in 14% (compared with 48% in long-pause patients who declined pacemakers, p=0.0001), and in short-pause patients without pacemakers in 21%.

4.2.2 Treatment

The European Society of Cardiology guidelines from 2004 on the management of neurally mediated syncope suggest that, in general, initial treatment (e.g. education on the importance of correct hydration and reassurance) is sufficient (Brignole 2004). Additional treatment may be necessary if the person is at high risk (e.g. the patient is a machine operator) or syncope is very frequent (e.g. alters quality of life) or syncope is recurrent and unpredictable (e.g. absence of premonitory symptoms). People should avoid trigger events as much as possible. Modification or discontinuation of hypotensive drugs may be required. Volume expansion by salt supplements, an exercise programme or head-up tilt sleeping may be helpful in posture-related syncope, as may tilt training in those with vasovagal syncope.

4.2.2.1 Drugs

A review of drug therapy for vasovagal syncope published in 2002 listed drugs that have shown benefit in randomised placebo-controlled trials as follows:

- Atenolol: one RCT of 42 people; at 1 month, those on atenolol 50-100mg daily, depending on resting heart rate 50-80 beats per minute or over 80 beats per minute, were more likely to have a negative tilt test 62% versus 5%, p=0.0004; 71% of the atenolol group versus 29% in the control group reported feeling better after the treatment, p=0.02; people in the atenolol group had their number of attacks reduced from 6.0 +/- 9.4 per week to 0.6 +/- 1.6 per week (Mahanonda 1995);

- Enalapril: one RCT of 30 people taking enalapril 5mg twice daily or placebo; tilt testing at 1 week was negative in all 15 people on enalapril versus 3/15 on placebo (Zeng 1998);
- Midodrine: one crossover RCT of 16 people taking midodrine 5mg three times daily or placebo for 1 month each; when tested during treatment, 14 people had tilt-induced syncope on placebo versus 6 on midodrine, p=0.01; those on midodrine had an average of 7.3 fewer symptom-days during the treatment month than on placebo, 95% confidence interval (CI) 4.6 to 9; p < 0.0001; eleven people reported a positive therapeutic response with midodrine versus none on placebo (p = 0.002); all domains of quality of life showed improvement with midodrine, [Ward 1998]);
- Paroxetine: one RCT of 68 people; 62% on paroxetine 20mg daily had a negative tilt test at 1 month versus 38% on placebo, p<0.0001; 18% versus 53% had spontaneous syncope during 2-year follow-up, p<0.0001 (Di Girolamo 1999b).

In addition, the review listed fludrocortisone as having consensus support but little trial evidence (Bloomfield 2002).

A randomised, placebo-controlled trial of metoprolol (highest tolerated dose, between 25 and 200mg daily) to prevent vasovagal syncope (known as the Prevention Of Syncope Trial, POST) was published in 2006 (Sheldon 2006). It involved 208 patients (mean age 42 +/- 18 years) with a median of 9 syncopal spells over a median of 11 years. The primary outcome measure was the time to first recurrence of syncope and this was not different between patients on metoprolol and those on placebo (hazard ratio stratified by treatment centre 0.99, 95% CI 0.69 to 1.43, p=0.97). This means that metoprolol did not benefit patients. This conclusion was also true in subgroup analyses of people with or without positive tilt tests.

In a randomised placebo-controlled trial of etilifrene in the treatment of vasovagal syncope in 126 people (mean age 44 years; 59% female) followed for a mean of 262 days, both groups had a recurrence rate of 24%; no deaths occurred in the study (Raviele 1999).

4.2.2.2 Tilt training

One non-randomised study evaluated 47 adolescents (mean age 16 years) with recurrent syncope and a positive tilt test refractory to previous traditional therapies (etilefrine 19 people; propranolol 15 ; either of these drugs 11; fludrocortisone 1; paroxetine 1) (DiGirolamo 1999a). All were offered tilt training (5 sessions in hospital, increasing from 10 to 50 minutes by increments of 10 minutes per day, then at home twice daily for up to 40 minutes, depending on tolerance during in-hospital training); 24 agreed and 23 declined (control group). After 1 month, 95.8% of the tilt training group became tilt negative compared with 26.1% of the control group ($p<0.0001$). Participants were followed for 15-23 months (mean 18.2 months). Spontaneous syncope recurred in 0% and 56.5%, respectively, $p<0.0001$.

