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Prevalence and Incidence of Arrhythmias and Sudden Death in Heart Failure

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Abstract. **Patients with heart failure are prone to a variety of arrhythmias, symptomatic and asymptomatic, that are prognostically significant and have an important bearing on the management of these patients. However there are some inherent problems in assessing the frequency of these arrhythmias within a large patient population, due to a lack of uniformity in defining heart failure and the transient nature of these rhythms. Patients with heart failure commonly die suddenly. The causes of these deaths are difficult to ascertain accurately and are often presumed arrhythmic. With the advent of effective interventions to prevent sudden death, accurately defining the causal relationship between the arrhythmias and sudden death has assumed great importance to appropriately target therapy. Several attempts have been made to predict such deaths on the basis of non-invasive and invasive diagnostic investigations with variable success. In this article we review the incidence and prevalence of atrial and ventricular arrhythmias and sudden deaths in epidemiological studies, surveys and randomised control trials of patients with heart failure. We discuss the prognostic significance of these arrhythmias, the inherent problems in their diagnosis and whether their presence predicts the risk of sudden deaths and the mode of such deaths in the heart failure population. The role of various investigations in risk stratification of sudden death has also been discussed**

Key Words. **heart failure, arrhythmia, sudden death, prevalence**

Introduction

Patients with heart failure are prone to a variety of arrhythmias that may have an important bearing on cardiac function, symptoms and prognosis [1–4]. More importantly, clinical trials suggest that treatment directed at arrhythmias can alter the natural history of heart failure, favourably or unfavourably [2,5–8]. Accordingly, when planning services for the management of patients with heart failure it is important to know the prevalence and incidence of the common types of arrhythmia that are likely to be encountered. Ascertaining the prevalence of important arrhythmias in heart failure is not as simple as it might first appear for a number of reasons. The purpose of this article is to review the existing data and some of its limitations and to determine if and how patients can be stratified for their risk of developing a serious arrhythmia so that treatment can be targeted appropriately.

Problems of Defining Heart Failure

There is no universally accepted definition of heart failure. Clinical trials have focussed mainly on patients with left ventricular systolic dysfunction (LVSD), but epidemiological surveys have focussed mainly on clinical symptoms and signs and have not distinguished between patients with and without LVSD [9–12]. Patients in clinical trials with LVSD are, on average, 10–15 years younger than patients in surveys [10,11]. There is a close concordance between the prevalence of heart failure and LVSD in younger patients [13]. However, while the prevalence of heart failure rises steeply beyond the age of 65 years, that of LVSD does not [13]. Identifying the prevalence and incidence of arrhythmias according to age, underlying pathophysiological type (ie systolic versus diastolic) and aetiology (e.g.:- ischaemic heart disease) of heart failure may be important for the proper understanding of the problem [12,13].

Problems of Defining Arrhythmias

The diagnosis of arrhythmias in heart failure may not be accurate either, for several reasons.

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The method for confirming or refuting the presence of atrial fibrillation is often not given in trials and surveys. It is often not clear whether the presence of sinus rhythm or of atrial fibrillation has been confirmed with an ECG. Ventricular arrhythmias are often reported on the basis of a single 24-hour recording. Whilst this duration of monitoring may provide an adequate assessment of the frequency of ectopic beats it may be inadequate for the assessment of more sustained, and therefore presumably more serious, ventricular arrhythmias [14]. It is also unclear how often syncope is due to arrhythmias in patients with heart failure. Syncope has been associated with a poor prognosis in some reports [15–17], but not all [18], whether or not an arrhythmic cause can be identified. Inadequate investigation, problems with the predictive accuracy of electrophysiological tests, lack of adequate follow-up, competing causes for death, interventions (both helpful and harmful) and the fact that syncope is a marker for more advanced disease mean that it is unlikely that the proportion of syncopal events due to arrhythmias in patients with heart failure will be identified accurately in the near future.

Sudden Death and Arrhythmias

However, it is the issue of the relationship between arrhythmias and sudden death that is, perhaps, of greatest concern [19]. Thankfully, for most patients with heart failure, death is not preceded by hours or days of intractable symptoms and signs at rest, although some premonitory worsening of symptoms on exertion is not uncommon. Most of these deaths occur out of hospital, are poorly medically documented and are reported as sudden deaths. Some typical examples that are often reported as sudden death in clinical trials follow:-

a) The patient is found dead in bed in the morning by their spouse who has often been sleeping in the same bed. b) The patient has been left at home while the spouse goes shopping. On their return, the patient is found dead in the kitchen. c) The patient complains of a short period of chest pain or breathlessness. The emergency services are called. When they arrive the patient is in ventricular fibrillation and cannot be resuscitated.

Each of these scenarios is open to interpretation. Case (a) could have been a sleep apnoea induced ventricular arrhythmia or maybe a massive stroke. Case (b) could have been an arrhythmia but maybe the patient choked on their breakfast toast. Case (c) could be almost anything; a myocardial infarction with or without a complicating arrhythmia, ventricular or supraventricular arrhythmia causing chest pain and pulmonary oedema, a ruptured aneurysm, ventricle or mitral valve leaflet.

It is clear that sudden death may be caused by a variety of problems including major arterial vascular events (stroke or myocardial infarction), venous events (pulmonary embolism), organ rupture (ventricle, aorta, valves) and possibly arrhythmias, such as atrial fibrillation [2,19–22] that would be relatively benign if the patient did not have heart failure. In many cases where one of the above has caused sudden death, a secondary, 'opportunistic' arrhythmia will occur although it is not the cause of death. In other cases, a primary event such as myocardial infarction will trigger a lethal arrhythmia and in these cases treatment of the arrhythmia could prevent death and the patient will present with a non-fatal myocardial infarction [2,19].

