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Mode of death in chronic heart failure

A request and proposition for more accurate classification

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The proportion of patients reported to die suddenly or from progressive circulatory failure is not consistent among studies of heart failure. Lack of an adequate or consistent classification of how patients die contributes to the current confusion over the mode of death in heart failure. Defining how patients with heart failure die could be important in developing strategies to reduce the continuing high mortality associated with this condition.

We identified 27 studies that reported 50 or more deaths among patients with heart failure to ascertain how death was classified. Definitions of sudden death appeared heterogeneous and the majority of studies failed to publish or make reference to how circulatory failure was defined.

A framework for the classification of the mode of death has been developed in which clear separation of the activity and place at the time of death, cause of death, mode of death, and events prior to death is made (ACME: Activity, Cause, Mode and Event). This mode of classifying death has been successfully piloted in two mortality studies; AIRE and NETWORK.

Classifying mortality in this way will help identify pathways leading to death and hence suggest therapies and strategies to reduce mortality in patients with heart failure, a group of patients whose prognosis remains poor.
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Key Words: Heart failure, mode of death, clinical trials.

Introduction

Studies of chronic heart failure reported over the last 60 years[1–8] have emphasized the poor prognosis of the condition, at least when left ventricular systolic dysfunction is the cause. Recent clinical trials have also demonstrated that angiotensin-converting enzyme inhibitors, and possibly some other vasodilators, can improve prognosis[3,9]. Although there is no dispute about the overall effects of ACE inhibitor therapy on prognosis there is considerable disagreement between studies as to the proportion of patients that die suddenly and the effects of treatment on the relative likelihood of sudden death or death due to circulatory failure.

The reason for these differences are unclear but may relate more to varying definitions rather than real differences between study populations. In the present overview we have identified studies of chronic heart failure that have recorded more than 50 deaths to identify how many studies had defined what was meant by sudden (cardiac) death and death due to circulatory failure. Analysis of the problems of classifying the mode of death was used to generate a new system for classification of death in cardiovascular trials.

Methods

MEDLINE and Current Contents databases and reference lists of relevant papers were reviewed to identify studies reporting more than 50 deaths due to chronic heart failure. MEDLINE was interrogated using the key words 'death' or 'deaths' or 'survival' or 'mortality' and combined with 'heart failure' or 'cardiac failure' or 'ventricular dysfunction'. Five hundred and ninety three studies published before February 1995 were identified using these methods. The abstract of each publication was read to identify original studies that could have reported more than 50 deaths. All relevant papers were then read in full to identify if they should be included.

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Only studies of patients with treated, symptomatic chronic heart failure have been included in the present overview. Studies of patients with asymptomatic or untreated left ventricular dysfunction e.g. the SOLVD prevention trial, have not been included. Similarly studies of new-onset heart failure, defined as heart failure of less than one month's duration, such as the AIRE trial, have not been included. Studies that did not report the mode of death, for example the PROMISE trial[6] and others[10], were also excluded. Where a series of reports derived from the same author or institution within a 5 year period only the last report was accepted[3,15,31–33].

The studies selected for this report were reviewed with regards to the number of patients studied, inclusion criteria, duration of follow-up, number of deaths and the mode of death. The various categories used for classifying the mode of death were noted and the definitions of sudden death and death due to circulatory failure were recorded. The data were pooled to determine the proportions of patients reported to die suddenly or with circulatory failure. Average values have been presented as mean ± 1 SD.

Results

Twenty seven studies were identified according to the above criteria[11–37]. These studies are detailed in Table 1. Most of the studies included patients with chronic heart failure due to various aetiologies including ischaemic heart disease, dilated cardiomyopathy, alcoholic heart muscle disease, hypertensive heart disease or valvular heart disease. Rockman *et al.*[23] included only patients with coronary artery disease, while patients with severe valvular heart disease were excluded in the SOLVD trial[1]. Three studies included only patients with dilated cardiomyopathy[19,21,35]. Most studies included patients of any age group, but the VHeFT trials and Madsen *et al.*[3,4,36] excluded patients older than 75 years and the SOLVD trial did not include patients over 80 years of age. On the other hand, Bedford *et al.* and Taffet *et al.*[11,28] excluded patients who were younger than 65 years and 75 years, respectively. The VHeFT trials, Franciosa *et al.* and Taffet *et al.*[3,4,12,28] evaluated only men while all other trials recruited both men and women, though overall 79% of patients were men. The patients included were in NYHA class II–IV. Some studies included patients with severe chronic heart failure only (NYHA class III–IV)[2,11,16,23–25,29,34,37]. Average left ventricular ejection fraction was reported in 17 studies, and the overall mean was 25% (SD 5%). The mean follow-up was recorded in 22 studies (overall mean 26 ± 21 months). These studies taken together evaluated 10 137 patients, and the total number of deaths was 3909, giving an overall mortality of 38·6%.

