Prevention of sudden death after myocardial infarction (MI) is a challenge on which governmental agencies and industry have spent millions of dollars over the past 3 decades. Although survival of patients after MI has improved over this time period, the major cause of this improvement derives from reduction of infarct size as a result of aggressive reperfusion with thrombolytic agents and percutaneous coronary intervention, as well as evolution of pharmacological management after the acute phase of MI, including β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists. In spite of these advances, we have seen little or no reduction in the relative contribution of sudden death to overall cardiac mortality after MI: Thirty years ago, sudden death accounted for approximately 50% of cardiac deaths in patients with left ventricular ejection fraction (EF) <40 after MI. Observations since the institution of reperfusion therapy for acute MI suggest the relative proportion of sudden deaths has declined to approximately 30% of cardiac deaths in some studies; however, other analyses find that sudden death remains the cause of one-half of all cardiac mortality after MI. In this issue of Circulation, we see that sudden death accounted for 50% of cardiac mortality in patients with recent MI and EF ≤0.40.

These findings document that in spite of recent impressive declines in mortality due to coronary disease, sudden death remains a significant challenge. This challenge persists for multiple reasons. First, sudden death in patients with coronary disease and MI is not a single entity; its mechanisms are heterogeneous and change over time after MI. The heterogeneity of mechanisms means one test will not suffice to identify all patients at risk, and one treatment modality will not be optimal for all. Thus, in spite of implantation of thousands of implantable cardioverter-defibrillators (ICDs) over the past decade, at least half for primary prevention of sudden death, sudden death remains the single most common cause of death due to medical causes in the United States today. Why do we find ourselves in this state? Because we do not have sufficient understanding of the underlying mechanisms that result in sudden death, and we do not understand the immediate factors that trigger cardiac arrest.

It is with this background that the article by Bloch Thomsen et al in this issue of Circulation assumes relevance. The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study is an observational study of 312 survivors of recent MI (within 21 days) whose EF was ≤0.40. Patients underwent a battery of invasive and noninvasive risk-stratification tests, followed by implantation of a loop recorder capable of detecting tachyarrhythmias (≥125 bpm for ≥16 beats) and bradyarrhythmias (≤30 bpm or asystole ≥4.5 seconds) for up to 2 years. After 2 years of follow-up, 25 patients (8% of the study population) experienced 1 of the primary end points: ECG-documented “fatal or near-fatal cardiac arrhythmia, adjudicated as ‘most probably treatable’ by an ICD.” Arrhythmias that occurred in patients with end-stage heart failure or during refractory ischemia were excluded. An earlier publication from this study described arrhythmias at the time of death. Twenty-six patients who had the loop recorder died, and 16 of these had an ECG recorded within 1 hour of death. Arrhythmias at the time of death were equally divided between ventricular tachycardia (VT)/ventricular fibrillation (VF) and bradyarrhythmias. Cardiac mortality was adjudicated as sudden death in 9 patients and as nonsudden death in 10. Among patients with interpretable loop recorder ECGs at the time of death, VF was present in 6 of 9 sudden deaths, and a bradycardia was present in 1 of 9 sudden deaths. It is interesting that VT was not observed at the time of any sudden death. The arrhythmias documented at the time of nonsudden cardiac death included VF (1), VT (1), and bradyarrhythmia (4).

In the present study, the CARISMA Investigators report on all arrhythmias documented by the loop recorder until 24 hours before death, as well as their relation to outcome. For the first time, we have a picture of spontaneous arrhythmias over the first 2 years after acute MI. Highlights of this report include the finding that high-grade atrioventricular (AV) block occurred in 9% of patients (n=29). This event was the most powerful predictor of subsequent cardiac death (10 cases). After discovery of high-grade AV block by the implanted loop recorder, 10 patients received a pacemaker, and 3 were given ICDs. In spite of this, 5 of the 13 patients subsequently experienced cardiac death, including 3 sudden deaths. Of the remaining 16 patients with AV block who did
not receive a pacemaker or ICD, 5 subsequently experienced cardiac death, but only 1 was classified as sudden.

The explanation for the link between high-grade AV block and subsequent cardiac mortality is not clear. It would help to know the level of block (AV node or lower). Intermittent high-grade AV block may reflect unfavorable autonomic balance, which is clearly linked to increased mortality after MI.\(^9\)\(^\text{--12}\) It also may reflect more advanced conduction system disease, which mirrors more advanced ventricular dysfunction. The lack of association between mode of death and AV block limits our ability to make therapeutic decisions based on this finding. The small number of events attenuates the significance of these observations.