The proportion of sudden deaths that can be attributed to an arrhythmia, primary or secondary to one of the above, can only really be determined by measuring the impact of a really effective therapy. Clinical trials of implantable cardiac defibrillators suggest that up to half of all sudden deaths in heart failure due to LVSD and secondary to ischaemic heart disease may be due primarily to an arrhythmia [2,5,23]. For other clinical settings we do not know. Although some observational trials have been able to show a reduction in sudden death in patients with heart failure due to dilated cardiomyopathy randomised trials have consistently failed to show a benefit in this population, although the studies have lacked power [2,24].

The proportion of total mortality due to sudden death is influenced greatly by the severity of heart failure and of ventricular dysfunction. As ventricular function and symptoms deteriorate, the risk of all-cause mortality and sudden death both increase, although the proportion of deaths that are sudden declines compared to death due to worsening heart failure (Figs. 1–3) [25–27]. However, it is likely that this is a naïve interpretation of these data. The contribution of arrhythmias to death in patients with advanced symptoms, confined to bed is probably underestimated. Providing that the patients symptoms cannot be improved this may be a welcome release but for patients who have not yet been adequately treated with beta-blockers or who may be amenable to surgery or cardiac resynchronisation, death could still be considered untimely.

It is also possible that the type of ventricular arrhythmia is influenced by the severity of heart failure. The common, initial, haemodynamically-significant arrhythmia in most patients with heart failure is ventricular tachycardia [20]. It has been suggested that brady-arrhythmias may be

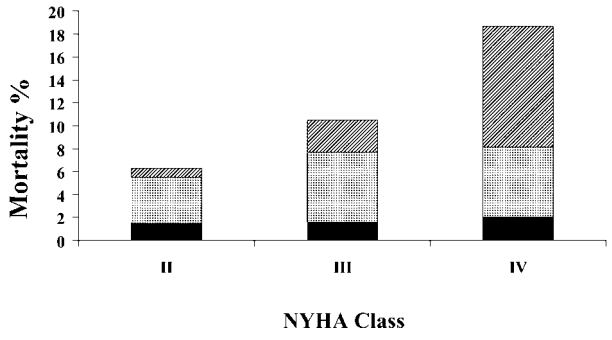

Fig. 1. *Relationship between severity of symptoms and risk of death, all-cause and sudden. (The MERIT-HF study) (based on data in Ref. [25]).* ▨ *Heart failure death,* ▭ *sudden death and* ■ *other.*

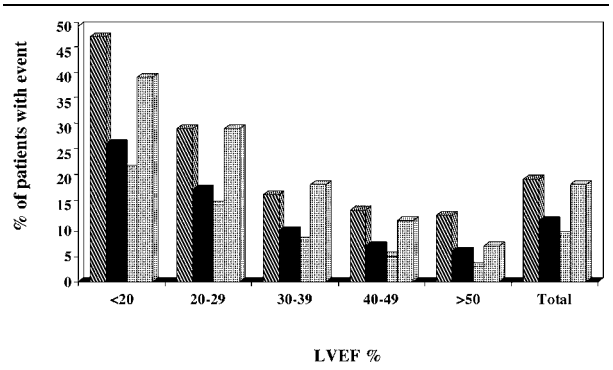

Fig. 2. *Relationship between Left Ventricular Ejection Fraction (LVEF) and risk of death, all-cause and sudden, and worsening heart failure events Data taken from the CAST Study (Based on data in Ref. [27]).* ▧ *Death/cardiac arrest,* ■ *sudden death/arrest,* ▦ *definite CHF events and* ▥ *All CHF events.*

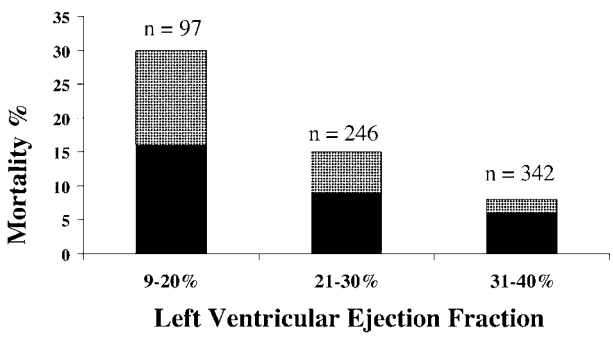

Fig. 3. *Relationship between LVEF and annual mortality, all-cause and sudden (personal communication 2002: JGF Cleland)* ■ *sudden death,* ▩ *non-sudden death.*

a common terminal arrhythmia in severe heart failure, but this may be misleading [28]. Cardiac rupture, pulmonary embolism and delayed discovery of cardiac arrest may all lead to a brady-arrhythmia, but this is an expression of a heart already dead rather than one that can be resuscitated.

Prevalence of Atrial Fibrillation

Epidemiological studies [13,29,30] (Fig. 4), surveys [10,11,31] and randomised controlled trials [4,19,25,32–60] (Fig. 5) all agree that atrial fibrillation is common in patients with heart failure. The prevalence of atrial fibrillation in patients with heart failure is influenced by many factors. Atrial fibrillation appears progressively more common as the severity of heart failure (Fig. 5) and the age [61] of the patients increase (Fig. 6). Atrial fibrillation appears more common in heart failure and in patients with preserved LV systolic function [62–64] (Fig. 7), perhaps because it is a frequent cause of heart failure in such cases and because of greater atrial pressure and distension. Mitral valve disease, especially stenosis, will increase the prevalence dramatically. Some epidemiological studies have suggested that atrial fibrillation may be the sole identifiable cause of heart failure (Fig. 8) [13].

