Editorial

Primary prevention of sudden cardiac death. Do we need to implant a defibrillator in all the patients with low ejection fraction?

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Despite the progress in prevention and treatment of cardiac diseases, sudden cardiac death (SCD) still claims a very high number of lives every year. In patients who have survived cardiac arrest or potentially life-threatening ventricular tachyarrhythmias, the implantable cardioverter-defibrillator (ICD) has been shown to be effective in reducing mortality[1].

In the last few years, several trials have been performed in order to answer the question if ICD implantation could reduce the incidence of SCD when utilized as a primary prevention management strategy, i.e. in patients without a previous episode of life-threatening ventricular tachyarrhythmias. However, the results of these trials varied significantly[2-9].

The first MADIT Trial[2] suggested that prophylactic ICD improved survival in patients with prior myocardial infarction (MI), left ventricular ejection fraction (LVEF) ≤ 35%, asymptomatic non-sustained ventricular tachycardia and non-suppressible ventricular tachycardia during electrophysiologic study (EPS). More recently, data from three large, prospective, randomized, multicenter trials (MADIT-II[5], COMPANION[8], and SCD-HeFT) became available. The MADIT-II Trial[5] demonstrated that in post-MI patients with LVEF ≤ 30%, ICD implantation reduced the relative risk of total death by 31% (5.6% absolute risk reduction during a mean follow-up of 20 months). In the COMPANION trial[8], ICD treatment associated with cardiac resynchronization therapy (biventricular stimulation) reduced the relative risk of total mortality by 36% in patients with heart failure, LVEF ≤ 35% and prolonged QRS duration, both in ischemic or non-ischemic cardiomyopathy during a mean follow-up of 16 months. Preliminary data from the SCD-HeFT Trial confirmed the efficacy of ICD prevention of SCD in patients with heart failure (NYHA class II and III) and LVEF ≤ 35%, with a 23% reduction of the relative risk of total death in the ICD treated group compared to the amiodarone and conventional therapy groups, during a mean follow-up of 40 months (Bardy G. Sudden Cardiac Death in Heart Failure Trial-SCD-HeFT. Oral presentation, American College of Cardiology Scientific Sessions 2004, New Orleans, LO, USA).

Although smaller studies (CAT[6], AMIOVIRT[7], DEFINITE[9]) were not able to demonstrate a reduction of total mortality in ICD treated patient, the current recommendation is to consider primary ICD prophylaxis in all patients meeting the inclusion criteria of MADIT, MADIT-II, COMPANION and possibly, SCD-HeFT. These trials have a low LVEF as a common denominator for risk stratification. To what extent should these trials modify our clinical practice? And do we really need to implant the ICD in all patients with low LVEF? The answer to these questions would have an important clinical and economical impact on the management strategy of SCD.

Low left ventricular ejection fraction as the sole indication for primary implantable cardioverter-defibrillator prophylaxis?

In primary ICD prevention, while the first MADIT Trial selected patients at high

risk for SCD using several different risk stratifiers (LVEF, Holter recording, EPS, drug testing) more recent trials (MADIT-II and SCD-HeFT) applied a rather simple protocol to stratify the patients by using only depressed LVEF.

It is known that the underlying cardiac substrate affects arrhythmia mechanisms and prognosis[10]. SCD is more frequent in patients with coronary artery disease and underlying ischemia may be present in many cases[11]. Thus, the evaluation of a possible need for cardiac revascularization must be the first step before deciding if a patient is eligible for primary ICD prophylaxis of SCD. The CABG-Patch Trial[4] found that prophylactic ICD implantation at the time of elective coronary artery bypass surgery in patients with LVEF < 36% and abnormality of the signal-averaged ECG did not improve survival. More than 80% of patients had a history of prior MI. This trial demonstrated that prophylactic ICD implantation may not be advantageous in patients with previous MI and decreased LVEF (e.g. MADIT-II type patients) if cardiac revascularization is to be performed.

In a meta-analysis of 44 post-MI trials[12], LVEF as a stratifier of SCD had a 59% sensitivity, 78% specificity, 19% positive predictive value, and a 96% negative predictive value. The value of LVEF in risk stratification was not better than other tests (Holter recording, EPS, signal-averaged ECG, and heart rate variability).

There is a relationship between reduced LVEF and the increased of risk of total cardiac death[13]. However, LVEF does not discriminate between sudden and non-SCD[14]. Moreover, the proportion of SCD generally decreases with increasing severity of heart failure according to NYHA functional class[15,16]. Finally, although patients with coronary disease and LVEF < 30% are a high-risk group, more than 50% of patients with MI who later die suddenly have a normal or moderately depressed LVEF[14,17].

