Timing of arrhythmic death after myocardial infarction: does it affect timing of ICD implantation?

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This editorial refers to 'Temporal trends on the risk of arrhythmic vs. non-arrhythmic deaths in high-risk patients after myocardial infarction: a combined analysis from multicentre trials' by Y.G. Yap et al., on page 1385.

In spite of significant reduction in total mortality observed in patients discharged after an acute myocardial infarction (MI), ventricular arrhythmias still account for 30–40% of deaths. This figure, which was initially provided by studies carried out in the pre-thrombolytic era, has been subsequently confirmed when most of the patients had been revascularized by thrombolysis or percutaneous coronary intervention (PCI).

Early revascularization and a more generalized use of beta blockers, angiotensin-converting enzyme-inhibitors, statins, and antiplatelet agents have largely contributed to the improvement in the prognosis of patients presenting with an ST-elevated acute MI. Nevertheless, identification of patients at risk remains an issue far from being adequately addressed. There is a general consensus that depressed ventricular function, as reflected by a left ventricular ejection fraction (LVEF) < 40%, represents the strongest negative prognostic factor in these patients. Different cut-off values have proved effective in recent clinical trials and an LVEF < 30% has been used as a single inclusion criteria in studies aimed to evaluate, for example, the beneficial effect of implantable cardioverter defibrillator (ICD) after MI. After the publication of MADIT II results that have clearly indicated a significant reduction of total and arrhythmic mortality in post-MI patients with ICD when compared with controls, ICD implantation has been recommended for almost all post-MI patients with an LVEF < 30%. This position has been only partially accepted by the most recent ACC/AHA/NASPE and ESC guidelines.

The issue has become even more controversial after the publication of the results of the DINAMIT study. More than 600 patients with a recent acute MI and reduced left ventricular function (LVEF < 35%) were randomized to ICD and control. Revascularization rate (either thrombolysis or PCI) was ~62%. The so-called ‘best’ medical treatment was provided to most of the patients. The main result of the study was that prophylactic ICD therapy did not reduce overall mortality in this high-risk population. Moreover, considering the type of death, it was evident that the reduction in the rate of death due to arrhythmia was offset by an increase in the rate of death from non-arrhythmic causes.

A careful comparison of MADIT II with DINAMIT study characteristics provides a partial explanation for such a difference. In addition to the inevitable differences in study population and patient management, it is evident that in MADIT II, the mean time for enrolment was 81 months, whereas in DINAMIT it was 6–40 days. Thus, timing of implantation in relation to the index event was a critical factor not fully considered in the original report and only recently appreciated in the discussion of ICD indication in post-MI patients. Indeed, on reviewing a recent report by MADIT II study group, it is evident that no benefit from ICD could be observed in patients with a less remote MI (<18 months), whereas a tendency for a favourable effect or a significant benefit from ICD was detectable, respectively, at 18–59 months or longer (from 60 to >120 months) after the acute event.

One could therefore extrapolate that, according to DINAMIT and MADIT II, ICD benefit cannot be detected in the first 2 years after an acute MI, thus casting additional doubts to the recommendation of an early ICD implantation in all patients with a depressed LVEF. The lack of benefit from ICD implantation in the first 2 years after an acute MI could be interpreted as an indirect evidence in which, in the reperfusion era, the risk of arrhythmic death becomes predominant only several months after the acute event. Is this opinion founded?

Yap et al. provide a precise description of the temporal trends on the risk of arrhythmic vs. non-arrhythmic deaths after an acute MI. Data were retrieved from the placebo limbs of five major studies carried out in the thrombolytic era on high-risk patients according to the presence of either a depressed ventricular function (LVEF < 40%) or ambient ventricular arrhythmias (more than 10 ventricular premature beats per hour or a run of non-sustained ventricular tachycardia at Holter). The main conclusion of the study was that the overall risk of arrhythmic death from either the index event or day 45 after MI was persistently higher than that of non-arrhythmic death and that this trend did not change over time in a 2-year follow-up period. Moreover,

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the absolute risk of both arrhythmic and non-arrhythmic death was higher in the first 6 months after MI and decreased with time.