Most studies used categories that could be equated with sudden death and death due to circulatory failure, in addition to other causes. The categories and definitions used in studies recording more than 100 deaths are given in Table 2 (data for other studies are available from the authors on request). Deaths due to 'arrhythmias without worsening of heart failure' were reported by the SOLVD group and represent a subset of patients dying suddenly. Deaths due to 'heart failure or arrhythmias with heart failure' were also reported in SOLVD but these deaths cannot be easily classified as sudden or due to circulatory failure. Accordingly pooled data are shown with and without the SOLVD data including the latter group as circulatory deaths (Table 3).

The term sudden death was not defined further in four studies[14,21,22,35] and was only defined as 'unexpected' in another four studies[16,25,27,28]. The definition of sudden death was heterogeneous. Nine studies used the term sudden to mean instantaneous death in a patient without severe or worsening heart failure. Three of these studies specified that sudden death could be recorded only if no new symptoms or worsening of heart failure had been reported in the 24 h prior to death[13,18,20]. Thirteen studies used a time period between the onset of new symptoms and death to define sudden death. This time period varied from 15 min[31,33] to 24 h[12,30]. Death was recorded as sudden if it occurred within 1 h of the onset of new symptoms in the CONSENSUS trial and as rapid if occurring between 1 and 24 h of onset of new symptoms. The VHeFT trials used an intermediate category of 'sudden death with some premonitory signs of worsening heart failure'.

A term that could be equated with death due to circulatory failure was defined more precisely in only nine of the 27 studies[3,4,11,23,25–28,31,33,36]. Two studies indicated that death due to circulatory failure should be accompanied by a low cardiac output[24,25] though this was not often formally measured. Three[11,23,28] studies reported that symptoms resistant to therapy had to be present though did not specify the severity of symptoms required. Only one study[31,33] specified that shock or pulmonary oedema had to be present.

Eight studies used a separate category for death subsequent to myocardial infarction, an event occurring prior to death rather than a mode or cause of death, but no study defined the mode (e.g. shock, arrhythmia etc.) or cause (e.g. myocardial rupture) of death subsequent to infarction. Death occurring during sleep was recorded in four studies and was assumed to be sudden in all[24,29,31,34]. Unwitnessed deaths were recorded in a further five studies and were assumed to be sudden in all[3,4,18,24,36].

Studies were categorized according to how 'sudden' death was defined: instantaneous death or death occurring within 15 min (Table 4(a)), deaths occurring within 1 h of onset of new symptoms (Table 4(b)), deaths occurring within 6 h or within 24 h of onset of new symptoms (Table 4(c)), and studies which defined sudden death only as an 'unexpected' death or where the definition was not available (Table 4(d)). Data in Table 4(a) are presented with and without the SOLVD data (see above).

Table 1 Studies included in the present overview

Study	No. of patients	No. of deaths (% of total patients)	Duration of follow-up	Age of patients (years)	Male: Female ratio	Cause of CHF	Severity of heart failure (NYHA class)	LVEF
Bedford *et al.* 1956[11]	231	146 (63%)	>2 yrs in 229 pts	>65 yrs	52:48	Any aetiology	All pts had decompensated CHF	NA
Franciosa *et al.* 1983[12]	182	88 (48%)	1–41 months mean 12 ± 10	mean 56 yrs	All men	IHD or idiopathic dilated	mean NYHA 3·1	NA (mean LVEDP 26 mmHg)
Wilson *et al.* 1983[13]	77	50 (65%)	5–40 months mean 12	61 ± 11 yrs	75:25	Any aetiology	NYHA: II-61%; III-39%	Mean 27 ± 10%
Sakurai and Kawai 1983[14]	174	87 (50%)	NA	31 ± 14 yrs	NA	Any aetiology	NA	NA
V-HeFT I 1986 (including Cohn *et al.* 1984)[3]	642	283 (44%)	0·5–5·7 yrs (mean 2·3 yrs)	18–75 yrs (mean 58·3 yrs)	All men	Any aetiology	symptom score 5·6 (possible score 3–12)	Mean 30%
Lee *et al.* 1986[16]	203	155 (76%)	6–94 mths	27–89 mean 64 ± 1	71:29	Any aetiology	NYHA III–IV	All pts had LVEF <30%
Cleland *et al.* 1987[18]	152	63 (41%)	mean 21 ± 12 mths	59 ± 9	84:16	Any aetiology	NYHA II–IV mean 2·8 ± 0·8	NA
Diaz *et al.* 1987[19]	169	104 (62%)	mean 5·5 ± 4·2 yrs	39 ± 14 yrs	78:22	Dilated cardiomyopathy only	Not stated	<45% in all; 29·2 ± 12·7% in
Likoff *et al.* 1987[20]	201	85 (42%)	10·8 ± 9 mths	25–84 mean 62 ± 10	75:25	IHD, idiopathic or HT	NYHA: I-3, II-47, III-84, IV-67	97 (57%) patients mean 20 ± 10% (in 145 pts)
Ogasawara *et al.* 1987[21]	111	54 (49%)	3 mths–15 yrs mean 51 ± 30 mths	40 ± 13 yrs	83:17	Dilated cardiomyopathy	NA	32 ± 2% in survivors and
CONSENSUS 1987[2]	253	118 (47%)	1 day–20 mths (mean 188 days)	mean 70·5 yrs	70·30	Any aetiology	All in NYHA IV	24 ± 2% in non-survivors