Incidence of Atrial Fibrillation in Patients with Pre-existing Heart Failure and Sinus Rhythm

Limited data exist on the incidence of atrial fibrillation in heart failure. Amongst patients with severe heart failure and LVSD about 4% of patients developed chronic atrial fibrillation in the PRIME-II study each year, compared with an annual placebo mortality of 20.8% [65]. The presence or development of atrial fibrillation was not independently associated with a worse outcome. Older patients were more likely to develop atrial fibrillation but other variables, including severity

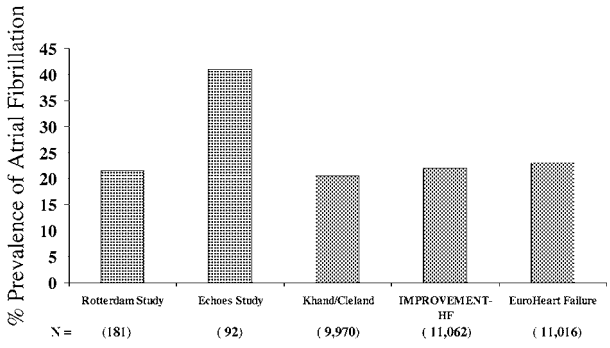

Fig. 4. *Prevalence of chronic atrial fibrillation in epidemiological studies (hatched bars) and surveys (stippled bars) (based on data in Ref. [10,11,13,29–31]).*

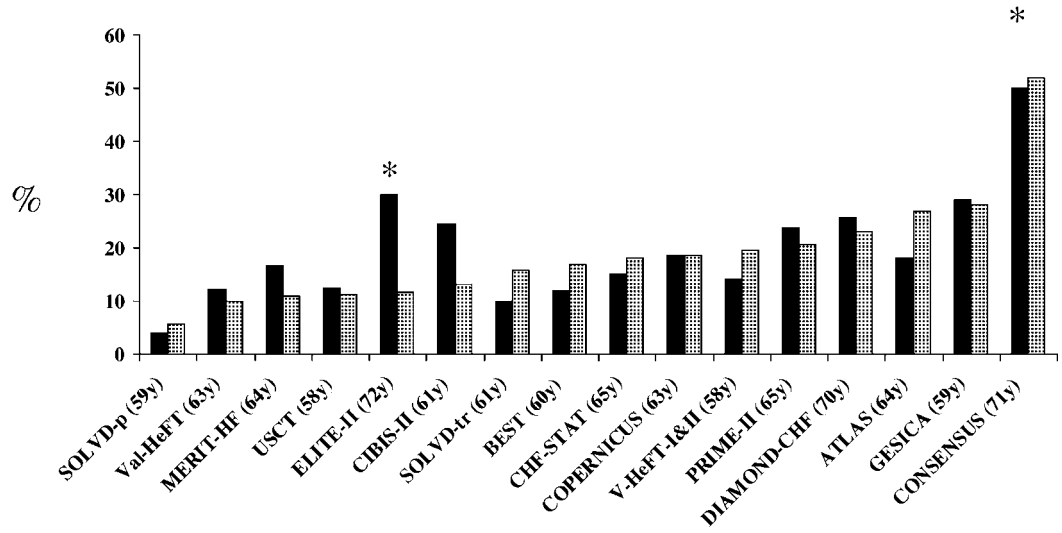

Fig. 5. *Prevalence of atrial fibrillation in pharmacological studies of heart failure ranked according to one year mortality in the placebo group as a marker of the severity of heart failure. Studies marked with a mean age >70 years (based on data in Ref. [4,19,25,32–60]).* ■ *Prevalence AF,* ▦ *Mortality at 1 yr (Placebo or Control).*

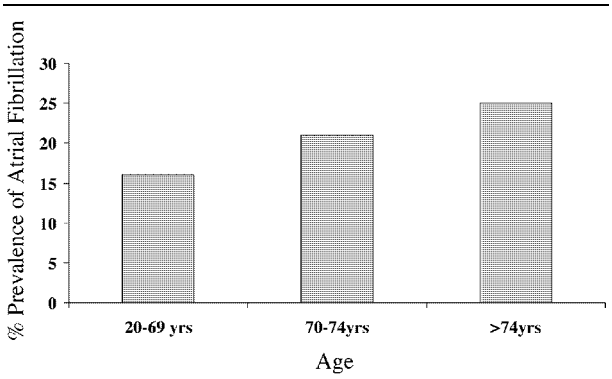

Fig. 6. *Influence of age on the prevalence of atrial fibrillation in patients with heart failure and LVSD: Data from the ATLAS Study (Based on data in Ref. [61]).*

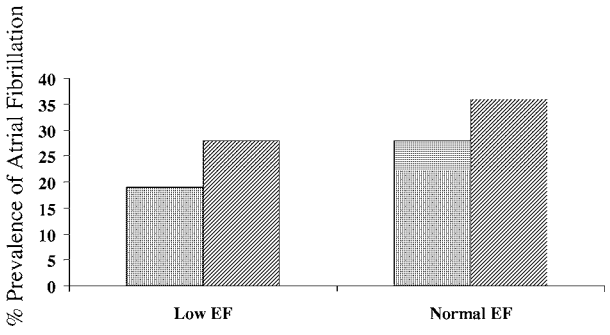

Fig. 7. *Prevalence of atrial fibrillation in patients with heart failure with and without LVSD (all studies shown included >200 patients. Based on data in Ref. [62,64]).* ⌴ *Andersson et al. (1995) and* ▨ *McAlister et al. (1999). Andersson et al.: Mean LVEF in low and high EF group 27% v 52% respectively.*

of heart failure and ejection fraction were poor predictors.

In an observational study of 344 patients, Pozzoli et al. [66] found that about 5% of patients (mean age 54 years) developed atrial fibrillation annually compared to an annual mortality or need for transplant of about 20%. Development of atrial fibrillation was associated with worsening symptoms and an increased risk of arterial occlusive events. Non-invasive and invasive investigations were of little help in identifying the risk of atrial fibrillation although paroxysmal atrial fibrillation predicted the development of chronic atrial fibrillation as well as declining atrial contractility.

