CORONARY DISEASE

The natural history of acute myocardial infarction

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The majority of readers of this article are likely to be hospital based clinicians whose experience of acute myocardial infarction is necessarily limited to examination of the survivors of a storm which has already taken its major toll. As has always been the case, most deaths from heart attack occur outside hospital and are medically unattended, as are about one quarter of non-fatal infarctions which are "silent" with no or atypical symptoms. For out-of-hospital deaths, even if a necropsy is carried out, it is in the majority of cases impossible to determine whether death had been caused by a developing infarction or by re-entrant ventricular fibrillation starting at the borders of a myocardial scar. Finally, it is impossible strictly speaking nowadays to speak about "natural" history. The history is inevitably "unnatural" in that it has in many cases been modified by treatment.

Myocardial infarction outside hospital

In the most recent study performed in the UK,[1], 74% of 1589 deaths from acute coronary heart attacks in people under 75 years of age occurred outside hospital; the proportion of out-of-hospital to total deaths varied inversely with age from 91% at age < 55 years to 67% at age 70–74 years (fig 1). Had the lives of 5% of potential victims of out-of-hospital sudden death not been saved by advanced life support given by ambulance staff, the proportion of out-of-hospital deaths to total deaths would have been even higher. The finding of three quarters rather than the previously quoted two thirds of deaths outside hospital may reflect a declining hospital fatality rate owing to better treatment, with no or a lesser reduction in the numbers of early sudden deaths.

Seventy five per cent of out-of-hospital deaths in our study occurred in the home and about 60% were witnessed. Advanced life support given by ambulance personnel was attempted in a little over half the cases. Of the 25% of deaths which occurred away from home, 16% happened in a public place, usually the street, 3% in an ambulance, 3% in nursing homes, 1% in doctors' surgeries, and only 2% at the place of work. Sudden death at mass gatherings such as football stadia or railway stations was unusual.

Pathology of out-of-hospital death

What proportion of out-of-hospital deaths are caused by developing infarction, and what proportion are caused by a re-entrant arrhythmia? Sudden unexpected death in England must be reported to a coroner unless the victim was known to have coronary disease and had been seen by a doctor within the last two weeks. Depending on the practice of individual coroners, the proportion of unexpected deaths coming to necropsy is high. However, developing infarction cannot be recognised in most cases of sudden death because the earliest histological change (invasion by leucocytes) does not develop until 12–24 hours after the onset. Evidence must be sought by examination of the coronary arteries.

Occlusion of the infarct related coronary artery by thrombus is nearly always present in patients with ST elevation myocardial infarction admitted early to hospital[2]; this is almost certainly the event which causes the infarct, so that the presence of occlusive thrombus at necropsy is almost pathognomonic of developing infarction. In a consecutive series of 168 sudden coronary deaths (within six hours of onset of symptoms)[3] in which the coronary arteries were examined by postmortem arteriography and histology of sections made at 3 mm intervals, occlusive thrombus was present in 30% of cases, and mural thrombus in 43%. In 8% of cases plaque fissuring only was present, and there was no acute lesion in

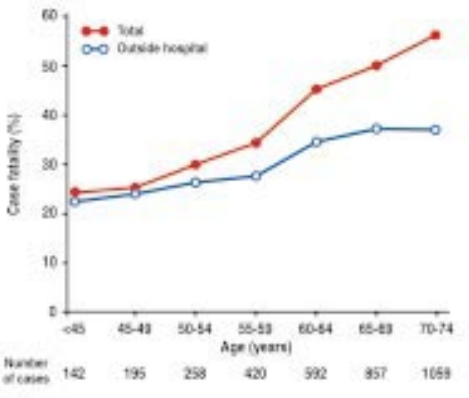

Figure 1: Total case fatality in the UK heart attack study and case fatality outside hospital by age group. Reproduced from Norris[1] with permission of BMJ Publishing Group.