Rolandi *et al.* 1989[22]	544	68 (13%)	median 159 days	22–88 median 68 yrs	65:35	Any aetiology	NYHA: II-183, III-319, IV-43	NA
Rockman *et al.* 1989[23]	238	156 (66%)	Minimum 6 mths Mean 40 mths	24–83 yrs	NA	Coronary artery disease	NYHA III–IV	mean 25·1%
Rouleau *et al.* 1990[24]	200	96 (48%)	13–65 mths (mean 40)	60 ± 0·9 yrs	83:17	Any aetiology	All in NYHA III	mean approx. 24%
Panciroli *et al.* 1990[25]	161	92 (57%)	1–60 mths	67 ± 10 yrs	70:30	Any aetiology	Severe CHF NYHA III–IV	NA
Keogh *et al.* 1990[26]	232	76 (33%)	2 wks–5·5 yrs; mean 10 ± 12 months	42 ± 12 yrs	84:16	Idiopathic or ischaemic	NYHA: II-13%; III-51%; IV-31%	Median LVEF 16%
Gottlieb *et al.* 1990[27]	199	93 (47%)	2 yrs	28–90 (mean 64)	63:37	Any aetiology	NYHA: II-37, III-77, IV-85	2–39% (mean 19%)
SOLVD treatment trial 1991[1]	2569	962 (37%)	22–55 months, mean 41·4	mean 61 yrs	80:20	Severe valvular heart disease excluded	NYHA: I-11%, II-57%; III-30%; IV-2%	Mean 25%
V-HeFT II 1991	804	285 (35%)	0·5–5·7 yrs (mean 2·5 yrs)	18–75 yrs (mean 60·6 yrs)	All men	Any aetiology	94% in NYHA II–III	Mean 29%
Taffet *et al.* 1992[28]	94	82 (87%)	3–10 yrs	>75 yrs (mean 82·5)	All men	Any aetiology	NA	<0·45 in 57·4% pts
Lee *et al.* 1993[29]	382	81 (21%)	1–62 mths (mean 9 mths)	mean 48 ± 13	78:22	Ischaemic or dilated	All in NYHA III–IV	7–29% (mean 20 ± 8%)
Katz *et al.* 1993[30]	264	56 (21%)	24·2 ± 8·9 mths	mean 61·8 ± 10·9	68:32	Any aetiology	NYHA: I-47, II-97, III-111, IV-9	10–46% (mean 27 ± 7·8)
Middlekauf *et al.* 1993[31]	491	154 (31%)	mean 365 ± 419 days	50 ± 12 yrs	80:20	Any aetiology	mean NYHA 3·4 ± 0·6	mean 20 ± 7%
Moser *et al.* 1994[34]	566	210 (37%)	mean 18·3 mths	50 ± 13 yrs	80:20	Any aetiology	all in NYHA III or IV	Mean 20 ± 8%
Fruhwald *et al.* 1994[35]	167	85 (51%)	93 ± 36 mths	55 ± 11 yrs in survivors	86:14	Dilated cardiomyopathy	NYHA: 1-15%, II-36%, III-39%, IV-10% (in survivors)	Mean 35 ± 12%
Madsen *et al.* 1994[36]	190	60 (32%)	14–35 mths (median 24·5)	42–75 yrs median 66 yrs	72:28	IHD, dilated or HT	NYHA: 1-16, II-87, III-83, IV-4	5·8–74·1% (median 29·8%)
CIBIS trial 1994[37]	641	120 (19%)	mean 1·9 ± 0·1 yrs	mean 60	83:17	Any aetiology	NYHA: III-609, IV-32	mean 25%

HT=hypertension.