In the DIG study [51], just over 1% of patients were hospitalised each year with an SVT compared to an annual mortality of 10%. In the ATLAS study [18] about 1.5% of patients were hospitalised with SVT each year compared to an average annual mortality of about 10% (although mortality in the first year was >25%). In the SHIPS survey [31], subsequent to surviving a first hospital admission with heart failure, the annual rate of re-admission with atrial fibrillation was 5.3%.

Prevalence of Complex Asymptomatic Ventricular Arrhythmias

Ventricular extrasystoles (VES) are a near universal finding in patients with heart failure and left ventricular systolic dysfunction [67], while over half will have ≥10 VES per hour [3,4,39,40,53,57,67–70] or complex ventricular arrhythmias including couplets or non-sustained

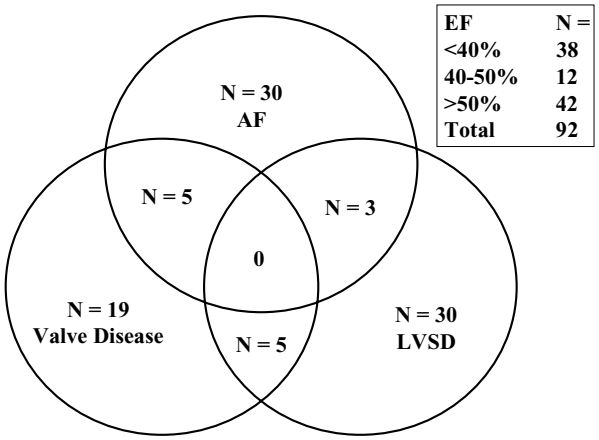

Fig. 8. *Contribution of left ventricular systolic dysfunction (LVSD), valve disease and atrial fibrillation (AF) to heart failure (based on data in Ref. [13]).*

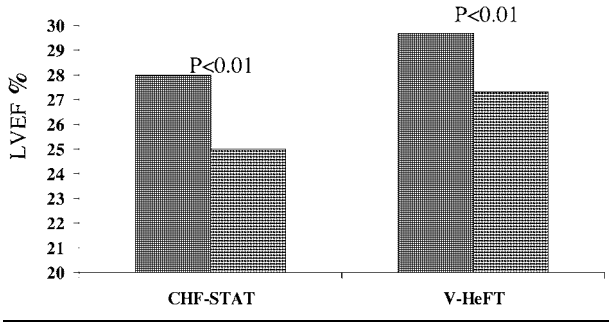

Fig. 10. *Left ventricular ejection fraction in patients with and without NSVT on Holter monitoring (based on data in Ref. [4,39,40,53]).* ⌴ *NSVT− and* ▨ *NSVT+.*

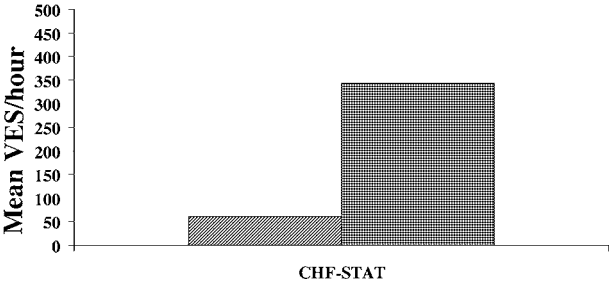

Fig. 11. *Density of ventricular extrasystoles in patients with and without NSVT on Holter monitoring (based on data in Ref. [53]).* ▨ *NSVT− and* ▪ *NSVT+.*

ventricular tachycardia (Fig. 9) in the absence of treatment with a beta-blocker or amiodarone. Patients with more severe LVSD and frequent VES are more likely to have complex arrhythmias including NSVT [3,4,39,40,53,68] (Figs. 10 and 11). The symptomatic severity and aetiology of heart failure and age appear a poor guides to the presence of complex ventricular arrhythmias (Fig. 12).

Complex ventricular arrhythmias indicate a higher risk of death but whether they predict the mode of death in patients with heart failure, as adjudicated by an end-points committee, remains controversial [3,4,39,40,53,57,68–70]. Lack of predictive power in some studies may be a genuine observation, reflect the inaccuracies of end-point adjudication or be due to the confounding effect of competing modes of death. Interrogation of the arrhythmia data collected by implantable defibrillators may help inform this issue.

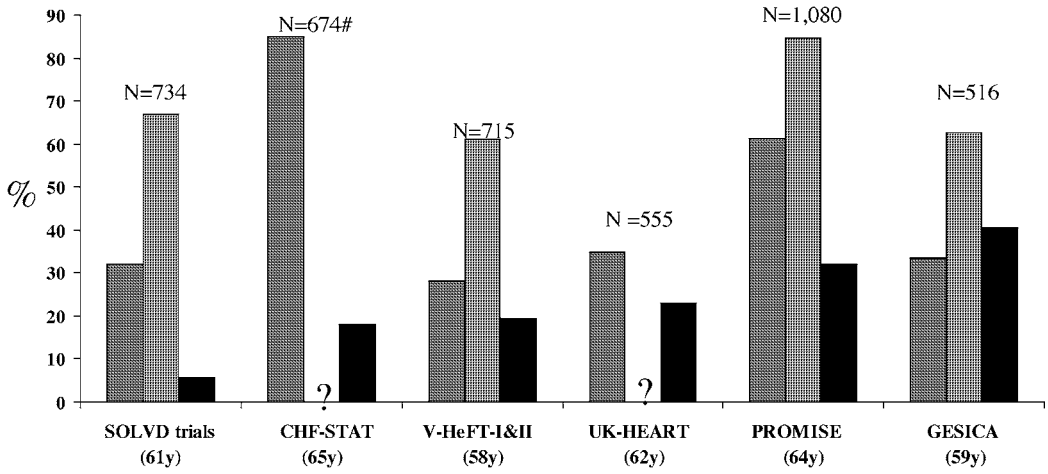

Fig. 9. *Prevalence of complex ventricular arrhythmias in pharmacological studies of heart failure ranked according to one year mortality in the placebo group as a marker of the severity of heart failure (based on data in Ref. [3,4,39,40,53,55,57,68–70])* ⌴ *Prevalence of NSVT,* ▨ *Prevalence of couplets or >30 VES/hr and* ■ *Mortality at 1 yr (Placebo). # Patients had to have ≥10 ventricular extrasystoles per hour on ambulatory monitoring to be eligible for recruitment. This may have eliminated up to 50% of patients at screening. ? data not given in the manuscript.*