Sustained VT occurred in 3% and VF in 2.7% of patients. Of note, 1 of 3 episodes of VF terminated spontaneously. This observation is important, because it explains one of the limitations of attempting to use “appropriate” ICD discharges as a surrogate for sudden death.

The time course of arrhythmias detected by the loop recorder is also of interest. The incidence of AV block was highest within the first 3 months after the MI, but events continued to accrue throughout the 2-year observation period. In contrast, sustained VT and VF were much more concentrated within 3 months after MI, with very few sustained tachyarrhythmias occurring during the remainder of the monitoring period. This is consistent with prior observations and suggests that there are 2 periods of high risk for sudden death via tachyarrhythmias: Early after MI, followed by a latent period, and then increasing numbers of events beginning much later (4 or more years) after the acute MI.\(^13\)\(^,\)\(^14\)

The information provided by the present study augments our understanding of sudden death after MI. The advantage of the loop recorder used for data acquisition is that it provides no therapy, which allows observation of the natural course of arrhythmias (such as spontaneous termination of VF). At the same time, use of the device carries little or no morbidity. However, a number of limitations of the loop recorder and the study must be acknowledged. The device memory is limited; as a result, in 3 cases, the initiation of terminal events was not seen because the event was overwritten. The rate limits that were programmed into the device limited the detection of some arrhythmias, such as atrial fibrillation, with slower ventricular rates that might carry prognostic significance. Although the loop recorder itself does not treat arrhythmias, the findings were used to guide therapy. As noted above, physicians acted on the arrhythmias detected, which resulted in the implantation of pacemakers (10 cases) and ICDs (3 cases). Thus, this is not a “clean” observational study. These device implantations may well have altered the clinical course in some patients and may explain the failure to document any relation between VT/VF discovered on the loop recorder and subsequent death.

There are other limitations to the study worthy of note. Perhaps the greatest weakness is the relatively small size of the study population. That the investigators were able to enroll within a fairly short period the number of patients who did receive the loop recorder, as well as undergo multiple noninvasive and invasive tests, represents a remarkable achievement. Nevertheless, the small number of end-point events limits the strength of conclusions. The enrollment criteria (understandably) limited participation to patients with EF $\leq 0.40$ after acute MI. Patients with EF $\geq 0.40$ accounted for only 24% of the post-MI survivors screened. We know that reduced EF identifies a high-risk group; however, by restricting the study population to patients with low EF, the investigators excluded at least 50% of acute MI survivors destined to die, whether suddenly or not.\(^13\)\(^,\)\(^15\)\(^,\)\(^16\) There are other limitations. Only 21% of the eligible patients actually had the loop recorder implanted. There were a variety of reasons for this, including the death of 89 patients (6% of the patients screened for participation in the study) before implantation. Patient or physician refusal accounted for many exclusions, probably in part because of the extensive risk-stratification testing that was incorporated into the protocol. Other patients were excluded because of planned coronary bypass surgery or serious concurrent illness. Did these exclusions seriously bias the study population? It is hard to know, but review of the patient characteristics suggests that it is probably a reasonably representative post-MI population, with 1 exception. There is no mention of ethnic minorities, and one suspects that these are probably underrepresented. Thus, care should be taken when trying to extrapolate these results to other populations.

Finally, we should question whether the information gathered by the loop recorders has clinical utility. High-grade AV block recorded by the implanted monitor had the strongest relationship to subsequent cardiac death; however, it did not predict the specific mode of death (sudden versus nonsudden), and it does not appear that devices implanted on the basis of the loop recorder–detected arrhythmias had a significant impact on subsequent mortality. Thus, it is difficult to imagine that the widespread use of this device to guide ICD or pacemaker implantation would result in a significant reduction in sudden death. It is interesting (and frustrating) that this innovative device, although able to provide so much information on spontaneous arrhythmias by virtue of its longevity, may be no more useful for guiding antiarrhythmic therapy after MI than a 24-hour Holter recorder, a technology that is 50 years old. The major clinical utility of the implanted loop recorder is in the evaluation of symptoms possibly related to arrhythmias; however, as the CARISMA Investigators have demonstrated, the implantable loop recorder remains an extremely valuable research tool.

This CARISMA substudy is certainly not the last word in describing post-MI arrhythmias; however, it provides a valuable piece in the puzzle of post-MI sudden death. The observations derived from this study provide a sobering reality check, demonstrating the limitations of preconceived notions of mechanisms responsible for sudden death, as well as the limitations of antiarrhythmic therapy such as the ICD.

Disclosures

None.

References


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Implantable Loop Recorder in Survivors of Acute Myocardial Infarction: A Glimpse of Reality?
Alfred E. Buxton

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