Table 2 Categories and definitions of different modes of death used in studies recording more than 100 deaths

Study	Categories	Definitions of 'sudden death'	Definition of '(progressive) heart failure death'
Bedford 1956[11]	(a) Known causes of death (all in hospital) Heart failure Cardiac infarction in CHF not in CHF Pulmonary embolism in CHF not in CHF Sudden death in CHF not in CHF Bronchopneumonia in CHF not in CHF Coexistent lethal diseases Other causes (b) Deaths outside hospital	Patients who died abruptly (within minutes), presumably from ventricular fibrillation or massive pulmonary embolism, and either no post-mortem examination was made, or necropsy did not reveal the immediate cause of death.	Resistant and recurrent congestive heart failure together with a few cases of acute left ventricular failure
VHeFT-I 1986 (including Cohn *et al.* 1984)[3]	Sudden instant unobserved Sudden with premonitory symptoms Pump failure Other cardiac Non-cardiac	Sudden, either observed to be instantaneous or unobserved but assumed to be instantaneous on the basis of the clinical setting. Sudden, but with premonitory worsening (hours, days or weeks) of cardiac status.	Pump failure, usually with progressively worsening of heart failure symptoms even if the terminal episode was an arrhythmia.
Lee 1986[16]	Progressive heart failure Sudden cardiac Acute identifiable cardiac event (AMI, pulmonary embolism) Non-cardiac causes	Unexpected circulatory collapse occurring in a clinically stable patient.	Separate definition not given.
Diaz *et al.* 1987[19]	Sudden Non-sudden (further breakdown not given)	Death which was unexpected and occurred within 24 h of the onset of new symptoms.	Separate definition not given

CONSENSUS 1987[2]	Cardiac death within 24 h Sudden cardiac death within 1 h Progression of CHF Other cardiac death Stroke Other cardiovascular deaths Non-cardiovascular deaths	Death within 1 h from the onset of new symptoms.	Separate definition not given.
Rockman 1989[23]	Sudden Low output Non-cardiovascular	Abrupt circulatory collapse without premonitory symptoms during a clinically stable period.	Death after a period of clinical deterioration in signs and symptoms of heart failure despite maximal medical treatment (included were those experiencing terminal arrhythmias while being hospitalized for progressive haemodynamic deterioration).
VHeFT-II 1991	Same as for VHeFT-I.	Same as for VHeFT-I.	Same as for VHeFT-I.
SOLVD 1991	(a) Cardiac deaths: Arrhythmias without worsening heart failure Heart failure or arrhythmia with CHF Myocardial infarction Other cardiac (b) Vascular deaths: Stroke Other vascular deaths (c) Non-cardiovascular deaths	The term 'Sudden death' not used for classification: Cardiac deaths were classified as: (a) arrhythmias without worsening heart failure (b) heart failure or arrhythmia with CHF (c) myocardial infarction (d) other cardiac.	Pump failure or arrhythmia with CHF
Middlekauf 1993[31]	Sudden Progressive heart failure Non-cardiac or unknown causes	Death occurring within 15 min of a change of symptoms or during sleep.	Separate definition not given
CIBIS trial 1994[37]	Sudden death Progressive pump failure Myocardial infarction Cardiogenic shock Documented VT or VF Other cardiovascular causes Uncertain aetiologies	Death occurring within 1 h without previous worsening of symptoms and without documented ECG or Holter recording of ventricular tachycardia or fibrillation.	Separate definition not given
Moser *et al.* 1994[34]	Sudden death Death due to heart failure Non-cardiac death	Death occurring within 1 h without previous worsening of symptoms and without documented ECG or Holter recording of ventricular tachycardia or fibrillation	Separate definition not given

Table 3 Proportions of sudden deaths and (progressive) heart failure deaths in different groups of studies

Group of studies (based on definition of sudden death	Number of studies	Sudden deaths: No. (% of total deaths in group)	(Progressive) heart failure deaths: No. (% of total deaths in group)	Total deaths
Instantaneous death or death within 15 min				
including SOLVD	9	756 (32%)	953 (40%)	2355
excluding SOLVD	8	538 (39%)	493 (35%)	1393
Death within 1 h of onset of new symptoms	6	197 (39%)	206 (41%)	505
Death within 6 h (1 study) or within 24 h of new symptoms	4	89 (27%)	57 of 85 deaths (67%) (data from 1 study only)	333
Only defined as unexpected or not defined	8	220 (27%)	235 of 536 deaths (44%) (data from 6 studies only)	803
Total of all studies				
including SOLVD	27	1264 (32%)	1451 of 3481 (42%)	3996
excluding SOLVD	26	1046 (34%)	991 of 2519 (39%)	3034

Altogether, a total of 3909 deaths occurred in these 27 studies. The proportion of patients dying suddenly and due to progressive heart failure are shown in Table 3 with the SOLVD data included and excluded for the reason stated above. Myocardial infarction, cerebrovascular accidents and pulmonary embolism were not defined as a separate category in most studies, therefore the pooled proportion will not be a valid estimate and hence pooled results are not reported.