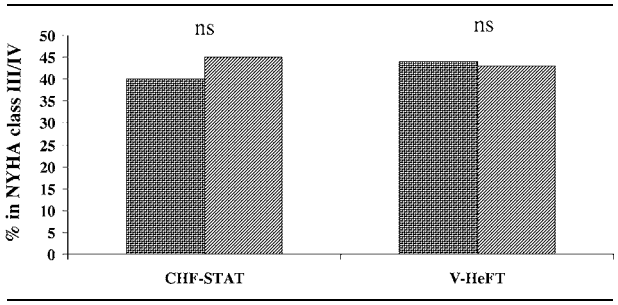

Fig. 12. *Proportion of patients in NYHA class III/IV (versus Class II) in patients with and without NSVT on Holter monitoring (based on data in Ref. [4,39,40,53]).* ▦ *NSVT− and* ▨ *NSVT+.*

Incidence of Complex Asymptomatic Ventricular Arrhythmias

The SOLVD study reported that about 17% of patients who had no baseline NSVT would have NSVT on repeated ambulatory ECG monitoring [67]. Senges et al. [14] carried out 24-hour ECG monitoring at weekly intervals on 3 occasions in patients with heart failure subsequent to a myocardial infarction. NSVT was identified on at least one recording in 41% of cases. Of these cases, NSVT was observed in only one recording in 50%, two recordings in 39% and in all three recordings in only 11%. NSVT was not observed if two prior 24 hour recordings had been negative. However, this study is too small to show that 48 hours of recording is sufficient to exclude NSVT. The V-HeFT and CHF-STAT studies reported that although the mean prevalence of NSVT was fairly stable over time, over 50% of patients changed category (ie NSVT developed or was not apparent on re-testing) [4,39,40,53,68]. Although this could represent a real variation in the prevalence of NSVT over time it is likely also to reflect a substantial sampling error which reduces the value of NSVT as a marker of risk.

Because VES are much more frequent events than NSVT, sampling error is greatly reduced, which is why frequent VES may perform as well as, or better than, NSVT as a risk marker [39,71]. It is likely that the true prevalence of NSVT is underestimated by 24 hour ambulatory monitoring. Extended monitoring would reveal a higher incidence and prevalence but is impractical using non-invasive technology. Implanted devices with the ability to record arrhythmias overcome some of these limitations but currently remain, largely, a research tool. The increasing use of implantable pacing and defibrillator devices that record information on heart rhythm is likely to lead to improved understanding of the clinical relevance of NSVT and other asymptomatic arrhythmias.

There is evidence of a diurnal variation in the incidence of malignant ventricular arrhythmias with a nadir between midnight and 6 am and peak between 9 am and noon. Diurnal variation is especially marked in patients without severe left ventricular systolic dysfunction (EF > 20%) but tends to be lost in those with very poor function [72].

Incidence of Cardiac Arrest or Sustained Ventricular Tachycardia

Few data are available with which to judge the frequency at which patients with chronic heart failure present with a cardiac arrest or symptomatic ventricular tachycardia. Many such events may be rapidly fatal and simply reported as sudden death.

The DIG study reported an annual risk of hospitalisation for cardiac arrest or ventricular arrhythmia of about 1%, which was not affected by digoxin [51]. Only 20 of 338 patients assigned to placebo in CHF-STAT reported a symptomatic ventricular arrhythmia during 4 years of follow-up [53,68]. The PRAISE-1 study reported non-fatal sustained ventricular tachycardia or fibrillation in only 3% of patients [43].

The ATLAS study [18] reported that 173 of 3,164 (5.5%) patients were hospitalised with ventricular tachycardia, 119 (3.8%) with syncope and 108 (3.4%) with a cardiac arrest over 4 years of follow-up. Overall mortality was 42.5%, while 30-day mortality in the above groups was 27%, 5% and 78% respectively, compared to a 30-day mortality from all admissions of 31.7%.

The SHIPS survey [31] reported that only 217 of 9,718 patients surviving a first hospital admission with heart failure were subsequently readmitted with ventricular fibrillation or a cardiac arrest.

Overall, the risk of a patient with heart failure being admitted with a malignant ventricular arrhythmia appear small probably because few patients with such arrhythmias survive to reach hospital.

Prevalence and Incidence of Brady-arrhythmias

Only 23 of 6,800 patients randomised in the DIG study were admitted to hospital for the treatment of atrio-ventricular block or brady-arrhythmia over 3 years of follow-up [51]. This will almost certainly have increased somewhat with the advent of beta-blockers but still appear to be an uncommon event. Only 16 of 1,990 patients were withdrawn from metoprolol because of bradycardia in the MERIT-HF study [10,25,73]. The EuroHeart Failure study [10] indicated that 6% of patients with a heart failure related admission also had bradycardia about half of whom required