In another study, 82 people with recurrent vasovagal syncope (mean age 41 years; 55% female) were randomised to conventional therapy (avoidance of dehydration, increase in dietary salt intake, head-up sleeping, patient education, reassurance regarding the benign nature of the condition, and avoidance of potential triggers) or conventional therapy plus additional tilt training sessions (Duygu 2008). After a mean follow-up period of 12 months, spontaneous syncope recurrence was 56% in the conventional therapy group and 37% in the tilt training group (not significantly different).

A randomised trial, involving 125 people (mean age 40 years) with a history of syncope and positive head-up tilt test, compared orthostatic training (daily 30-minute sessions of upright standing against a vertical wall 6 days a week for at least 4 weeks) with a no treatment control group (Zeng 2008). After 1 year of follow up, 72.6% of the treated group had no recurrence of syncope compared with 36.1% of controls, $p<0.05$.

4.2.2.3 Pacing

Pacing for NM syncope is discussed in chapter 6.

4.3 Situational syncope

In a study of 36 people with situational syncope (mean age 47 years; 72% male; 44% micturition; 42% postprandial; 8% defecation; 3% cough; 3%

swallowing) and 126 with vasovagal syncope (mean age 41 years; 52% female), followed for a mean of 12 months, the mean numbers of recurrences were 0.4 and 0.5 respectively, and no deaths were reported, indicating a benign course in situational syncope (Livanis 2004).

4.4 Orthostatic hypotension

In a prospective study of 650 people who presented to the emergency department with syncope, followed for 18 months, 15% with orthostatic hypotension had at least one episode of recurrence during follow-up (Sarasin 2001).

4.5 Carotid sinus syndrome

4.5.1 Prognosis

In a study of 262 people (mean age 71 years; 70% male) with carotid sinus syncope followed for a mean of 44 months, there was an overall mortality rate of 7.3 per 100 patient-years (cardiovascular 66%; sudden death 9%), which was similar to the standardised mortality rate of the general population (8 per 100 person-years) (Brignole 1992b). The cumulative survival rates at one, three, five and seven years were 92%, 80%, 66% and 53% (Brignole 1992b). Independent predictors of survival were higher age ($p<0.0001$); heart failure ($p=0.019$) and an abnormal ECG ($p=0.046$).

4.5.2 Treatment

The European Society of Cardiology guidelines from 2007 (Task Force 2007) recommend pacing for recurrent syncope caused by inadvertent carotid sinus pressure and reproduced by carotid sinus massage (CSM), associated with ventricular asystole of more than 3 seconds duration, in the absence of medication known to depress sinus node activity.. They also recommend pacing for patients as above but without clear inadvertent carotid sinus pressure.

The use of pacemakers for carotid sinus syncope is reported in chapter 6.

5 Exercise induced syncope

In a study of 33 athletes (mean age 21 years, 61% female) referred for recurrent unexplained episodes of exercise-related syncope and followed up for a mean of 33.5 months, in whom no major cardiac, metabolic or neurological abnormality was revealed on initial evaluation, 67% were tilt-test positive and 33% had at least one recurrence of syncope (Colivicchi 2002). The Kaplan-Meier estimates of first recurrence of exercise-related syncope after 12 months was 9.1%; after 36 months was 24.4% and after 60 months was 42.9%. No other adverse events were noted during follow-up.

6 Unexplained syncope

6.1 Recurrence - prognosis

The recurrence rate for unexplained syncope is usually reported as around 30% per year (Brignole 2006).

In a prospective study of 650 patients who presented to the emergency department with syncope, followed up for 18 months, 15% of those with unexplained syncope had at least one episode of recurrence during follow-up (Sarasin 2001).

In a study of 123 patients with unexplained syncope in the absence of heart disease (mean age 44 years; 52% male), followed up for a mean of 24 months, 15% had at least one recurrent episode of syncope (Gatzoulis 2003).

In another study, 85 patients (mean age 59 years; 52% male) had prolonged monitoring with an implantable event recorder and 73% had recurrent symptoms (of which 25% of events were syncope and 75% pre-syncope; some people had both) during a 12-month follow up (Krahn 2001).