Studies that only recruited patients with severe heart failure (NYHA III or IV) reported a slightly higher incidence of sudden death than studies that recruited patients regardless of the severity of heart failure (mean 35% vs 31%). The proportion of patients dying of (progressive) heart failure was 43% in the studies that included only class III–IV patients and 38% in those that recruited patients with milder disease as well. Class III–IV studies had a mean of 22% deaths attributed to other causes as compared to 28% in studies including all patients. The overall mortality in III–IV only studies was 41% as compared to 38% in the group of studies which included milder patients as well. The proportions of sudden, heart failure and other modes of death in relation to the *mean* left ventricular ejection fraction in different studies are shown in Fig. 1. This shows that heart failure deaths were more common in studies with a low mean ejection fraction while modes of death other than sudden or heart failure were commoner in studies with a higher mean LVEF.

Discussion

The lack of reporting of and heterogeneity of the definitions for the mode of death in studies of chronic heart failure is the principal finding of this paper. Although this finding is perhaps not unexpected, at least with hindsight, it is of major concern. That the definition of sudden death is heterogeneous has been known for some time, but the lack of any clear definition of death due to circulatory failure in all but one study[31,33] is surprising.

The pooled data show that circulatory failure was the most frequently reported mode of death in chronic heart failure, accounting for up to 42% of all deaths. However, this may be an overestimate as the SOLVD trial's definition of death 'with heart failure or arrhythmia with heart failure' includes many patients that others would have classified as dying suddenly. Nonetheless, even excluding the SOLVD data, death due to circulatory failure remains the most commonly reported mode of death (39% of all deaths). Sudden death accounted for 32% to 34% of deaths depending on inclusion or exclusion of the SOLVD data.

Evolving classifications of the way in which patients die is not a matter of semantics and is of real clinical importance. Knowing accurately how patients die could have a major bearing on new strategies to reduce mortality in chronic heart failure further. Prevention of sudden death prior to the onset of terminal ventricular dysfunction may require a different strategy to the prevention of circulatory failure.

The lack of any clear definition of death due to circulatory failure needs to be rectified. As circulatory failure implies that the pump has failed this could be narrowly defined as cardiogenic shock or intractable pulmonary oedema. It could be argued that this definition is too narrow and that many patients die in a low output state albeit with a terminal sudden event. Such deaths could be recorded as sudden but with clarification of the clinical status prior to death. Defining the severity of heart failure prior to death, by the level of symptoms or amount of therapy required, and worsening heart failure, by a change in symptoms or therapy would help identify patients in whom treatment for worsening heart failure might have prevented sudden death.

Table 4(a) Stated causes of mortality in heart failure in studies defining sudden death as death occurring instantly or within 15 min

Study	Sudden	Rapid	(Progressive) heart failure	MI	Other cardiovascular	Non-cardiac	CVA	Unknown or indeterminate	Total deaths
Bedford *et al.* 1956[11]	16 (11%)		24 (16%)	8	20 (pul. embolism)	78 (including 46 bronchopneumonia)		46 (out-of-hospital)	146
VHeFT-I 1986 (including Cohn *et al.* 1984[3]	124 (44%)	40	89 (31%)	—	14	16	—		283
Cleland *et al.* 1987[18]	47 (75%)		5 (8%)	5		4	2		63
Rockman *et al.* 1989[23]	50 (32%)		78 (50%) (low output state)			28			156
Rouleau *et al.* 1990[24]	30 (31%)		41 (43%)			25			96
VHeFT-II 1991	104 (36%)	45	90 (32%)	—	10	36	—		285
SOLVD treatment trial 1991	218 (23%)		460 (48%)	93	46	102	21	22 (other vascular or unknown)	962
Middlekauf *et al* 1993[31]	69 (45%)		66 (43%)			19 non-cardiac or unknown)			154
Moser *et al.* 1994[34]	98 (47%)		100 (48%)			12			210
Total									
including SOLVD	756 (32%)		953 (40%)						2355
excluding SOLVD	538 (39%)		493 (35%)						1393

Table 4(b) Stated causes of mortality in heart failure in studies defining sudden death as one occurring within 1 h of onset of new symptoms

Study	Sudden	Rapid	(Progressive) heart failure	MI	Other cardiovascular	Non-cardiac	CVA	Unknown or indeterminate	Total deaths
Wilson *et al.* 1983[13]	19 (42%)		23 (46%)		2 (unwitnessed cardiac)	6			50
CONSENSUS 1987	28 (24%)	11	66 (56%)	—	9	1	3		118
Lee *et al.* 1993	51 (63%)		30 (37%)						81
Madsen *et al.* 1994	20 (33%)		29 (48%)		9	2			60
CIBIS trial 1994	43 (36%) (11 documented VT/VF)		42 (35%) (9 cardiogenic shock)	1	13	7		14	120
Keogh *et al.* 1990	36 (47%)		16 (21%)		2 (emboli)			22	76
Total	197 (39%)		206 (41%)						505

Sudden death is difficult to define. A definition based predominantly on exclusion of other modes of death may be preferred. Thus, sudden cardiac death could be defined as death in the absence of terminal pump failure, stroke or non-cardiac causes of death. Most patients would be expected to be able to call for help or to be roused from sleep if a non-sudden mode of death were operating and it is not unreasonable to regard such patients as dying suddenly. A patient dying before help can even be requested does not have an opportunity for therapeutic intervention regardless of the actual cause of that mode of death and could legitimately be considered to have died suddenly.