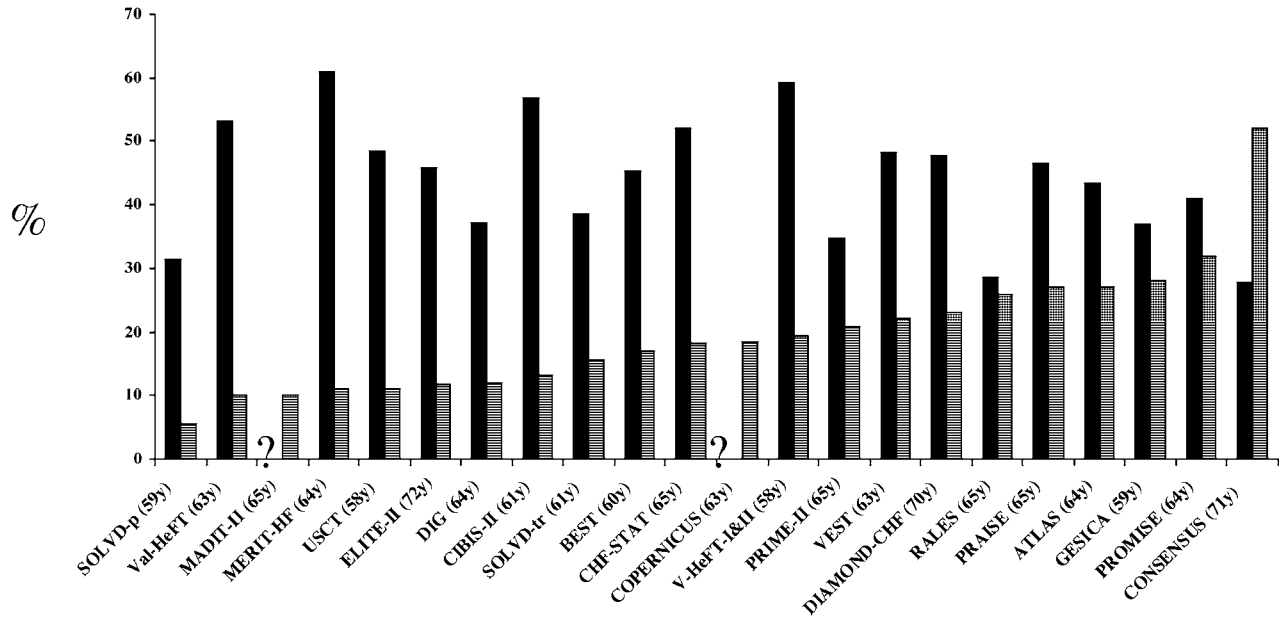

Fig. 13. *Percent of deaths that were sudden plotted against annual mortality. Note sudden deaths include sudden death with premonitory worsening of symptoms. Hydrallazine/nitrate groups reported from V-HefT I&II, in CIBIS II data include deaths of unknown cause, SOLVD-treatment data are taken from EJHF (based on data in Ref. [4,18,19,25,32–60]).* ■ *Sudden death as % of all deaths and* □ *mortality at 1 yr (placebo or control). ? data not given in manuscript.*

a permanent pacemaker insertion. Over 8% of this population ($n = 11{,}016$) had a pacemaker implanted and the clinical course was complicated by a brady-arrhythmia in about one in six patients. As discussed above, it is uncertain whether death due to brady-arrhythmias makes an important contribution to sudden death in patients with heart failure [28].

Incidence of Sudden Death

Most clinical trials of heart failure suggest that sudden death is the commonest mode of death (Fig. 13). A summary of the mode of death reported in large clinical trials is shown in Tables 1–4 [4,18,19,25,32–60]. Despite the fact that ACE inhibitors and beta-blockers reduce the risk of

Table 1. *Prevalence of sudden cardiac death in some of the randomised controlled trials of ACE inhibitors*

Trial	NYHA[a]	LVEF[b] (%) (mean)	Mean follow up (months)	Drugs	*n*	Total mortality[c] (%)	CVS mortality[c] (%)	SCD mortality	SCD mortality[c] (%)
CONSENSUS [56]	IV	NA	6.3	Enalapril	127	39.37	34.65	14	11.02
				Placebo	126	53.97	50.79	14	11.11
SOLVD [33] (treatment)	I–IV 56.7% II	24.8	41.4	Enalapril	1285	35.18	31.05	105	8.17 (12.9)[d]
				Placebo	1284	39.72	35.90	113	8.80 (15.3)[d]
V-HeFT II [37]	II–III	29	30	Enalapril	403	37.96	27.79	41	10.1
				Hydralazine/ ISMN	401	32.91	34.16	63	15.7
SOLVD [32] (prevention)	I–II 60% in I	28	37	Enalapril	2111	14.83	12.55	98	4.64
				Placebo	2117	15.78	14.08	105	4.96
ATLAS [18,44,61]	II–IV 77% in III	23	48	Lisinopril (low dose)	1596	44.92	40.16	Variable[e]	Variable[e]
				Lisinopril (high dose)	1568	42.47	37.18		

[a]New York Heart Association class.

[b]Left ventricular ejection fraction.

[c]As a % of the total numbers enrolled.

[d] Sudden death including those that showed some premonitory worsening.

[e]25% among 171 autopsied patients and 45% among the 1212 non-autopsied patients.

Table 2. *Prevalence of sudden cardiac death in some of the randomised controlled trials of beta-blockers*

Trial	NYHA[a]	LVEF[b] (%) (mean)	Mean follow up (months)	Drugs	*n*	Total mortality[c] (%)	CVS mortality[c] (%)	SCD mortality	SCD mortality[c] (%)
MERIT-HF [25,73]	II–III (55.5% III)	28	12	Metoprolol CR/XL	1990	7.29	6.43	79	3.97
				Placebo	2001	10.84	10.14	132	6.60
CIBIS II [52]	III–IV (83% III)	27.6	15.6	Bisoprolol	1327	11.76	8.97	48	3.62
				Placebo	1320	17.27	12.20	83	6.29
US CARVEDILOL [42]	II–IV (53% II)	23	6	Carvedilol	696	3.16	2.87	12	1.72
				Placebo	398	7.79	7.79	15	3.77
COPERNICUS [45]	IIIB–IV	19.8	10.4	Carvedilol	1156	11.25	NA	NA	NA
				Placebo	1133	16.77			
BEST [60]	III	24	24	Bucindolol	1354	30	25.26	182	13.44
				Placebo	1354	33	28.73	203	14.99

[a]New York Heart Association class.
[b]Left ventricular ejection fraction.
[c]As a % of the total numbers enrolled.
NA: Not available.