In another study of 43 people (mean age 63 years; 60% female) with unexplained syncope (38), near-syncope (4) or phantom defibrillator shocks (1) who had an implantable event recorder, followed for a mean of 11 months, symptoms recurred in 74% (Mason 2003).

In a study involving 167 patients who underwent prolonged monitoring for unexplained syncope, two thirds of patients had recurrence, of which 90% occurred in the first year (Assar 2003). There was a low risk of syncope if there had been a year of monitoring with an implantable event recorder without an event (92% symptom-free at 2 years) (Assar 2003).

6.2 Death - prognosis

Data from the Framingham study suggest that people with unexplained syncope are 30% more likely to die than patients without syncope (Quinn 2008).

In a study of 55 people (mean age 70 years; 65% male) with unexplained syncope followed for a mean of 44 months, there was an overall mortality rate of 5.8 per 100 patient-years (cardiovascular 82%; sudden death 18%), which was similar to the standardised mortality rate of the general population (8 per 100 person-years) (Brignole 1992b). The cumulative survival rates at one, three, five and seven years were 85%, 80%, 73% and 69% (Brignole 1992b).

In a prospective study of 650 patients who presented to the emergency department with syncope, followed for 18 months, 7% of patients died (Sarasin 2001).

In a study of 329 patients (mean age 70 years; 58% male) with a lone episode of syncope or near syncope and a negative electrophysiological test, followed

In a study of 94 people with unexplained syncope (mean age 61 years; 61% male) who underwent electrophysiological testing, 31 were classified as normal; 37 had intermediate abnormalities of sinus node function or atrioventricular conduction (group 1) and 26 in whom the abnormalities were felt to represent the cause of the syncope (group 2) (Crozier 1988). Specific therapy was instituted in 31 patients: 5 patients in the normal group were paced; 11 in group 1 were paced; 14 in group 2 were paced; and 2 in group 2 had amiodarone. Follow-up for a mean of 52 months revealed recurrent syncope in 37% of the participants and 15% of them died (including 3% sudden death) (Crozier 1988). Mortality was predicted by group 2

abnormalities (p<0.02) and the presence of heart disease (p<0.05); specific therapy did not protect against death.

In a study of 54 people with syncope of unknown origin (34; mean age 37 years; 71% female) or pre-syncope of unknown origin (20; mean age 44 years; 75% female), tilt table testing was positive in 21 people (38%) (Ludovice 2006). People were followed for a mean of 38 months; of the 21 who were tilt-positive, 8 were given general recommendations only (of whom all had remission of symptoms) and 13 received pharmacological treatment (of whom 3 had recurrence of symptoms, 23%). There were no deaths in the study.

7 Multiple potential causes of syncope

In a retrospective cohort study, 987 people with syncope of uncertain cause who were referred for electrophysiological study were assessed (Chen 2003). Ten diagnostic categories were established (bradyarrhythmias; ventricular tachyarrhythmias; supraventricular tachyarrhythmias; hypertrophic cardiomyopathy/long QT syndrome; neurocardiogenic/situational syncope; carotid sinus syncope; cerebrovascular disease; orthostatic hypotension/autonomic dysfunction; others including drug-induced, dehydration and hyperventilation; and unknown aetiology). A person was determined to have multiple potential causes of syncope when more than one diagnostic category was established. At least one cause of syncope was established in 80% of people, including 18.4% who had multiple potential causes. The recurrence rate was around 30-35% over 4 years.

In multivariate analyses, the presence of multiple potential causes was an independent predictor of increased mortality (risk ratio 1.91, 95% CI 1.22 to 2.97, p=0.004), along with age, myocardial infarction, chronic renal failure, atrial fibrillation and diabetes mellitus. The survival rate for people with multiple causes was 89.4% at 1 year compared with 95.2% with a single cause; at 2 years the rates were 83.1% versus 92.9%; and at 4 years, the rates were 73.1% versus 89.3% (p<0.001).

8 Summary table of available data

NB the populations described are not necessarily comparable between those studied under 'natural history' and those studies addressing treatment (e.g. may be different ages/comorbidities).

