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Predictors of sudden death up to 18 years after a first attack of unstable angina or myocardial infarction

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SUMMARY Factors related to the occurrence of sudden death were examined in 551 men aged <60 years who survived a first attack of unstable angina or myocardial infarction by at least 28 days. There were 301 deaths over an average follow up period of 9·4 years and 138 (46%) of these were sudden. Life table techniques permitted the estimation of mortality up to 18 years after the index event. The proportion of sudden deaths showed a decrease with length of follow up. In those who were non-smokers and in those aged <45 years on admission sudden deaths in the first two years were very common (80% (95% confidence interval: 69%–91%) and 79% (95% confidence interval: 68%–90%) respectively). The proportion of sudden deaths in the remaining 16 years of follow up was related inversely to age at initial attack. After the first two years of follow up sudden death rates were similar in those who continued to smoke and those who stopped smoking, although those who continued to smoke had a significantly higher overall mortality.

The risk of sudden death should be borne in mind when planning the investigation and rehabilitation of young and non-smoking subjects presenting with a first coronary event.

In survivors of an acute coronary event there is a high risk of sudden death particularly during the first year after hospital discharge.[1-3] The purpose of this investigation was to examine patterns of sudden death up to 18 years after a first coronary event and to identify factors related to this mode of death.

Patients and methods

Between 1 January 1965 and 31 December 1975, 555 consecutive male patients aged <60 years who survived a first attack of unstable angina or myocardial infarction by 28 days were entered into a long term follow up study (the St Vincent's Heart Study). One hundred and two (18·4%) had confirmed unstable angina. The remainder had a myocardial infarction.

The methods of study have been described elsewhere.[4] Diagnosis of myocardial infarction was based on a history of cardiac pain, fresh Q waves in the electrocardiogram, and/or a twofold or greater increase in the activity of cardiac enzymes (creatine kinase, lactic dehydrogenase, and aspartate transaminase). Unstable angina was diagnosed in patients with cardiac pain, serial ST and T wave changes, no abnormal Q waves, and no enzymatic evidence of recent myocardial necrosis.

A full risk factor profile for each patient was recorded at entry to the study and included information on age, pre-existing angina, hypertensive state, and cigarette smoking habits. Only patients with angina of effort for at least three months before entry were classified as having angina before the event. For four patients this information was missing and they were excluded. This left 551 for analysis. Patients with at least one of the following criteria were deemed to have hypertension: average diastolic pressure on fourth day after admission of >90 mm Hg; history of antihypertensive drug treatment before admission; diastolic pressure >100 mm Hg at subsequent outpatient visits during the first three months after discharge; known hypertension requiring treatment; the presence of at least two of the following: (*a*) past history of hypertension; (*b*) electrocardiographic evidence of left ventricular hypertrophy, or (*c*) hypertensive retinopathy. For the purposes of this analysis all other patients were classified as normotensive.

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Those smoking ⩾5 cigarettes daily during the three months before the initial attack were classified as current smokers; those who had already ceased smoking for at least three months or were smoking <5 cigarettes a day were classified as ex-smokers, and those who never smoked cigarettes were classified as non-smokers. Primary pipe and cigar smokers were classified as non-smokers.

Each patient was seen annually at a rehabilitation and secondary prevention follow up clinic. A change in smoking habit at the first follow up was examined as a variable in this report. Initial current smokers who survived two years after the index event were classified on this basis as stopped smokers if they had ceased for at least three months at the time of the examination. We found a high degree of veracity in the stated smoking habits of a sample of these patients.[5]

Subjects were followed up to the end of 1984. Cause and mode of death were derived from hospital records, necropsy reports, death certificates, and through contact with the family physician and patients' relatives. Sudden death was defined as instantaneous death, death within one hour of the onset of symptoms, or unwitnessed death. Three hundred and one patients had died by the end of 1984. All but eight (3·2%) of the survivors were known to be alive in 1983 or 1984. The average length of follow up to death or last contact was 9·4 years.