These results confirm previous reports and provide a strong rationale for what should be done before discharge in patients with an ST-elevated acute MI: early stratification and, if suggested by guidelines, ICD implantation. It is not clear why ICD trials in post-MI patients fail to demonstrate a clear benefit when the risk of arrhythmic death is greater. The results of DINAMIT study may provide some answers to this question. The authors reported that in ICD carriers, there was indeed a reduction of arrhythmic mortality in the time frame characterized by the greatest risk of arrhythmic death, but this benefit was offset by an increase in non-arrhythmic mortality. It has been suggested that patients saved from arrhythmic death died, at greater extent than controls, from other cardiac causes. In addition, in DINAMIT as well as in other previous studies, almost half of the patients did not present major ventricular arrhythmias during the first years after ICD implantation. Thus, identification of patients with the greatest arrhythmic risk remains a real clinical challenge that urges the reconsideration of the clinical value of available prognostic markers. For example, it is possible that depressed LVEF, which is the strongest predictor of total mortality, might be less effective for arrhythmic risk stratification, in patients with an LVEF < 30% who are at higher risk for death from other cardiac causes. Indeed, data from the MUSST study confirm that ejection fraction by itself does not discriminate between modes of deaths, whereas inducible tachyarrhythmias identify patients for whom death, if it occurs, is significantly more likely to be arrhythmic especially if the ejection fraction is > 30%. Results of the Yap study confirm that the risk of arrhythmic vs. non-arrhythmic death was not different in patients with LVEF < 30% or > 30%.

Evaluation of autonomic tone has been used to improve risk stratification in DINAMIT patients, but SDNN (standard deviation of normal RR intervals), i.e. the most accepted prognostic parameter of heart rate variability (HRV), failed to identify patients with greater arrhythmic risk. A partial explanation for these negative findings is the fact that measures of autonomic tone such as SDNN or baroreflex sensitivity are inversely correlated with LVEF and therefore are less effective in risk stratification of high-risk post-MI patients with depressed left ventricular function.

Recently, in order to identify post-MI patients with increased arrhythmic risk and possible benefit from ICD therapy, attention has been redirected to non-invasive parameters known to reflect alterations of ventricular electrical properties such as QRS duration, ventricular late potential, or microvolt T-wave alternans (MTWA). Hohnloser et al. identified 129 patients with LVEF < 30% from two previously published clinical trials in which MTWA was prospectively assessed within 2 months after an acute MI. At follow-up, no sudden cardiac death or cardiac arrest was observed in patients with negative test, whereas an event rate of 15.6% was detected in patients with abnormal MTWA. A recent report by Bloomfield et al. provides additional support to the potential value of this methodology in the identification of patients at risk. These authors studied 177 MADIT II-like patients with a remote MI. Abnormal QRS duration (>120 ms) and MTWA were detected in, respectively, 32 and 68% of patients. Patients with an abnormal MTWA had a 2-year actuarial mortality rate of 17.8%, whereas patients with a normal test had a very low mortality rate (3.2%). QRS duration did not add any significant additional prognostic information. MTWA testing was therefore highly effective in identifying two subgroups of patients early and late after MI with low LVEF: those at high risk for arrhythmic event and those who will not experience ventricular tachyarrhythmia and thus, likely, will not benefit from ICD implantation. These results, if confirmed in larger prospective studies, could indeed improve our capability of identifying patients at high and low arrhythmic risk not only in the remote but also in the post-acute phase of MI.

Yap et al. provide additional relevant information on the timing of arrhythmic risk in relation to gender, age, hypertension, and smoking habit. While female patients had a similar risk of arrhythmic vs. non-arrhythmic death in the initial months after MI, cardiac non-arrhythmic deaths became predominant later on. This finding, in addition to the small number of women enrolled in ICD trials, makes the interpretation of the effects of ICD implantation in the female gender even more difficult. In contrast, a history of hypertension was associated with a higher ratio of arrhythmic vs. non-arrhythmic deaths. Interference of left ventricular hypertrophy with the remodelling process and persistent adrenergic activation related to hypertension and acute MI may indeed provide an explanation for such a finding and a target for therapeutical strategy. Finally, quite surprisingly and at variance with common expectations, no interactions between mode of cardiac death and smoking status and presence of diabetes were found.

In conclusion, this study based on combined analysis of multicenter trials provides an accurate description of temporal trends of arrhythmic vs. non-arrhythmic risk after MI. The finding that in post-MI patients with LVEF <40% or frequent VPB the risk of arrhythmic death is superior to that of non-arrhythmic death for up to 2 years after the acute event has important clinical implication in relation to risk stratification and identification of patients who can benefit from ICD implantation. Assessment of left ventricular function and evaluation of electrical substrate must be combined to provide the most promising strategy for identifying patients at risk even in the first 2 years after MI when arrhythmic death is predominant.

References