It is illogical to define sudden death according to a span of time from a change in symptoms to the time of death. For instance, a patient who develops a myocardial infarction and cardiogenic shock followed by death 1 h later clearly has a different mode of death from the concept of sudden instantaneous death. Such a patient might have benefited from thrombolysis or emergency revascularization.

It is important not to confuse the mode of death and the cause of death although few studies attempt this distinction. The term sudden death is often used to mean arrhythmic death, although the evidence that the majority of sudden deaths are due primarily to arrhythmias

Table 4(c) Stated causes of mortality in heart failure in studies defining sudden death as one occurring within 24 h or within 6 h (1 study) of onset of new symptoms

Study	Sudden	Rapid	(Progressive) heart failure	MI	Other cardiovascular	Non-cardiac	CVA	Unknown or indeterminate	Total deaths
Franciosa *et al.* 1983[12]	40 (45%)		(?)*						88
Likoff *et al.* 1987[20]	26 (31%)		57 (67%)	2					85
Diaz *et al.*[19]	9 (9%)		(?)*						104
Katz *et al.* 1993[30]	14 (25%)		(?)*			10		11	56
Total	89 (27%)		57 of 85 (67%) (only 1 study)						333

*Breakdown of non-sudden deaths not given.

Table 4(d) Stated causes of mortality in heart failure in studies where sudden death was only defined as unexpected or not defined

Study	Sudden	Rapid	(Progressive) heart failure	MI	Other cardiovascular	Non-cardiac	CVA	Unknown or indeterminate	Total deaths
Sakurai *et al.* 1983[14]	19 (11%)		(?)*						87
Lee *et al.*[16]	58 (37%)		84 (54%)	7 (MI or pulmonary emboli)		6			155
Ogasawara *et al.* 1987[21]	23 (43%) (6 sudden & 17 (sudden on basis of heart failure)		31 (57%)						54
Rolandi *et al.* 1989[22]	19 (28%) (8 VF)		33 (49%) (9 cardiogenic shock, 8 pul. oedema)	2		8	6		68
Gottlieb *et al.* 1990[27]	25 (27%)		(?)*						93 (cardiac deaths
Panciroli *et al.* 1990[25]	37 (40%)		43 (47%)			8			92)
Taffet *et al.* 1992[28]	16 (20%)		20 (24%)	3		32		11	82
Fruhwald *et al.* 1994[34]	23 (27%)		24 (28%)		2 (pul. embolism)	4	3	29	85
Total	220 (27%)		235 of 536 (44%)						803

*Breakdown of non-sudden deaths not given.

rather than recurrent coronary events is lacking. Indeed, several studies have suggested[38,39d] that the majority of sudden deaths in the general population are due to coronary occlusion rather than primarily arrhythmic. Sudden death may be due to tachy- or brady-arrhythmia, coronary occlusion, electromechanical dissociation, myocardial rupture or stroke. It is also possible that the cause of sudden death depends on the severity of heart failure. Pulmonary embolism could be the most important cause of sudden death in severe heart failure[40], arrhythmias in mild to moderate heart failure with dilated cardiomyopathy and coronary occlusion in similar patients with heart failure due to ischaemic heart disease. Similarly, the onset of atrial fibrillation, ventricular tachycardia or a recurrent myocardial infarction may cause progressive deterioration in pump function. All deaths due to pump failure are not due to progressive ventricular remodelling.

The severity of heart failure may alter the recorded mode of death. Patients with severe heart failure are a selected group who have already demonstrated 'resistance' to dying suddenly. Alternatively, there may be a bias by doctors against recording death as sudden when severe heart failure is already present. Milder cases appeared more likely to die of modes other than sudden death or death due to progressive heart failure (Fig. 1). This is consistent with the better prognosis of patients with mild heart failure and therefore increased likelihood of intercurrent events. However, analysis of data from multiple studies may introduce a number of confounding factors and it is inappropriate to draw any firm conclusion from the data presented here.

