Arrhythmic death and ICD implantation after myocardial infarction - 2008

Federico Lombardi, MD, FESC

from:

Cardiologia, Dipartimento di Medicina, Chirurgia e Odontoiatria, Osp. San Paolo, University of Milan, Italy

Address for correspondence:
Federico Lombardi, MD, FESC
Cardiologia,
Dip. di Medicina, Chirurgia e Odontoiatria,
Osp. San Paolo, University of Milan,
Via A. di Rudinì 8
201442 Milan, Italy
Tel-Fax: 39 02 50323145
E Mail: Federico.Lombardi@unimi.it

In spite of significant reduction in total and cardiac arrhythmic mortality in post- myocardial infarction patients, ventricular arrhythmias still accounts for 30-40% of deaths. This figure, which was initially provided by studies carried out in the pre-thrombolytic era, has been subsequently confirmed in patients in whom revascularization was obtained by means of either thrombolysis or percutaneous coronary intervention (PCI) (1, 2).

Early and effective reperfusion and, a more generalised use of beta blockers, ACE inhibitor, statines and anti-platelet agents have largely contributed to improve prognosis in patients with ST elevated myocardial infarction. Nevertheless, a still unacceptable number of patients die within two years from the index event and the mortality rate is even greater when myocardial infarction is complicated by a marked depression of left ventricular function. To deal with this problem, identification of patients at risk, which is rarely accomplished in the day by day clinical practice, should become one of the most important features of patient's management (2).

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 post-myocardial these patients (1,2). The relative simplicity of computation and the fact that almost all patients with an acute myocardial infarction have a two-dimensional echocardiographic evaluation before discharge, have largely contributed to this practice. Different cut-off values have been proven effective in recent clinical trials and a LVEF<30% has been used as 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 (3) that have clearly indicated a significant reduction of total and arrhythmic mortality in post- myocardial infarction patients with ICD in comparison to controls, ICD implantation has been recommended for almost all post-myocardial infarction patients with a LVEF < 30%. This position has been only partially accepted by the most recent ACC/AHA/NASPE and ESC guidelines (4, 5) but has been recently put

in discussion after the publication of the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial (6). This study has demonstrated that ICD prophylaxis can improve survival in patients selected primarily by a substantially reduced LVEF. It must be however pointed out, that the absolute benefit of ICD prophylaxis on mortality is relatively small in both studies (5.6 % or 7.2%) that based patients' selection only on LVEF. As a consequence, one could speculate that only a few of ICD implanted prophylactically, deliver appropriate therapy and reduce arrhythmic mortality, thus providing an incomplete answer to this major clinical problem.

Efficacy of ICD in patients with an acute myocardial infarction

The beneficial effect of ICD in patients discharged after an acute MI is even more controversial when considering with accuracy the results of published studies. This issue has been object of renewal interest after the publication of the results of DINAMIT study (7). More than six hundred patients with a recent acute myocardial infarction and reduced left ventricular function (LVEF< 35%) were randomised to ICD or control on the top of best medical therapy. Revascularization (either by means of thrombolysis or PCI) was performed in about 62% of patients. During one year follow-up period, prophylactic ICD therapy did not reduce overall mortality in this high risk population. Moreover, by considering type of death, it became 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 the study design and patients' characteristics of MADIT II and DINAMIT study provides a partial explanation for such a difference. Whereas in MADIT II, the mean time to enrollement after the index event was 81 months, in DINAMIT all patients were randomized within 6-40 days from the acute event. Thus, timing of implantation in relation to the index event appears to be the factor that may explain the difference in the efficacy results. Indeed, by reviewing a recent

report by MADIT II Authors (8), the lack of benefit from ICD implantation is detectable when considering patients with a less remote myocardial infarction (<18 months), whereas a tendency for a favourable effect or a definite and significant benefit becomes evident there after and, in particular, from 60 to > 120 months after the acute event.

One could therefore extrapolate that, according to DINAMIT and MADIT II studies and at variance with our expectations, the benefit from prophylactic ICD implantation is barely detectable in the first two years after an acute myocardial infarction. Further doubts to the recommendation of an early ICD implantation in all post-myocardial infarction patients with a depressed LVEF are a logic consequence of the above findings (9).