All patients were managed conservatively with particular and repeated emphasis on risk factor modification. β blockers were used to control hypertension or in the management of severe angina of effort to facilitate an exercise program. β blockers were discontinued when exercise capacity returned to a satisfactory level. Otherwise they were not routinely used during follow up.

STATISTICAL ANALYSIS

We used the Kaplan-Meier life table[6] to estimate mortality up to 18 years after the presenting event. Eighteen patients were alive at this point. Because the numbers were small, estimates of mortality beyond 18 years were considered unreliable and are not considered in this report.

Cox's proportional hazards regression model[7] as implemented in the SAS computer package[8] was used to examine the independent effects on mortality of the factors mentioned above: age (<45; 45–49; 50–54; 55–59), severity of attack (unstable agina or myocardial infarction), angina before the coronary event, hypertension, and smoking status. These factors were entered as binary or dummy variables and were chosen because of their known influence on short or long term mortality from previous analyses.

Cause specific mortality (also taken to refer to mode specific mortality) analysis was performed with the particular cause as an end point and treating all other deaths as censored data. This allowed estimation of the "net" mortality[9]—that is the mortality from a particular cause if all other causes of death were eliminated. These net mortalities were then adjusted to give the actual cause specific mortality which is presented in the report. An appendix giving the adjustment procedure and the derivation of the variance estimates is available from the authors.

To evaluate differences between early and late mortality, and to allow for differing effects of the factors studied, separate analyses were performed for mortality in the first two years and for the subsequent 16 years of follow up. In the former case all two year survivors were treated as censored at two years and for the next sixteen years the analysis was confined to two year survivors only. Results are expressed in terms of an average annual mortality (total or cause specific) in the early or late follow up periods, which permits direct comparison between the periods. Confidence intervals are based on an approximate variance estimate.

Results

Table 1 shows the distribution of the patient characteristics that were examined for all 551 patients included in the study and for the 500 two year survivors. At two years those who were cigarette smokers at the time of their attack were further categorised into those who had stopped and those who had continued. There were 51 deaths in the first

Table 1 *Characteristics at entry to study of all patients and those surviving two years*

	All patients No (%)	*Two-year survivors No (%)*
Age:		
<45	97 (17·6)	88 (17·6)
45–49	129 (23·4)	121 (24·2)
50–54	150 (27·2)	136 (27·2)
⩾55	175 (31·8)	155 (31·0)
Severity of initial attack:		
Unstable angina	102 (18·5)	93 (18·6)
Myocardial infarction	449 (81·5)	407 (81·4)
Angina preceding the episode:		
Absent	405 (73·5)	375 (75·0)
Present	146 (26·5)	125 (25·0)
Hypertension:		
Absent	471 (85·5)	432 (86·4)
Present	80 (14·5)	68 (13·6)
Cigarette smoking:		
Non	49 (8·9)	43 (8·6)
Ex	96 (17·4)	84 (16·8)
Current	406 (73·7)	233 (46·6) (stopped) 140 (28·0) (continued)
Total	551 (100·0)	500 (100·0)

two years and 250 therafter. One hundred and thirty eight (45·8%) were sudden and 119 (39·5%) were attributed to other vascular causes including myocardial infarction. Table 2 shows the cumulative total, sudden death, and vascular and non-vascular mortality at selected times from study entry, based on the Kaplan-Meier life table. The proportion of sudden deaths since the index coronary event decreased with length of follow up and deaths from non-vascular causes became increasingly more important.

Table 3 shows the average annual mortality and percentage of sudden deaths separately for the two year period after the initial event and for the remaining sixteen years of follow up. The all-cause mortality increased with length of follow up ($p < 0·05$) while the sudden death rate showed only a marginal and non-significant increase. As a consequence the proportion of sudden deaths was lower in the later follow up period.