Myocardial infarction is a key event to recognise in patients who subsequently die but should not be confused with the mode of death. Many patients survive myocardial infarction, although possibly not the

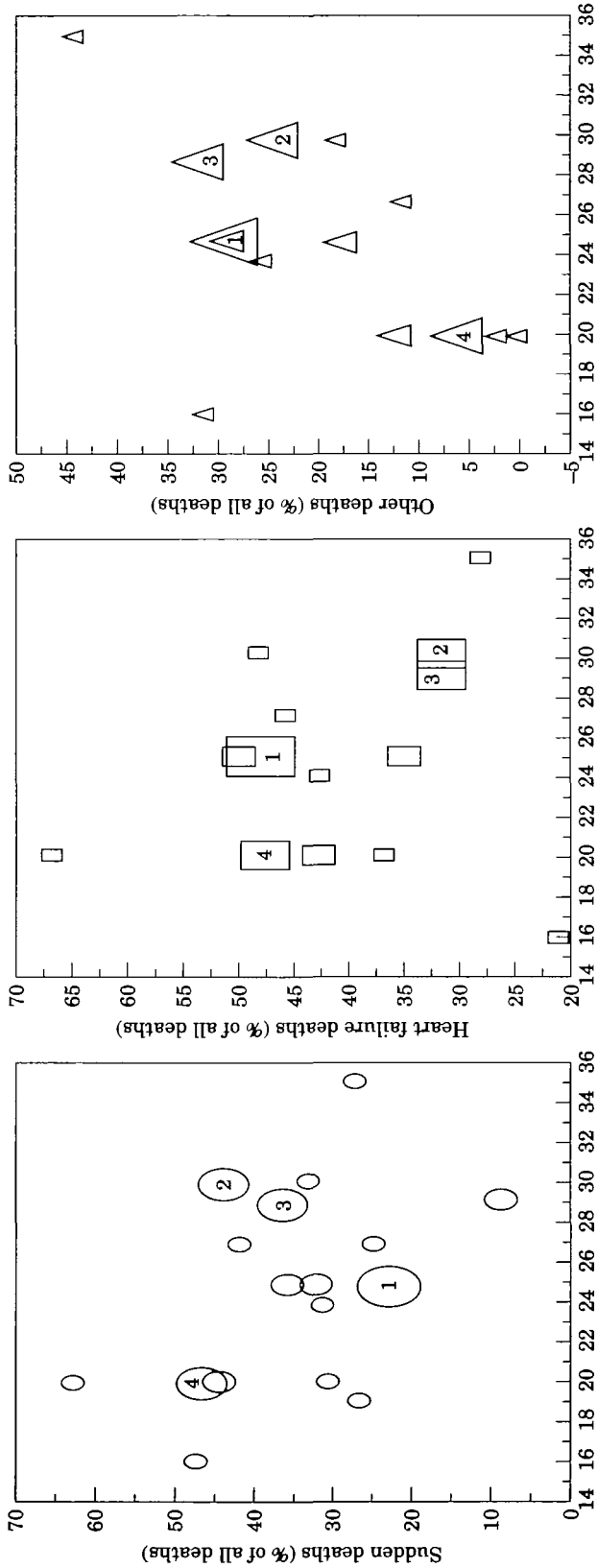

Figure 1 **Scatterplots of mean left ventricular ejection fraction for the study against sudden, heart failure and other deaths recorded in the study. Studies with greater number of deaths have been shown with larger points. The four largest studies are indicated by numbers: 1 — SOLVD[11], 2 — VHeFT I[13], 3 — VHeFT II[41] and 4 — Moser *et al.*[34].**

Classification of Death in Heart Failure: The ACME System

Name or initials: Gender: Date of Birth:

Time of discovery of the deceased : _____
Likely time of death (if different): _____

Duration of heart failure: [ ][ ] years [ ][ ]months [ ][ ]days
Last recorded NYHA (please circle): I II III IV

Each of the following must be answered:

	Yes	No	Don't know
A. Activity & Place of death:			
1. Hospital:	[ ]	[ ]	[ ]
If yes: Duration of stay ≤ 24 hours:	[ ]	[ ]	[ ]
2. Out of Hospital:	[ ]	[ ]	[ ]
If yes: During sleep:	[ ]	[ ]	[ ]
During routine activities:	[ ]	[ ]	[ ]
During heavy exertion:	[ ]	[ ]	[ ]
3. Witnessed:	[ ]	[ ]	[ ]
C. Cause of Death*:			
1. Witnessed arrhythmia:	[ ]	[ ]	[ ]
2. Post-mortem done:	[ ]	[ ]	[ ]
If yes, state principal findings:			
3. Cause known:	[ ]	[ ]	[ ]
If yes, state cause of death:			
M. Mode of death :**			
Sudden	[ ]	[ ]	[ ]
Circulatory failure	[ ]	[ ]	[ ]
Stroke	[ ]	[ ]	[ ]
Other cardiovascular	[ ]	[ ]	[ ]
Non-cardiovascular	[ ]	[ ]	[ ]

E. Events associated with death (add details as necessary):

	Yes	No	Don't know	Timing
Worsening heart failure***	[ ]	[ ]	[ ]	[ ]
Preceding chest pain	[ ]	[ ]	[ ]	[ ]
Preceding myocardial infarction	[ ]	[ ]	[ ]	[ ]
Preceding syncope	[ ]	[ ]	[ ]	[ ]
Preceding arrhythmia	[ ]	[ ]	[ ]	[ ]
Other prior vascular event	[ ]	[ ]	[ ]	[ ]
Other non-vascular event	[ ]	[ ]	[ ]	[ ]

For each event, please indicate timing as follows: **H** if within 48 **hours** of death; **D** if within 7 **days** of death; **W** if within 4 **weeks** of death; **M** if within 12 **months** of death or **Y** if more than 1 **year** of death.