Timing of arrhythmic death after myocardial infarction

The lack of benefit from ICD implantation in the first two years after an acute myocardial infarction, could be interpreted in two different ways: first that available data are inadequate to draw definitive conclusions and additional studies are necessary; second that, in the reperfusion era, the risk of arrhythmic death becomes predominant and play a major role only after several month from the acute event. This latter point had been recently addressed by two studies that have provided consistent information.

YAP and co-workers (10) have accurately described the temporal trends of arrhythmic versus non arrhythmic deaths after an acute myocardial infarction. In this retrospective study, data were retrieved from the placebo limbs of five major studies carried out in the thrombolytic era on high risk post-myocardial infarction patients according to presence of either a depressed ventricular function (LVEF <40%) or ambient ventricular arrhythmias (>10 ventricular premature beats/hour or a run of non sustained ventricular tachycardia at 24 hour Holter monitoring). 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, the absolute risk of both arrhythmic and non-arrhythmic death was higher in the first six month after MI and decreased with time.

Similar results were reported by Scott and co-workers (11) who studied 14,609 patients with left ventricular dysfunction or heart failure after an acute myocardial infarction. Seven percent of patients had an event a median of 180 days after myocardial infarction: 903 died suddenly, and 164 were resuscitated after cardiac arrest. The risk was highest in the first 30 days after the index event and decreased slowly thereafter. Patients with LVEF <30% were at highest risk in this early period. Nineteen percent of all sudden deaths or episodes of cardiac arrest with resuscitation occurred within the first 30 days after myocardial infarction and 83% of all patients who died suddenly did so in the first 30 days after discharge. It was also found that each decrease of 5 percentage points in LVEF was associated with a 21% adjusted increase in the risk of sudden death or cardiac arrest with resuscitation in the first 30 days.

These dramatic results, which are consistent with previous reports (1,2) and common clinical experience, unequivocally demonstrate the presence of a higher arrhythmic risk in the first months after an acute myocardial infarction and force to perform in each patients with a ST elevated acute myocardial infarction, an early stratification for the evaluation of the arrhythmic risk. Only thereafter, an ICD implantation should be taken into consideration if supported form guidelines (4, 5).

Timing of arrhythmic death and ICD efficacy.

But why ICD trials in post-myocardial infarction patients fail to demonstrate a clear benefit in the time frame when the risk of arrhythmic death is greater? The results of DINAMIT study (7), as pointed out above, 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 characterised by greatest risk of arrhythmic death but this benefit was offset by an increase in non arrhythmic mortality. It has been hypothesised that patients saved from arrhythmic death might die, and at greater extent than controls, from other cardiac causes (7). If this interpretation is correct, one could draw the conclusion that in the reperfusion era, the presence of a markedly depressed left ventricular function might be less effective in identifying arrhythmic risk, being patients with a LVEF < 30% also at higher risk for death from other cardiac causes. Indeed, data from the MUSST study (12) confirm that ejection fraction by itself does not discriminate between modes of deaths, whereas inducible tachy-arrhythmias identifies patients for whom death, if it occurs, is significantly more likely to be arrhythmic especially if the ejection fraction is ≥30%.

Following these data, one could put in discussion the traditional interpretation according to which, risk stratification has to be mainly or solely performed in patients with a reduced LVEF. By doing so, it is possible that from one side, we only switch the type of death in very sick patients without prolonging life, from the other one; we do not provide adequate protection against arrhythmic risk in patients with a relatively preserved LVEF in whom arrhythmic risk is not trivial and prophylactic ICD implantation could be of benefit.

How to identify patients at risk?

If LVEF is not adequate to identify patients with an increased arrhythmic risk after an acute myocardial infarction, are there any other parameters which can be used in the clinical setting? Evaluation of autonomic tone has been utilised to improve risk stratification in patients enrolled in the DINAMIT study (7). Unfortunately, SDNN (standard deviation of normal RR intervals), i.e. the most accepted prognostic parameter of heart rate variability (13-17), failed to identify patients with greater arrhythmic risk. This negative finding could be partially explained by the fact that measures

of autonomic tone such as SDNN or baroreflex sensitivity are inversely correlated with age and LVEF. For these reasons, they are less effective when used to evaluate arrhythmic risk in patients with depressed left ventricular function (13-17).