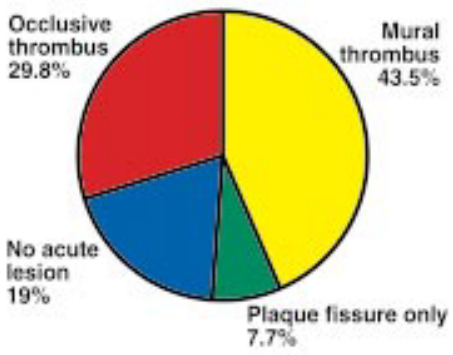

Figure 2: Necropsy findings in 168 cases of sudden coronary death in which the coronary arteries were examined by post mortem arteriography and histology of sections made at 3 mm intervals. Reproduced from Davies[3] with permission of the American Heart Association.

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19% (fig 2). Thus from this series it appeared that perhaps 30% of sudden cardiac deaths were definitely caused by developing infarction, and in an additional 45% infarction was highly likely (because the finding of intraluminal thrombus is unusual in definite non-coronary death). In the remaining 25% infarction was unlikely because plaque fissuring is quite common in people who die from an unrelated cause.[3]

Postmortem arteriography and serial sectioning of the coronary arteries is not carried out routinely by hospital pathologists who frequently limit the procedure, as far as the heart is concerned, to cursory section of the coronary arteries. Histological examination is not routine, and in these circumstances neither non-occlusive thrombus nor plaque fissuring are often commented upon. In the UK heart attack study (UKHAS)[4] 1037 (83%) of the 1247 out-of-hospital coronary deaths which we recognised in people up to 75 years of age came to necropsy. Occlusive thrombus was recognised by hospital pathologists in 23% of cases, recent myocardial infarction in 20%, and an old myocardial scar in 56%. Stenoses of one or more coronary arteries were present in all cases.

Clinicopathological correlations

In about half of the victims of out-of-hospital coronary death in the UKHAS study we were able to discover whether death had been truly sudden or if there had been prodromal symptoms (usually chest pain) before death. Of particular interest was that necropsy evidence of old infarction was more common and recent infarction less common in 124 victims who apparently had had no prodromal symptoms before death (70% and 11%) than in the 386 who had had prodromal chest pain (45% and 29%) ($p < 0.001$). However, occlusive thrombus was no more common in people with symptoms (26%) than in those without symptoms (29%). This latter finding is at variance with that of Davies[3] who was able to show a much higher number of thrombi with serial sectioning of the arteries. Of the 168 cases of sudden cardiac death mentioned earlier, occlusive thrombus was more common when prodromal pain had been present than when it had been absent. To summarise the evidence from necropsies, it is impossible to give any reliable estimate of the proportion of sudden coronary deaths which were caused by developing infarction and what proportion were caused by "electrical" death. However, both the detailed anatomical studies of Davies[3] and our own larger series of routine necropsies do support the existence of at least two separate mechanisms for out-of-hospital coronary death.

Resuscitation from out-of-hospital arrest

Further evidence does, however, come from one of the earliest studies of patients resuscitated from out-of-hospital cardiac arrest.[5] In Seattle, Washington, between 1970 and 1973, 146 patients were resuscitated from out-of-hospital ventricular fibrillation and were followed for two years. The subsequent survival of the 17% of patients whose arrest was caused by Q wave infarction was significantly better ($p < 0.005$) than the survival of the 83% who did not develop new pathological Q waves (fig 3).[5] It was this seminal observation that led to the recognition of "electrical" coronary death as a distinct pathological entity and its consequent electrophysiological investigation and treatment with implantable defibrillators. The Seattle findings also suggested that the majority of sudden deaths were "electrical". However, this conclusion, based on findings in a subset of survivors, may be incorrect in view of those from the detailed pathological examinations described above. [3]

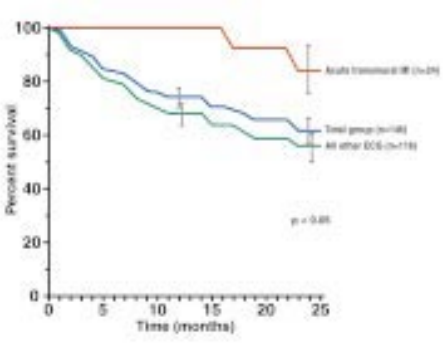

Figure 3: Two year survival after resuscitation from out-of-hospital arrest according to whether or not new pathological Q waves developed. Reproduced from Baum and colleagues[5] with permission of the American Heart Association.