Condition	Natural history	Natural history altered by:
sick sinus syndrome	ranges from benign sinus brady to sinus arrest or brady-tachy syndrome	Sinus node disease has a generally good prognosis, so **pacemaker** implantation is usually indicated for **symptomatic** rather than prognostic **benefit**.
atrio-ventricular (AV) block	Advanced AV block (Mobitz II/ complete) has a poor prognosis with clear risk of sudden death. **Complete**: 32% of 193 patients (only **22% with syncope**) died within 4 weeks of diagnosis of complete heart block; 44% within 6 months; and 50% at 1 year. 1-year mortality in patients aged 80 years or more 78% versus 43% in those aged 59 years or younger. The *excess* 1-year mortality compared to the age-matched population was 41% in those aged 59 or younger; 42% at ages 60-69 years; 38% at 70-79 years; and 56% at ages 80 years or more.	**Complete block**: **pacing improves survival** especially in patients with syncope In a series of 36 patients with complete heart block treated with a pacemaker, of whom 30 (83%) had a history of syncope, over a mean follow up of 12 months after pacemaker insertion (37 months after onset of syncope), 17% had died; patients with syncope and complete heart block treated medically, 50% of whom had died at 42 months after the onset of syncope (14% per year). Among the patients **with syncope** and complete heart block, 1-year survival 45% versus 58% among patients without syncope. There was no difference in 1-year survival between the patients who had or had not been treated medically (e.g. with atropine, ephedrine or isopropylnoradrenaline). With pacemaker: 17% died at 6 months and no further deaths by 1 year; 19% of these patients died overall (maximum follow up 4.5 years). In a study of 44 patients treated with a pacemaker for heart block 42 had prior syncope and 2 had pacemaker for congestive cardiac failure), survival rates were: 1 year: 81%; 2 years: 78%; 3 years: 72%. All patients had relief of syncope with pacemaker, except 9 who had return of syncope and 19 who had pre-syncope when their pacemaker malfunctioned (e.g. battery failure). The authors compared their results to other published studies of similar patients treated medically, in whom there was a 35% hospital mortality and an additional 15% mortality within 1 year (i.e. total survival 50% at 1 year with medical treatment versus around 80% at 2 years with pacing).

Condition	Natural history	Natural history altered by:
	2nd degree type I: 147 people with chronic Mobitz type I block (45 syncope and/or pre-syncope (i.e. **31% only**); 23 with cardiac symptoms but not TLoC; 58 coincidental); un-paced patients had a worse survival than population norms (20% at 10 years versus 50% at 10 years in the un-paced general population).	**2nd degree type I block: pacing improves survival** in older people and can improve symptoms People with 2nd degree AV block and no evidence of heart disease at a mean follow up of 1395 days, 5/6 people with syncope asymptomatic without a pacemaker, and one who had a pacemaker for recurrent syncope (at day 220 of the study) had syncopal symptoms alleviated by the pacemaker. Among those with heart disease also, at a mean follow up of 1347 days, neither of the 2 patients with pacemakers for syncope had recurrence, although 1 of these 2 patients died with congestive failure. 214 patients (syncope not stated) with 2nd degree AV block (77 **type I block**, mean age 69 years; 86 patients with **type II block**, mean age 74 years; 51 with 2:1 or 3:1 block), five-year survival was **57%**, **61%** and 53%, respectively. In each group, symptomatic patients were paced, and more paced patients than un-paced patients survived. In the Mobitz type I group, 5-year survival for paced patients 78%, similar to age- and sex-matched healthy population versus 42% for the un-paced patients ($p<0.01$). Of 90 patients with chronic Mobitz type I block who had pacemakers; symptomatic bradycardia did not persist in any patient after pacing. The patients with syncope or cardiac symptoms (of whom 81% received a pacemaker) had a survival rate of around 45-50% at 10 years, whereas those with Mobitz type I block as a coincidental finding (36% paced) had a 20% survival at 10 years. None of the patients aged 20–44 years, with or without a pacemaker, died within 14 years, but at 45–64 years and 65–79 years the difference in survival between patients with and without a pacemaker was highly significant ($p=0.001$ and $p=0.003$, respectively). At > 80 years, patients with a pacemaker had a better five year survival than those without (46% versus 33%), but the difference was not significant.

