References


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Risk of sudden death after discharge following myocardial infarction

See page 1214 for the article to which this Editorial refers

Attempts to predict sudden cardiac death in survivors of myocardial infarction have assumed a greater importance with the development of an effective treatment — the implantable cardioverter defibrillator. The goal is thus to identify those at highest risk and the paper by Jordaens et al.[1] in this issue is a useful although ultimately negative contribution.

They prospectively studied 708 consecutive hospital survivors of myocardial infarction in the thrombolytic era and followed them for 2 years. There were 83 (12%) deaths of which only 12 (1.7%) were sudden. The only variables that were independently predictive of sudden death in a multivariate analysis were admission NYHA class >I and a long filtered QRS duration on a signal averaged ECG. They pre-defined a ‘high risk’ group as patients with transmural myocardial infarction and an ejection fraction <35%. During the follow-up none of the 25 patients with this high-risk profile died suddenly.

The first message from this study is that non-invasive assessments are very poor at predicting sudden cardiac death, largely because these events are so infrequent (and increasingly so). Why was the incidence of sudden death so low? In other similar studies sudden death rates have been 3-6% over 3 years[2,3] and 5% in 2 years[3]. In the current study the authors state that ‘the cause of death was available in 74 patients’. Thus the cause of death was not available in nine cases and they do not offer any explanation for this and it is possible that some of these were due to malignant tachyarrhythmias. Another explanation is the commendably high (47%) use of beta-blockers in the study in comparison to other post infarction studies (25-90%)[2, 40%][3]). In a meta-analysis of 25 trials of beta-blockers post myocardial infarction[4] the relative risk reduction for total mortality was 23% and for sudden cardiac death 32%. In the recent heart failure studies, beta-blocker therapy led to even greater reductions in sudden death (by 55% in the United States Carvedilol Heart Failure Study[5], 44% in CIBIS II[6] and 55% in MERIT–CHF[7]).

How then are we to decide which post-infarction patients should have implantable cardioverter defibrillators for the primary prevention of sudden cardiac death? There have been three large studies to

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help us with this question. The CABG patch study$^6$ used an abnormal signal-averaged ECG and an ejection fraction <36% to define a high risk population following CABG. In this study there was no benefit from implantable cardioverter defibrillator therapy and the most likely explanation for this negative result is that the signal-averaged ECG did not select a sufficiently high-risk population. The Multicentre Automatic Defibrillator Implantation (MADIT) Study$^9$ recruited 196 patients with a previous myocardial infarction, a left ventricular ejection fraction <35%, asymptomatic non-sustained ventricular tachycardia and inducible monomorphic ventricular tachycardia at electrophysiological study. During an average follow-up of 27 months there were 15 deaths in the implantable cardioverter defibrillator group and 39 in the conventional therapy group (hazard ratio 0.46, $P=0.009$). The Multicentre Unsustained Tachycardia Trial (MUSTT)$^{10}$ examined a population very similar to the MADIT study and recruited 704 patients. The treatment protocol was more complex than the MADIT study, but the conclusion was the same — that implantable cardioverter defibrillators significantly reduce mortality in this very select group of post-infarction patients.

In the paper by Jordaens et al.$^1$, 54 patients (7.7%) had non-sustained ventricular tachycardia on ambulatory ECG monitoring prior to discharge, and 122 (17.5%) had a left ventricular ejection fraction <35%. However, according to their Table 6, the prevalence of the combination of non-sustained ventricular tachycardia and left ventricular ejection fraction <35% was only 15/497 (3.0%). By extrapolation to the full cohort of 708 patients, 21 patients would have met MUSTT/MADIT study enrolment criteria and undergone electrophysiological testing. In MUSTT, 767/2202 (34.8%) of patients had inducible ventricular tachycardia and went on to randomization. Thus it follows that in the paper from the MIRRACLE investigators$^{11}$ only seven (1.1%) patients would have had MUSTT/MADIT entry criteria and therefore be candidates for implantable cardioverter defibrillator implantation. A similar analysis was recently performed using the 94 797 patient Cardiac Arrhythmia Suppression Trial Registry$^{11}$ and from this population only 0.3% to 1.7% would have met strict MADIT/MUSTT entry criteria.