Epidemiological studies

The final arbiter of the classification of acute coronary events, both fatal and non-fatal, is the epidemiologist. Discussion of global differences in incidence of new coronary events and prevalence of the disease is not the purpose of this article. However, methods used by the World Health Organisation MONICA (monitoring trends and determinants in cardiovascular disease) investigators[6] highlight the difficulties in exact definition. MONICA recognised both fatal and non-fatal events in the two categories of "definite" and "probable", and constructed their main analyses of incidence, mortality, and case fatality on "definite" only non-fatal events and "definite" plus "probable" fatal events. A third category of "unclassifiable" fatal events was also encountered; these were unexpected deaths in which no necropsy had been carried out and cause of death had been certified as coronary disease in the absence of definite evidence for or against the diagnosis. These deaths too were included in the analyses. MONICA definitions are not in dispute, but the problems in applying them to differing cultures with differing legal requirements for death certification are immense. From the epidemiologists' perspective the problem of "unclassifiable" deaths and the frequent unreliability of death certificates, particularly in the elderly, is very real. Different counting methods used by clinicians and epidemiologists yield differing results; this problem is discussed in a recent editorial.[7] Of

Problems in defining the true natural history of myocardial infarction

- Two thirds to three quarters of fatal events occur outside hospital. Such deaths may be caused by infarction or may be electrical. Although it may be possible to differentiate these mechanisms in some individual cases, it is impossible to do this in the majority.
- Death certificates are unreliable; many deaths certified as being caused by coronary heart disease, particularly in the elderly, are in truth unclassifiable.
- About 25% of non-fatal infarctions are silent and medically unattended.
- These facts must be taken into account for interpretation of all community and epidemiological studies, and also for interpretation of demographic data which show geographical differences or secular changes in mortality from coronary heart disease.

course no attempt at distinction between infarction and electrical death is possible in purely epidemiological studies.

Yet another problem in identification of the natural history of acute myocardial infarction is that fully 25% of non-fatal infarctions are silent.[8] Silent infarction can be detected only when a subject is seen more than once at annual intervals or longer, and an ECG performed on the second occasion shows new pathological Q waves. Most clinicians can remember such cases, but an estimate of the incidence can be made only when a cohort of the population free from coronary heart disease is followed for a number of years. This happened in the Framingham study—a unique and prestigious study which has taught us more than any other about the changing pattern of coronary heart disease during the latter half of the 20th century.[9]

The declining mortality from coronary heart disease

There is no doubt that mortality from coronary heart disease is falling. Figure 4[10] shows that age specific mortality for males aged 35–44 years during 1997 was about one third, and of those aged 65–74 years about two thirds of the figures for 1968 when the coronary epidemic was at its height. Age groups 45–54 and 55–64 showed intermediate changes and the picture was similar in women. Data in fig 4 stop at age 75, however. If evidence from death certificates is to be believed, more than 60% of coronary deaths occur in people aged > 75 years.[10] Death is being postponed, not prevented; it has been estimated that the global burden of coronary heart disease will continue to increase up to the year 2020.[11] Although the incidence of new events is falling, the prevalence of coronary heart disease in the community is increasing.[10]

How does the decline in mortality shown by the demographers relate to the natural history of acute myocardial infarction? Of course only acute events rather than infarctions can be monitored. However, the most recent evidence from the MONICA study suggests that over a 10 year period in populations where mortality decreased, reduction in coronary event rates accounted for about two thirds of the decrease while reduced case fatality accounted for about one third.[12]

Acute myocardial infarction in hospital

For the hospital clinician there is much less difficulty in the definition of acute myocardial infarction. Most clinicians will accept that infarction should be diagnosed when at least two of the following three conditions are present: a typical or compatible clinical history; sequential electrocardiographic changes; and a rise in cardiac enzyme activity to at least twice the upper limit of normal for the hospital laboratory. For patients who die very soon after presentation, a history of prolonged chest pain with one ECG showing an infarct pattern is sufficient for the diagnosis. However, even this seemingly simple definition is open to differing interpretations. In a recent survey (unpublished) of cases admitted to a district general hospital we found a substantial overlap between diagnoses based on the above criteria and those specified by clinical coding using the *International Classification of Diseases*, 10th revision (ICD 10) codes. The most common reason for disagreement was differentiation between acute myocardial infarction and unstable angina. This of course reflects the uncertainties described in epidemiological studies.[6]