Figure 2(a)

majority among those with pre-existing chronic heart failure[41]. Of those that die some will die of cardiogenic shock or in pulmonary oedema, that is circulatory failure, while others will die suddenly of arrhythmias or cardiac rupture. Thus, it is important to know if and when a myocardial infarction occurred but the mode of death should also be recorded.

Surprisingly, an important, simple feature lacking in most studies is a record of where the patient died. If patients die in hospital this implies that some event anticipated their death and that an opportunity may exist to intervene. It is likely that most patients who die in hospital with heart failure are admitted for worsening symptoms or signs, aborted out-of-hospital sudden death, syncope or recurrent myocardial infarction. Opportunities to intervene in each of these situations exist.

The incidence of stroke in CHF studies is low, assuming that stroke does not constitute a large proportion of sudden deaths. Little is known about whether the strokes that did occur were thrombotic, embolic or haemorrhagic. The low incidence of stroke may reflect the fact that patients are dying of cardiac causes before strokes have had time to occur[42–44]. Treatments for chronic heart failure also reduce blood pressure and this could reduce the risk of stroke. Alternatively, it is possible that a high proportion of patients with chronic

Notes on filling the ACME form:

*:

Cause vs Mode of death:
Stroke is a cause as well as a mode of death. Pulmonary oedema and cardiogenic shock are modes of death (circulatory failure); their cause (eg:- severe global ventricular dysfunction, myocardial rupture, etc.) should be recorded as cause of death.

**:

Sudden Death defined as:-

i) witnessed death in the absence of pre-existing circulatory failure (see below) or other modes of death

or

ii) unwitnessed death in the absence of pre-existing circulatory failure or other modes of death

or

iii) patients resuscitated from a cardiac arrest in the absence of pre-existing circulatory failure or other modes of death and who die within 24 hours or similar *patients who die during an attempted resuscitation.*

Circulatory Failure as defined by the presence at the time of death of at least one of the following:-

i) cardiogenic shock (that is hypotension resulting in a failure to maintain normal renal or cerebral function for >15minutes prior to death)

or

ii) pulmonary oedema sufficient to cause tachypnea and distress

or

iii) heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration.

or

iv) confinement to bed but only if confinement is due to heart failure symptoms.

Stroke Death as defined by:-

i) the rapid onset of localising neurological symptoms or signs leading to death

or

ii) sudden loss of consciousness without circulatory failure leading to death and no other reason for loss of consciousness identified

Other Cardiovascular deaths include: peri-operative deaths, mesenteric infarction, peripheral vascular occlusion etc.

Non-Cardiovascular deaths include: death due to infection, cancer etc.

***:

Worsening Heart Failure defined as increasing symptoms and/or signs requiring an increase in treatment directed at heart failure.

Figure 2(a) and (b) **A suggested scheme for recording the mode and cause of death for patients dying with chronic heart failure.**

heart failure receive warfarin or aspirin although the studies do not support such a conjecture. It is not clear whether anti-thrombotic treatment reduces the thromboembolic rate in chronic heart failure[40,45,46].

All the large scale studies have been conducted among hospital-based patients apart from the Framingham study and some caution needs to be exercised in extrapolating the pooled results presented here to the wider population of patients with chronic heart failure. The median of the mean ages recorded in the trials being discussed here was 58 years, considerably less than the median age of 74 years of patients with heart failure in the community[47].

In summary, future trials describing death in CHF trials should make a clear separation between the mode of death (e.g. pump failure, sudden death), the cause of death when it can be identified (e.g. arrhythmia, cardiac rupture) and the patients' clinical status prior to death (e.g. proximity of myocardial infarction and the severity of and worsening of heart failure). Finally, reporting the place of death is highly objective, is likely to be a powerful indicator of the patient's clinical status prior to death and could be important in determining the strategy for new directions in treatment. Inevitably this sort of classification will throw up some anomalies, e.g. are stroke and cardiogenic shock a mode or a cause

of death or both? Ultimately practicality and clinical utility will be important in defining how death in studies of heart failure is reported. One possible scheme is shown in Fig. 2. This way of classifying death has been successfully piloted in the AIRE and NETWORK studies; reports from both these studies will soon be available.

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