Table 4 shows the effect of age at study entry on subsequent mortality. In general, sudden death rates tended to increase with age. Exceptionally, in the first two years of follow up, however, those aged <45 years had the highest annual mortality from sudden deaths (3·8%) and a very high proportion of sudden deaths (79%). After two years the proportion of sudden deaths decreased with increasing age from 63% in the under 45s to 38% in those over 55.

Hypertension and the existence of angina before the index event were independently associated with increased sudden death rates—significantly so in the last 16 years of follow up. These factors also increased total mortality to the same extent and thus did not influence the proportion of sudden deaths. The effect of the severity of the initial attack (unstable angina versus myocardial infarction) on mortality was confined to the first two years of follow up. Sudden death rates and total mortality in this period were higher in those who had a myocardial infarction initially.

Based on the ordered category of non-smokers, ex-smokers, and current smokers at study entry the amount of smoking was associated with an increase in mortality from non-sudden causes and a decrease in mortality from sudden death over the first two years (table 5). Consequently the proportion of sudden deaths decreased from a high of 80% in non-smokers to a low of 50% in those smoking at the time of the initial event ($p < 0·05$). Over the last 16 years of follow up, however, those who had ever smoked cigarettes (initial ex-smokers and current smokers who either ceased or continued after their coronary episode) had similar sudden death rates, though mortality from non-sudden causes was considerably higher in those continuing to smoke. In this period non-smokers had the lowest sudden death rate (table 5).

Discussion

The World Health Organisation expert committee on sudden death concluded that "there is an urgent need to identify the various predisposing and precipitating factors that in the presence or absence of coronary heart disease and ischaemia may lead to fatal arrhythmias".[10] The purpose of the present study was to identify factors related to sudden death in survivors of an acute coronary episode followed for up to 18 years. Sudden death in the post-infarct patient over short follow up periods of a year or less[1] seems mainly related to ventricular arrhythmias and impaired left ventricular function. A recent editorial

Table 2 *Life table mortalities and percentages of sudden deaths (study group 551)*

Time from initial episode (yr)	*No at risk (at end of period)*	*Cumulative mortality*			
		Total (%)	*Sudden death (%)*	*Other vascular (%)*	*Non-vascular (%)*
0–2	500	9·3	5·5	3·6	0·2
2–5	430	21·3	11·6	7·5	2·2
5–10	270	39·4	18·9	15·5	5·0
10–15	63	63·2	28·2	26·0	9·0
15–18*	18	72·4	33·2	27·7	11·5

*There were six further deaths beyond this point

Table 3 *Average annual mortality and percentage of sudden deaths (95% confidence intervals are given in parentheses)*

Period after initial episode (yr)	*Average annual mortality*		*Percentage of sudden deaths*
	Total	*Sudden death*	
0–2	4·7 (3·5–6·0)	2·8 (1·8–3·7)	58·3 (44·8–71·9)
2–18	7·2 (6·3–8·0)	3·2 (2·6–3·8)	44·4 (38·2–50·5)

Table 4 *Age related to average annual mortality (95% confidence intervals are given in parentheses)*

Period after initial attack (yr)	Age (yr)	Average annual mortality			Percentage of sudden deaths
		Total (%)	Other causes (%)	Sudden death (%)	
0–2	<45	4·8	1·0	3·8 (2·6–4·9)	79 (68–90)
	45–49	3·0	1·6	1·4 (0·7–2·1)	47 (34–61)
	50–54	4·0	2·4	1·6 (0·9–2·4)	41 (28–55)
	⩾55	4·8	2·0	2·8 (1·9–3·8)	60 (46–73)
2–18	<45	3·8	1·4	2·4 (1·9–2·8)	63 (57–69)
	45–49	6·9	3·5	3·4 (2·8–4·0)	48 (42–55)
	50–54	7·6	4·5	3·1 (2·5–3·7)	41 (35–47)
	⩾55	10·6	6·6	4·0 (3·3–4·7)	38 (32–44)

suggests, however, that ventricular tachycardia may be the initiating event.[11] Though many studies have reported on long term total mortality after infarction,[12] none seems to have studied the end point of sudden death in detail. In men free of overt coronary heart disease it has been shown that the risk factors for sudden death cannot be distinguished from the classic risk factors for the other manifestations of coronary heart disease.[13–15]