Table 3. *Prevalence of sudden cardiac death in some other randomised controlled trials*

Trials	NYHA[a]	LVEF[b] (%) (mean)	Mean follow up (months)	Drug	*n*	Total mortality[c] (%)	CVS mortality[c] (%)	SCD mortality	SCD mortality[c] (%)
V-HeFT I [36]	NA	<45	27.6	Prazosin	183	49.7	45.9	39	21.3
				Hydralazine/ISMN	186	38.7	37.63	32	17.2
				Placebo	273	43.96	41.39	53	19.41
Val-HeFT [34]	II–IV 62% II	26.8	23	Valsartan	2511	19.71	15.13	262 (+16[d])	10.43[e]
				Placebo	2499	19.37	15.33	258 (+26[d])	10.32[e]
ELITE II [50]	II–IV 52% II	31	18	Losartan	1578	17.74	14.58	130 (+12[d])	8.24[e]
				Captopril	1574	15.88	12.64	101 (+14[d])	6.42[e]
RALES [49]	III–IV 70% in III	25.4	24	Spironolactone	822	34.55	27.49	82	9.98
				Placebo	841	45.90	37.34	110	13.08
DIG [51]	I–IV 54% II	28.5	37	Digoxin	3397	34.77	29.91	NA	NA
				Placebo	3404	35.08	29.49	NA	NA
PRAISE [43]	III–IV 81% in III	21	13.8[f]	Amlodipine	571	33.3	29.9	81	14.2
				Placebo	582	38.3	33.8	104	17.87
PROMISE [41]	III–IV 58% in III	21	6.1[f]	Milrinone	561	30	29.4	NA	NA
				Placebo	527	24	22.6		
PRIME II [54]	III–IV 68% in III	23	11.8	Ibopamine	953	24.3	22.2	69	7.2
				Placebo	953	20.3	18.3	46	4.8
VEST [47]	III–IV	20.9	9.5	Vesnarinone (high dose)	1275	22.9	21.3	157	12.3
				Vesnarinone (low dose)	1275	21	19.5	136	10.7
				Placebo	1283	18.9	18	117	9.1

[a]New York Heart Association functional class.
[b]Left ventricular ejection fraction.
[c]% of the total numbers enrolled in each category.
[d] Resuscitated arrests.
[e]Resuscitated arrests are not included in the calculations.
[f]Median follow up.
NA: Not available.

sudden death, this mode of death remains the most frequent in patients on modern medical therapy. As discussed above, this covers a range of processes from instantaneous death in a 'well' individual, to patients who have symptoms on minor exertion but who are relatively stable, to patients who develop a rapid worsening of symptoms over minutes or hours. Also, some studies report

Table 4. *Prevalence of sudden cardiac death in randomised control trials of anti-arryhthmic interventions*

Trials	NYHA[a]	LVEF[b] (%) (mean)	Mean follow up (months)	Drug	*n*	Total mortality[c] (%)	CVS mortality[c] (%)	SCD mortality	SCD mortality[c] (%)
CABE-PATCH [101,102]	II–III	27	42	ICD	446	22.9	17.0	15	3.4
				Control	454	21.1	17.4	28	6.2
MADIT II [5]	I–III	23	20	ICD	742	14.2	NA	NA	NA
				Control	490	19.8	NA	NA	NA
CHF-STAT [53,68]	II–III	26.5	45	Amiodarone	336	39	32.4	64	19.04
				Placebo	338	42.3	35.2	75	22.18
GESICA [55]	II–IV	18.2	24	Amiodarone	260	33.46	29.61	41	15.76
				Placebo	256	41.4	35.15	30	11.7
DIAMOND-CHF [58,59]	II–III	0.9[d]	18	Dofetilide	762	40.81	33.46	156	20.47
				Placebo	756	41.9	33.2	151	20.0

[a]New York Heart Association functional class.
[b]Left ventricular ejection fraction.
[c] % of the total numbers enrolled in each category.
[d] Wall motion Index.
NA: Not available.

myocardial infarction as a mode of death. The proportion of infarct deaths that are primarily sudden and potentially arrhythmic versus those due to cardiogenic shock and pump failure is uncertain. Overall, the proportion of sudden deaths that have an important treatable arrhythmic component is unclear but trials of implantable defibrillators suggest about 50% [2,23].

Few substantial epidemiological study or community surveys have reported the mode of death in patients with heart failure. A 4-year follow-up of 181 patients with heart failure identified in a community survey identified 55 deaths of which 15 (27%) were reported to be sudden, giving an incidence of 2.5% per year [30]. Diabetes, ECG evidence of myocardial infarction or hypertrophy, greater QT dispersion and T-wave abnormalities all indicated a higher risk of sudden death as did echocardiographic evidence of left ventricular systolic dysfunction. The Framingham study suggested that 50% of deaths among patients with the new appearance of heart failure will be sudden [74]. Croft et al. [75] reported that among U.S. Medicare patients with a first hospitalisation for heart failure in 1986, 33% of all deaths were sudden.

Khand et al. [31] reported that of 9,718 patients who survived a first hospital admission for heart failure 4,877 (50.2%) died over the following 3 years, of which 2,087 (42.8%) deaths occurred out of hospital. Clinical trials suggest that most out of hospital deaths are considered to be sudden by endpoint committees, although a substantial number of in-patient deaths may also be considered sudden [18,76].