Prognosis of hospital treated infarction

Definitions aside, the prognosis of hospital treated patients has improved considerably over recent years although the factors determining survival have not changed. More than 30 years ago we constructed a coronary prognostic index[13] which was based on the age of patients and the then available methods for assessment of left ventricular function, namely the chest radiograph and the systolic blood pressure on admission to hospital. The index

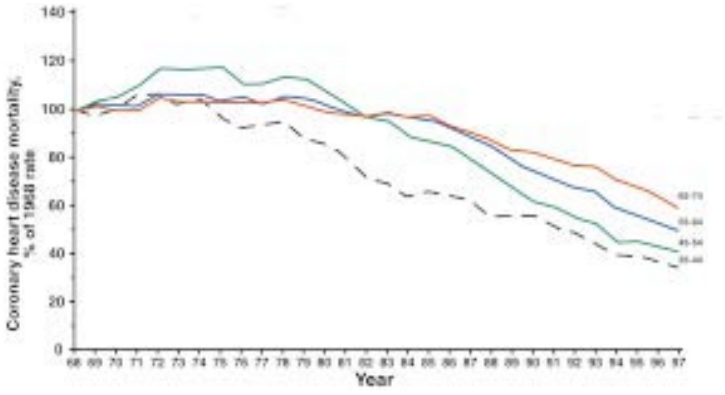

Figure 4: Age specific death rates from coronary heart disease in men 1968 to 1997, plotted as a percentage of the rates in 1968. Reproduced from British Heart Foundation Coronary Heart Disease Statistics 1999, with permission.

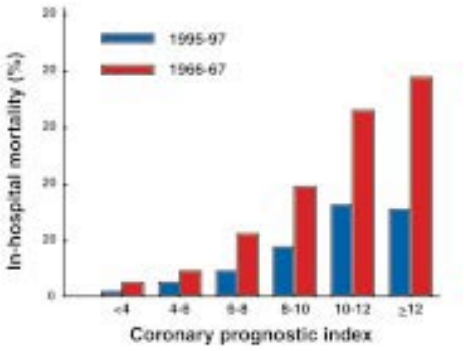

Figure 5: Hospital fatality predicted by a coronary prognostic index in patients treated in 1966-67 and 1995-97. Modified and reproduced from Christiansen and Liang[14] with permission of the publisher.

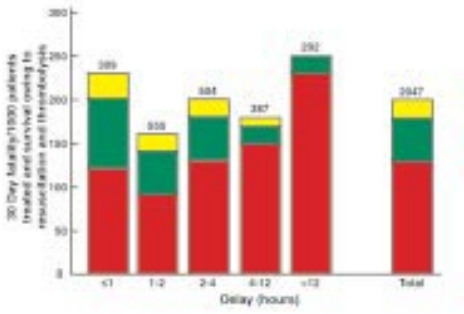

Figure 6: Thirty day fatality (red bars), lives saved by resuscitation from cardiac arrest (green bars), and lives estimated to have been saved by thrombolytic treatment (yellow bars) according to delay in presentation to the hospital. Numbers above the bars refer to the numbers of patients in each group. Reproduced from UK heart attack study[17] with permission of BMJ Publishing Group.

has proved to be remarkably robust in predicting relative although not absolute risk. This is shown by a study of 830 patients treated between 1995 and 1997[14] which showed that hospital fatality had fallen by 50% or more compared with 30 years previously (fig 5). This decline was most striking in the high risk patients (elderly patients with cardiac failure). Data such as those in fig 5 also underline the potential unreliability of crude figures for case fatality as a performance indicator. Both case mix and differences in definition of acute myocardial infarction (see above) can influence hospital fatality rates considerably.