The identification of factors related to sudden death has important implications. Those with a high absolute risk should be advised to avoid situations, such as public service vehicle driving, where such an event could have serious consequences to themselves or others.[16] Patients at high risk of sudden death, especially in the early post-event period, may show greater benefit from prophylactic β blockade or other antiarrhythmic treatment,[17] although secondary prevention trials of such drugs still leave many unanswered questions about the use and efficacy of these agents. It is also not clear whether the reported mortality reductions in recent secondary prevention trials[18 19] are the result of the anti-ischaemic or antiarrhythmic effect of β blockers.[15]

In this study we have shown that sudden death in survivors of a coronary event becomes relatively less frequent as follow up increases. Aging seems to affect sudden death less than other modes of death, perhaps because the influence of the initial coronary event wanes with time. In fact over time the proportion of non-vascular and non-coronary deaths increased sharply. It should be emphasised that non-fatal reinfarction was not included as an end point in this analysis.

During the first two years after a coronary episode the younger patient is at particularly high risk of sudden death but not from other modes of death. The decreasing proportion of sudden deaths with age at initial attack, which was noted here only in those who survived the initial two years, has also been reported in those without coronary heart disease.[13] Hypertension, angina preceding the episode, and the severity of the initial attack were associated to the same degree with increased risks of sudden death and other modes and causes of death. The high sudden death rate and high proportion of sudden deaths in the non-smoker in the first two years are particularly surprising since among those without coronary heart disease non-smokers have a low risk of sudden death.[13] After two years, however, the sudden death rate in the initial non-smokers dropped significantly and it was also lower in this period than the rate in those who had ever smoked cigarettes. This might be attributable to the fact that those susceptible to sudden death in this group may have already died. The low sudden death rate in the current smokers in the first two years is difficult to explain.

In the later period of follow up the sudden death rate is similar in initial ex-smokers and current

Table 5 *Initial and follow up smoking habit related to average annual mortality (95% confidence intervals are given in parentheses)*

Period after initial attack (yr)	Smoking habit	Average annual mortality			Percentage of sudden deaths
		Total (%)	Other causes (%)	Sudden death (%)	
0–2	Non	4·3	0·9	3·4 (2·3–4·5)	80 (69–91)
	Ex*	5·1	2·0	3·2 (2·2–4·3)	63 (49–76)
	Current	3·8	1·9	1·9 (1·1–2·7)	50 (36–63)
2–18	Non	4·8	3·2	1·6 (1·2–2·0)	33 (27–39)
	Ex*	5·7	2·2	3·5 (2·9–4·1)	61 (55–67)
	Stopped	6·7	3·4	3·3 (2·7–3·9)	49 (43–55)
	Continued	10·9	7·0	3·8 (3·1–4·6)	35 (29–41)

*Before initial attack.

smokers, irrespective of whether the latter continued or stopped smoking afterwards. The beneficial effect of stopping smoking on total mortality is not reflected in sudden death. This present analysis, corrected for the presence of other factors, did not include interaction terms in the regression model; thus the results cannot be compared directly with our previous report on the same patients.[20] We then showed that those who ceased smoking had a lower total mortality than the non-smokers and ex-smokers combined, and that stopping smoking reduced the rate of sudden death only in those with less severe coronary attacks.

In this study we have shown that in patients surviving a first episode of documented unstable angina or myocardial infarction the factors that relate to overall mortality also tend to influence sudden deaths. The proportion of sudden deaths decreases with age, however, and, unlike its effect on total mortality, stopping smoking does not reduce the absolute sudden death rate. The young patient and non-smoker are at particularly high risk of sudden death, especially in the first two years after an initial attack. Special attention with a view to prevention should be given to these groups.

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