More recently, in order to identify post-myocardial infarction patients with increased arrhythmic risk and possible benefit from ICD therapy, other non invasive parameters known to reflect alterations of ventricular electrical properties such as QRS duration, ventricular late potential or microvolt T-wave alternans (MTWA) have been object of investigation (17). Hohnloser et al. (18) identified 129 patients with LVEF <30% from two previously published clinical trials in which MTWA was prospectively assessed within two months after an acute myocardial infarction. At follow-up, no sudden cardiac death or cardiac arrest was observed in patient with negative test, whereas an event rate of 15.6% was detected in patients with abnormal MTWA. A recent report by Bloomfield et al. (8) provides additional support to the potential value of this methodology in the identification of patients at risk after a remote myocardial infarction. These Authors studied 177 MADIT II like patients. Abnormal QRS duration (>120 msec) 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.

A recent report (19) from the same Authors extended pervious observations and provided additional results. The study enrolled 549 patients with LVEF <40% and no history of sustained ventricular arrhythmias. One half of the patients had a previous and remote myocardial infarction (5 year average time). During a two year follow-up 51 end points (40 deaths and 11 non fatal sustained ventricular arrhythmia) were observed. Comparing patients with normal and abnormal MTWA tests, the hazard ratio for the primary endpoint was 6.5 at two years. Survival of patients with normal MTWA test was 97.5% at two years. All the above findings indicate that MTWA testing was

highly effective in identifying two subgroups patients: those at high risk for arrhythmic event and those who will not experience ventricular tachy-arrhythmia and thus, likely not to benefit from ICD implantation.

It must be noticed that whereas MTWA testing appears appropriate to identify high and low risk subgroups of MADIT-II or SCD-HeFT like patients, more controversial remains the definition of the predictive value of MTWA testing in the early months after an acute myocardial infarction, i.e. in the time frame characterized by the highest risk of arrhythmic mortality.

It has been proposed (20) that MTWA may predict outcome if measured at least 30 days after the acute event; results, however, are not unequivocal. For example, Ikeda et al (21) showed that positive MTWA measure 2.7±5.4 months after myocardial infarction predicted sudden cardiac death or resuscitated ventricular fibrillation. However, when MTWA testing was performed (17) before discharge (eight days) in patients with a relatively preserved LVEFG, it failed to predict mortality. A similar negative result was reported by Schwab et al (22) who measured MTWA 15±5 days after an acute myocardial infarction in patients with a LVEF >40%. A partial explanation to these contradictory findings is due to the fact that as a consequence of changes in cardiac electro-mechanical properties due to remodelling, results MTWA testing evolve from the first days to the first weeks after the acute event with a 67% concordance. This pattern of change and poor reproducibility in the first weeks after the acute event prevent the possibility of using what appears to be the most sensitive indicator of arrhythmic risk, for routine stratification before hospital discharge.

More recently, the value of non-invasive risk assessment early after myocardial infarction has been confirmed by the results of two studies(23,24) that have evaluated the predictive role of baroreflex sensitivity and T wave alternans and heart rate turbulence. In the first study carried out in patients with preserved LVEF (23), non invasive evaluation was performed 4 weeks after the index event

and a depressed baroreflex sensitivity but not LVEF and age, was predictive of cardiovascular mortality. In the REFINE study (24) testing 2 to 4 weeks after MI did not reliably identified patients at risk, whereas non invasive evaluation at 10-14 weeks was effective in identifying 52% of subjects at risk with good positive and negative accuracy.

Conclusions.

The finding that in post-myocardial infarction patients with LVEF <40% or frequent VPB the risk of arrhythmic death is superior that that of non arrhythmic death for up to two years after the acute event has important clinical implication in relation to risk stratification and identification of patients who can benefit from ICD implantation. Recent clinical studies, however, indicate that if patients are stratified only according to a reduced LVEF, ICD therapy has little effect on overall mortality. This derives from the fact that the reduction in arrhythmic mortality is counterbalanced by an increase in non arrhythmic cardiac mortality. Recent data have confirmed the limited value of risk stratification at the time of discharge after the index event. Recovery of LVEF due revascularisation and anti-remodelling therapy as well as instability of the electrical substrate are two possible factors that may explain this finding. Nevertheless, arrhythmic mortality is higher in the first month after MI and we have to continue our search for an evaluation of individual risk profile not limited to the determination of the extent of left ventricular function but combined with the analysis of other risk marker such as those reflecting autonomic dysfunction, cardiac electrical instability and presence of subclinical inflammation (25).