Condition	Natural history	Natural history altered by:
		13 patients with syncope and bifascicular block: 4/5 patients with HV interval 70msec or more or inducible infranodal block had pacemakers; 4/4 with VT had antiarrhythmic therapy and 3/4 with non-diagnostic studies had no therapy (1 had pacemaker). During a mean follow up of 19 months, all but 3 patients were free of syncope (1 later diagnosed with basilar migraine; 1 not taking their medication; 1 sudden death). 93 patients with bifascicular block and unexplained syncope; EPS +ve: 36 distal conduction disease, sick sinus syndrome 6, CSH 2, and sustained VT 1 of whom 42 had pacemaker; 1 had antiarrhythmic drugs, 2 had both: at a mean follow up of 39 months, recurrence occurred in 4% and 47% died (including 5 sudden deaths). EPS –ve: 8 had pacemaker (0% recurrence; 25% died; no sudden deaths). 40 had no specific therapy: 25% recurrence and 35% died (2 sudden deaths).
ventricular tachy-cardia	VT + syncope: 2-year survival rate 76%. Right ventricular outflow tract VT usually good prognosis VT + IHD or HCM high risk	Patients (mean age 58 +/- 13 years) with an **ICD** for cardiac arrest, VT or both: actuarial survival rate free of syncope was 90% at 12 months, 85% at 24 months and 81% at 36 months after implantation Patients with an **ICD** for syncope of unknown origin with sustained VT induced at EPS when drug therapy ineffective, not tolerated, or not preferred: 92% survived at 3.6 years of follow up Patients with life-threatening ventricular arrhythmias (VF cardiac arrest, syncopal VT or symptomatic VT): **ICD** associated with 39%, 27% and 31% reductions in mortality at 1, 2 and 3 years, respectively, compared with antiarrhythmic drug therapy (mainly amiodarone) 2-year survival around 75.7% for patients with VT and syncope (around 50% with **ICD** and 50% with **antiarrhythmic drugs**) Right ventricular outflow tract VT can be treated very effectively with **drugs** or by **radiofrequency ablation**. VT+IHD or HCM requires treatment (e.g. **ICD**) **to reduce risk**.

Condition	Natural history	Natural history altered by:
supra-ventricular tachy-cardia	AF most likely to be associated with TLoC	Ablation? Drugs? Anticoagulation?
Carotid sinus syncope	patients (mean 71 years): mortality rate 7.3/ 100 pt-yrs; similar to general population (8/ 100 pt-yrs); cumulative survival rates at 1, 3, 5 and 7 years 92%, 80%, 66% and 53%	Patients with CSS: after a mean follow-up of 36+/- 10 months, **syncope recurred** in 9% of the **pacemaker** group, compared with 57% in the untreated patients (p<0.0002).
vasovagal syncope	actuarial rates of absence of syncope at 40 months around 60%	**drug therapy** for vasovagal syncope: **atenolol** (1 RCT of 42 patients; at 1 month, those on atenolol 50-100mg daily more likely to have a **negative tilt test** 62% versus 5%, p=0.0004; 71% of the atenolol group versus 29% in the control group reported feeling better after the treatment, p=0.02; patients in atenolol group had number of attacks reduced from 6.0 +/- 9.4 per week to 0.6 +/- 1.6 per week); **enalapril** (1 RCT of 30 patients; **tilt testing** at 1 week **negative** in all 15 patients on enalapril 5mg twice daily versus 3/15 on placebo); **midodrine** (1 crossover RCT of 16 patients for 1 month each; 14 patients had **tilt-induced syncope** on placebo versus 6 on midodrine 5mg three times daily, p=0.01; those on midodrine had 7.3 fewer symptom-days during the treatment month than on placebo, 95% confidence interval (CI) 4.6 to 9; p < 0.0001; 11 patients reported a positive therapeutic response with midodrine versus none on placebo (p = 0.002); and **paroxetine** (1 RCT of 68 patients; 62% on paroxetine 20mg daily had a **negative tilt test** at 1 month versus 38% on placebo, p<0.0001; 18% versus 53% had spontaneous syncope during 2-year follow up, p<0.0001). **Time to first recurrence not different** between patients on **metoprolol** and those on placebo (hazard ratio 0.99, 95% CI 0.69 to 1.43, p=0.97). **Tilt training**: after 1 month, 95.8% of the tilt training group became **tilt negative** compared with 26.1% of the control group (p<0.0001); after follow up for 15-23 months (mean 18.2 months), spontaneous syncope recurred in 0% and 56.5%, respectively, p<0.0001. **Pacing**: **syncope recurred** in 21% of paced patients and 44% of the unpaced patients (p<0.001). Median follow up of 9 months, **syncope recurred** in 9% of paced (burden 0.05 +/- 0.15 episodes per year; actuarial recurrence rate 0% at 3 months, 2% at 6 months, 5% at 12 months and 12% at 24 months) compared with 31% unpaced; 90% relative risk reduction (95% CI 57-98%, p=0.002).