The two major advances in treatment which have changed the natural history of hospital treated infarction over the last 30 years are resuscitation from cardiac arrest and restoration of flow to the infarct related coronary artery by thrombolytic drugs or primary angioplasty. It has been estimated that thrombolysis saves about 30 lives per thousand patients treated,[15] although the benefit may be doubled for those treated within the "golden hour" after the onset of symptoms.[16] Reduction in delay in giving thrombolytic treatment has been a major goal for hospitals in recent years, and various strategies for "fast track" administration either in accident and emergency departments or in coronary care units have been proposed. Pre-hospital treatment on a large scale has so far proved impracticable, and emphasis is placed on reduction in patient delay and use of ambulance paramedics rather than medical practitioners in providing early resuscitation and transport to hospital. Delay is inevitable with this strategy, however; in a recent hospital survey only 2% of patients had thrombolytic treatment started within the "golden hour".[17]

Recent enthusiasm for improving delivery of thrombolytic treatment has to a degree caused clinicians and health administrators to lose sight of the fact that resuscitation from cardiac arrest has done much more than thrombolysis to change the natural history of myocardial infarction for the better. Moreover reduction of delay in coming under care saves more lives by timely defibrillation than by early recanalisation of the infarct related coronary artery. This is shown in fig 6[17] which examines the effect of delay on salvage of patients by resuscitation and estimated salvage by thrombolytic treatment, taking delay in its administration into account.[16] Altogether, 80% of the salvage was attributable to resuscitation, and benefit from the "golden hour" was greater for resuscitation than for thrombolysis. Part of the reason for this was, of course, that patients did not receive thrombolytic treatment immediately after coming under care.

Survival after recovery from myocardial infarction

As for early survival, long term survival is most closely related to age and to left ventricular function. Function is traditionally described by ejection fraction which is an arithmetical term derived from the volumes of the ventricle at end diastole and end systole. In a series of patients under 60 years of age studied by left ventriculography before the thrombolytic era, we identified end systolic volume as the major functional determinant of long term survival.[18] For patients with an ejection fraction < 50%, the five year fatality rate was more than twice as great (36%) when end systolic volume was above the median value of 110 ml as when it was below the median (14%). Apart from age and ventricular dilatation, electrical instability as evidenced by occurrence of non-sustained ventricular arrhythmias on Holter monitoring and inducibility on electrophysiologic testing[19] are powerful additional predictors of a poor prognosis.

Conclusion: future prospects for improving the natural history

Many years ago the Framingham investigators concluded that the only road to substantial reduction in premature mortality from coronary heart disease lay in prevention of the disease. Primary prevention in the UK by a population strategy to encourage people to reduce their dietary fat intake has had limited success, although smoking has declined in the coronary age group.[10] Nevertheless, at least some of the decline in mortality must presum-

The natural history of acute myocardial infarction

- There are major difficulties in defining the natural history because of:
  - –differentiation from "electrical" death.
  - –difficulties in pathological examination.
  - –unreliability of death certification.
  - –impossibility of recording silent non-fatal infarcts.
- The decline in coronary mortality is occurring among younger people and is caused mainly by reduction in new events.
- The single most promising therapeutic strategy is secondary prevention.

ably be the result of primary prevention.[12] Secondary prevention for patients with known coronary disease has great potential for reducing mortality and has the attraction that potential methods for achieving it are soundly evidence based. Recent evidence from the USA[20] suggests that the decline in mortality between 1987 and 1994 may be largely caused by improvements in secondary prevention.[20]

As far as the treatment of myocardial infarction is concerned, it is probably true to say that better application of treatments already known to be effective in the year 2000 have more to offer than the development of new treatments. Reduction of patient delay in calling for help through public education on the symptoms of heart attack and the importance of access to emergency services, and improved response time of ambulances, are of paramount importance. The search for better thrombolytic and antiplatelet agents continues, but is less likely to improve the natural history than is earlier delivery of drugs already known to be effective.

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• *This is the most recent study of out-of-hospital coronary death to have been performed in the UK.*

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• *The first study of myocardial infarction by coronary arteriography during the acute stage finally established that coronary thrombosis was the proximate cause of infarction.*

3. Davies MJ. Anatomic features in victims of sudden coronary death. *Circulation* 1992;**85**(suppl 1):19–24.
• *Summarises the best available evidence from detailed anatomical studies carried out by an expert pathologist.*

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• *This important epidemiological study is quoted to show the difficulties of definition of acute coronary events and consequent uncertainties of geographical comparisons.*

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