Therefore in this population of 708 patients, performing 122 ambulatory ECGs and 21 electrophysiological studies would have resulted in seven implantable cardioverter defibrillator implantations. However, although Jordaens et al.$^1$, do not actually tell us the number of sudden deaths in patients with an ejection fraction <35% and non-sustained ventricular tachycardia, this can only be four at most from the data presented. Thus the MADIT strategy could only have prevented one third of the sudden deaths.

What of the other sudden deaths and the 46 patients who died of non-sudden cardiac causes? As noted above, higher beta-blocker usage would reduce total cardiac mortality and other secondary preventative measures would be vital too. For example, the statin usage in this current study is not documented, presumably reflecting the recruitment period. Assuming 50% of the population met the now conservative 4S study$^{12}$ criteria (total cholesterol >5.5 mmol.l$^{-1}$) and received a statin for 5 years, this would have saved 11.4 lives. Thus in pursuing the laudable aim of identifying those at high risk of sudden cardiac death we must not forget standard secondary preventative measures.

The goals for the future are clear: to continue to develop better techniques to identify those subjects at high risk of sudden death and who might benefit from implantation of an implantable cardioverter defibrillator. Although the best available evidence indicates that patients with ejection fraction <35% and non-sustained ventricular tachycardia on post-infarction ambulatory ECGs should undergo electrophysiological testing for risk stratification, this approach will have a small overall impact on overall survival in the post-infarct population. A greater impact will be made by full translation of evidence-based secondary prevention measures into clinical practice.

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References


Cell adhesion molecules and inflammation in acute coronary syndromes: markers and emerging risk factors

See page 1226 for the article to which this Editorial refers

Accumulating evidence implicates an integral role for inflammation in all aspects of coronary syndromes, from the pathogenesis of atherosclerosis to plaque rupture and myocardial cell death. In each of these steps, infiltration of cardiovascular tissue with inflammatory cells is evident and is orchestrated by a number of cytokines and cell adhesion molecules. Furthermore, soluble markers of cellular inflammation are present in different stages of ischaemic heart disease and these markers of inflammation may be used to predict subsequent cardiovascular events[3].

Nonetheless, the role of different inflammatory mediators in various stages of acute coronary syndromes is not fully defined and the prognostic information provided by these biomarkers remains controversial. Recent studies, including the innovative study by O’Malley and colleagues[3] in this issue, have tried to more specifically determine the predictive significance of many of these inflammatory makers in acute coronary syndromes. They observed that plasma levels of C-reactive protein (CRP), interleukin-6 (IL-6) and soluble intracellular adhesion molecule-1 (ICAM-1) were all elevated early in acute coronary syndromes, with 71% of the levels drawn within 10 h of the index chest pain. Thus, this provides one of the most detailed studies with regard to the timing of alterations in inflammatory markers. These biomarkers were also strongly correlated with smoking, whereas soluble vascular cell adhesion molecule-1 (VACM-1) and platelet P-selectin were not and were not increased in their study population. Both the IL-6 and the CRP levels normalized during the 3-month follow-up period, while ICAM-1 remained elevated in the acute coronary syndrome patients. This study suggests that smoking may mediate some of its proatherogenic effects through inflammation and ICAM-1 and supports the premise that inflammation is a fundamental component of the development of acute coronary syndromes.

The study by O’Malley and colleagues does have a few limitations. First, the study was done only in patients under the age of 65. This resulted in a population with less co-morbidity and allowed them to more closely determine the interaction of these markers with cardiac risk factors, in the setting of acute coronary syndromes. However, this makes their data less applicable to the general cardiac patient, as typically these patients are older and have other medical conditions. To what extent the changes in serum markers noted in this study can be expanded to a more general population is undefined.

The persistent elevation in ICAM-1 at 3 months, in contrast with a decline in IL-6 and CRP levels may be a reflection of this particular marker in the development of, or in the initiation of, the acute coronary syndrome.