Condition	Natural history	Natural history altered by:
Cardio-myopathy	patients mean age 41 at diagnosis of HCM, followed for mean of 10 years, annual mortality rate for CVD 0.6% and sudden cardiac death 0.1%; cumulative survival rates 97% at 5 yrs; 95% at 10 yrs and 92% at 15 yrs	patients with syncope + heart failure due to non-ischaemic cardiomyopathy; at 22 +/-26 months, hazard ratio for **death** with **ICD** versus **conventional medical therapy** (AF/ frequent non-sustained VT had amiodarone) was 0.46 (95% CI 0.22-0.98); actuarial 2-year survival higher with ICD (84.9% versus 66.9%, p=0.04). At 2 years, actuarial rate of **sudden-death-free survival** 100% with **ICD** versus 78.3% with **conventional treatment**, p=0.05.

9 Excluded studies

Study name	Reason for exclusion
Benditt 1997	fewer than 20 patients with CSS
Bexton 1997	Abstract only; insufficient detail to include (e.g. no length of follow up stated)
Blanc 1995	not our clinical questions
Böhm 1998	not our clinical questions
Bottero 1990	not pacemaker versus none/other intervention/placebo
Brignole 1989	duplicate of Brignole 1988b
Brignole 1990	not pacemaker versus none/other intervention/placebo
Brignole 1991	duplicate of Brignole 1992c
Brignole 1992d	review not primary study
Brignole 2001b	recommendations for treatment not primary study
Brignole 2003	review not primary study
Crilley 1997	not pacemaker versus none/placebo/other treatment
Denes 1985	fewer than 20 patients with carotid sinus hypersensitivity
Gaggioli 1995	not pacemaker versus none/other intervention/placebo
Gersh 1984	not primary study
Girodo 1990	fewer than 20 patients
Homoud 2002	duplicate of Kenny 2001
Karunaratne 2002	fewer than 20 patients
Kay 1988	fewer than 20 patients with carotid sinus hypersensitivity
Kenny 1999	protocol of study only
Kenny 1999b	protocol of study only
Kenny 2001b	duplicate of Kenny 2001
Lagi 1991	not pacemaker versus none/other intervention/placebo
Maggi 2007	fewer than 20 patients with pacemaker
McIntosh 1997	relevant outcomes not reported; 37% drop out from 1 arm of study
Morley 1982	not pacemaker versus none/other intervention/placebo
Nelson 1987	fewer than 20 patients
Nishizaki 1994	fewer than 20 patients
Parry 2009	not syncope
Peretz 1973	fewer than 20 patients
Peretz 1985	not pacemaker versus none/other intervention/placebo
Richardson 2000	duplicate of Kenny 2001
Richardson 2001	thesis - unavailable
Romme 2009	Protocol for review not primary study
Schellack 1986	not pacemaker versus none/other intervention/placebo
Seifer 2003	not syncope
Sgarbossa 1992	Not carotid sinus hypersensitivity
Shaw 1998	not primary study
Simon 1982	fewer than 20 patients with carotid sinus hypersensitivity

Study name	Reason for exclusion
Solomon 1999	review not primary study
Sotti 1980	no usable data
Streian 2006	fewer than 20 patients with pacemaker
Stryjer 1985	not pacemaker versus none/other intervention/placebo
Stryjer 1986	not pacemaker versus none/other intervention/placebo
Sutton 1989	relevant outcomes not reported
Turner 2000	case report only
von Lehe 1971	case report only
von Maur 1972	case report only
Voss 1970	case report only
Walter 1978	fewer than 20 patients
Woie 1973	case report only
Zaman 1983	fewer than 20 patients with syncope

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