References

1) Antman EA. ST-elevation myocardial infarction: management. In:. Zipes DP, Libby P, Bonow RO, Braunwald E, eds; Braunwald's Heart Disease, Elsevier Saunders, Philadelphia Pennsylvania, USA, 2005, pp 1167-226.

2) Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J med 2001;345:1473-82.

3) Moss AJ, Zareba W, Hall WJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.

4) Gregoratos G, Abrams J, Epstein AE et al. ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemaker and antiarrhythmia devices-summary article: a report of the American College of cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2002;40:1703-19.

5) Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Europ Heart J 2003;24:13-15.

6) Bardy GH, Lee KL; Mark DB et al. Amiodarone or implantable cardioverter-defibrillator for congestive heart failure. N Eng J Med 2005;352:225-37.

7) Hohnloser SH, Kuck KH, Dorian P et al. on behalf of the DINAMIT investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481-88.

8) Bloomfield DM, Steinman RC, Namerow PB et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardioverter defibrillator therapy. A solution to the Multicenter Automatic defibrillator Implantation Trail (MADIT) II conundrum. Circulation 2004;110:1885-89.

9) Lombardi F. Timing of arrhythmic death after myocardial infarction: does it affect timing of ICD implantation ? Europ Heart J 2005, 26:1350-2.

10) Yap YG, Duong T, Bland JM et al. Temporal trends on the risk of arrhythmic versus non-arrhythmic deaths in high risk patients after myocardial infarction. A combined analysis from multi-centre trials. Europ Heart J 2005 in press.

11) Solomon SD, Zelenkofske S, McMurray JV et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both. New Engl J Med 2005;3562:2581-8.

12) Buxton AE, Lee KL, Hafley GE et al. for the MUSST investigators. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease. An analysis of patients enrolled in the Multicenter Unsustained Ventricular tachycardia Trial. Circulation 2002;106:2466-72.

13) Camm AJ, Malik M, Bigger JT, et al. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043-1065.

14) Lombardi F. Chaos theory, heart rate variability and arrhythmic mortality. Circulation 2000;101:8-10.

15) Lombardi F, Makikallio TH, Myerburg RJ, Huikuri HV. Sudden cardiac death: role of heart rate variability to identify patients at risk. Cardiovasc. Res. 2001;50:210-217

16) Lombardi F. Clinical implications of present physiological understanding of HRV components. Cardiac Electrophysiological Review 2002;6:245-249.

17) Tapanainen JM, Still AM, Airaksinen KEJ, Huikuri HV. Prognostic significance of risk stratifiers of mortality including T-wave alternans, after acute myocardial infarction: results of a prospective follow-up study. J Cardiovasc Electrophysiol. 2001;12:645-52.

18) Hohnloser SH, IkedaT, Bloomfield DM, Babbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection fraction and benefit from defibrillator implantation. Lancet 2003;362:125-26.

19) Bloomfield DM, Bigger JT, Steinman RC et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;47:456-63.

20) Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 2006;46:269-81.

21) Ikeda T, Saito H, Tanno K et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. Am J Cardiol 2002;89:79-92.

22) Schwab J, Weber S, Schmitt H et al. Incidence of T wave alternation after acute myocardial infarction and correlation with other prognostic parameters: results of a prospective study. Pacing Clin Electrophysiol 2001;24:957-61.

23) De Ferrari G, Sanzo A, Bertoletti A et al. Baroreflex sensitività predicts long-term mortalità after myocardial infarction even in patients with preserved left ventricular function. J Am Coll cardiol 2007;50:2285-90

24) Exner DV, Kavanagk KM, Slawnych M et al. Noninvasive risk assessment early after myocardial infarction. The REFINE study. J Am Coll Cardiol 2007;50:2275-84.

25) Lombardi F. Sympathetic activation and sub-clinical inflammation: a new combination to identify high risk subjects. Eur Heart J 2004;25:359-360.