Risk Stratification for Sudden Death

Risk stratification for all-cause mortality has recently been extensively reviewed [77]. Greater age, severity of cardiac dysfunction (especially LV systolic dysfunction) and severity of heart failure symptoms as well as lower arterial pressure and serum sodium concentration are simple clinical markers for an increased risk of death. However, these factors have little specificity for the mode of death. Sicker patients are relatively more likely to die of worsening heart failure but also have an absolute increase in the risk of sudden death [27]. The following have been considered at some time useful for predicting a high risk of sudden death.

Syncope

It has been suggested that syncope is an ominous symptom [15,16,78] whether or not it is associated with an identified arrhythmia. Some studies suggest that these patients are at a high risk of sudden death [16] although this has not been confirmed by other reports [18]. One observational study suggested that patients with heart failure and syncope benefited from an ICD even if an arrhythmic cause could not be identified [17].

Ventricular Arrhythmias

A documented history of severe ventricular arrhythmias carries an adverse prognosis [79]. In patients with heart failure who have survived a cardiac arrest prognosis may be especially poor if it was preceded by acute pulmonary oedema or drug-induced torsades [80]. There is good evidence that

defibrillators are effective in reducing mortality in this relatively small subgroup of patients [2].

A high frequency of ventricular ectopics, ventricular couplets or non-sustained ventricular tachycardia on Holter monitoring indicate a worse prognosis in most [3,4,39,40,53,57,67–71,81–85] but not all [86] studies. Longer runs of ventricular tachycardia also indicate a worse outcome [83]. Whether arrhythmias predict the mode of death is disputed [3,4,39,40,53,57,67–70,82,87] and they may merely reflect the severity of ventricular dysfunction. The aetiology of heart failure may affect the predictive power of arrhythmias [88]. Patients with coronary disease have a worse overall prognosis than patients with heart failure due to other aetiologies and coronary disease tends to increase the risk of sudden death [18].

A number of substantial multi-centre trials have reported their findings. Ambulatory ECG monitoring was carried out for only 4 hours in the V-HeFT trials. In VHeFT-I, ventricular arrhythmias were associated with a worse overall mortality and higher risk of sudden death on a univariate analysis, but on multivariate analysis only the latter association persisted [4,40]. In VHeFT-II, arrhythmias were also univariate predictors of all deaths and sudden deaths but on multivariate analysis the latter association did not persist [4,39,40]. This may have been due to a reduction in the risk of arrhythmias with the ACE inhibitor, enalapril. In the PROMISE trial the presence of non-sustained or sustained (>10 beats) ventricular tachycardia predicted cardiovascular death but did not predict sudden death [3], although exacerbation of arrhythmias by milrinone did predict sudden death [89]. The GESICA study [57] suggested that NSVT and couplets predicted specifically an increased risk of sudden death but the CHF-STAT study suggested that after adjusting for the severity of cardiac dysfunction, it did not [53].

Signal-Averaged Electrocardiogram (SAECG)

The SAECG is not of established clinical value for risk stratification in heart failure. Whether abnormalities of the SAECG indicate an increased risk of sustained ventricular arrhythmias and/or death, particularly sudden death, in patients with DCM [90–96] or CHF due to IHD [93,95] is disputed. Some studies have noted a high specificity of some indices but low sensitivity [93,97] others that an abnormal SAECG predicts sustained ventricular tachycardia but not prognosis [98] or an increased risk of worsening heart failure [99] or that a normal SAECG may identify a low-risk group but that an abnormal test is of little value [100]. The SAECG failed to identify patients who might benefit from an implantable defibrillator in the CABG-PATCH study [101,102]. The presence of bundle branch block appears to detract from the little prognostic value that late potentials have in heart failure [90,103,104].

QT Dispersion

QT dispersion is another proposed method of stratifying risk in CHF although this cannot be evaluated properly in atrial fibrillation or bundle branch block. Studies supporting [30,105–108] and refuting [109–111] the usefulness of this measure exist. One report suggested that the dispersion of the heart rate corrected JT interval (JTc-d) had over a 90% sensitivity and specificity for predicting sudden death or serious ventricular arrhythmias [112]. Only arterial pressure added to the predictive value of JTc-d for all cause mortality.

Electrophysiological Provocation of Arrhythmias

Formal electrophysiological (EP) studies have been disappointing as a means of stratifying risk in heart failure patients. The ability to induce ventricular tachycardia by programmed ventricular stimulation does not reliably predict a worse prognosis or an increased risk of sudden death [96,113–116]. The largest study to have addressed this issue so far, the MUSTT study, suggested that 2 and 5 year all-cause mortality of patients with LVSD subsequent to a myocardial infarction were no different in patients with and without inducible ventricular tachycardia, although there was a 25–30% increased risk of cardiac arrest or sudden death in those with a positive test [117,118]. The sensitivity of the EP test may be particularly low in patients with dilated cardiomyopathy [116,119], even if the patient has already had a cardiac arrest [119]. One study suggested that an abnormal SAECG and inducible arrhythmias indicate an increased risk of serious arrhythmias or sudden death with a positive predictive value of 50% [120] but this was not supported by another [96]. There is little evidence of a clinically useful role for ventricular stimulation studies in patients with heart failure according to current knowledge.

Summary

The advent of proven, effective interventions to prevent sudden death is likely to stimulate further attempts at risk stratification in order to target the use of implantable defibrillators, which

are costly and have an associated morbidity. Several simple measurements may be more useful than one complex one. However, only about half of sudden deaths are arrhythmic, therefore it is unlikely that conventional strategies to determine risk will be very effective in targeting which patients require an implantable defibrillators. The main argument for risk stratification is to target treatment more effectively and so it is likely that the important advances in risk stratification will come from populations who have had a device implanted, with risk stratification worked out 'retrospectively' and then applied prospectively to the population. In addition, once in a life-time risk stratification is clearly inappropriate. The frequency with which risk should be assessed has yet to be determined.

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