Cost-effectiveness and number needed to treat

In analyzing the effect of a new treatment, it is important to define the NNT (number needed to treat to gain 1 life-year). NNT is very difficult to define in ICD trials. The efficacy of ICD increases with the square of time during the first 3 years of follow-up[18]. In clinical or economic evaluations of device implantation it is important to use life-years gained as the measure variable and not to cut short the duration of follow-up to the date at which statistical significance becomes evident. Thus, the MADIT-II Trial has a NNT of 17 at 2 years of follow-up and of 8 at 3 years. Although this may not seem to be a very high number compared to drug based trials, it is nevertheless higher compared to former ICD primary prevention trials, like MADIT and MUSTT[3], which had a NNT of 2 and 2.5 respectively, using a more complex stratification protocol.

Another important issue is to define the cost-effectiveness of a proposed treatment. For the MADIT-II Trial, the final data have not been published. An analysis performed by Reynolds and Josephson[19] showed a very unfavorable cost-effectiveness ratio of ICD treatment at 3 years of follow-up (> $200 000 per life-year saved) for patients meeting MADIT-II criteria. Taking into account the increased longevity of new ICD devices, we could expect that the cost-effectiveness ratio would improve for a longer follow-up. The effect of the ICD on the quality of life should also be considered. For example, up to one third of patients may experience inappropriate shocks, particularly related to paroxysmal atrial fibrillation with high ventricular rate. This side effect could be improved by refinement of algorithms for arrhythmia discrimination.

Finally, it should be appreciated that cost-effectiveness of a certain intervention may change in opposite directions when it is used in lower risk groups or when the cost is reduced. Thus, effective, yet expensive strategies, such as the ICD, are initially utilized in the highest risk patients. As the target groups broaden, its attendant risk and the accrued effectiveness decrease while the cost increases, making cost-effective analysis imperative for each new indication. In other words, what is cost-effective in a small group of high-risk patients may not be so in a larger, lower risk population. *For the immediate future, attempts to optimize the selection process for primary ICD prophylaxis that goes beyond depressed LVEF must continue.*

Conventional risk stratifiers of sudden cardiac death

All recent primary ICD trials addressed patients with one or more conventional risk factors for SCD. The electrophysiologic surrogates for SCD, including measures of myocardial conduction disorders, dispersion of repolarization, and autonomic imbalance, are based on sound scientific evidence. However, the majority of conventional risk stratifiers of SCD have a relatively low positive predictive value that would preclude their wide application as guidelines for ICD implantation in patients known to be at risk for SCD. This is not to mention the impracticality of their use for risk stratification in the general asymptomatic public. Therefore, concern has been raised regarding the cost and potential morbidity of implanting ICD in a large group of patients when only a fraction of them would be expected to benefit from the treatment. In order to maximize the benefit while minimizing expense, an optimal risk stratification strategy should be considered. Unfortunately the ideal strategy for risk stratification for primary ICD prophylaxis has yet to be developed and universally accepted.

The subgroup analysis of the MADIT-II Trial[20] found increasing benefit in patients with wider QRS in-

tervals. In ICD recipients with a QRS > 0.12 s, the reduction in mortality was 63%, substantially greater than the 31% reduction in the trial including all patients. In the COMPANION Trial[5], patients with heart failure, LVEF ≤ 35% and wide QRS were randomized to the best conventional treatment versus cardiac resynchronization therapy in the form of biventricular stimulation or ICD plus cardiac resynchronization. ICD plus cardiac resynchronization therapy reduced by 36% the relative risk of total mortality versus pharmacological treatment. Unfortunately, due to premature trial termination, it was impossible to establish if the reduction in total mortality risk was related to cardiac resynchronization therapy or to ICD therapy. The difference between the cardiac resynchronization group and the ICD plus cardiac resynchronization group was not statistically significant.

Ventricular arrhythmias on Holter recording, signal-averaged ECG, heart rate variability and EPS evaluation have low sensitivity and only modest specificity in post-MI risk stratification[12]. The MUSTT Trial found that EPS-guided antiarrhythmic therapy (including the ICD) reduced the risk of SCD in patients with coronary artery disease, LVEF ≤ 40%, asymptomatic non-sustained ventricular tachycardia and inducible sustained ventricular tachycardia. The CABG-Patch Trial found that prophylactic ICD implantation at the time of elective bypass surgery in patients with LVEF < 36% and abnormality of signal-averaged ECG did not improve survival[4]. The ongoing DINAMIT Trial[21] randomized post-MI patients with LVEF < 35% and additional evidence of impaired autonomic tone. In this regard, the ATRAMI study[22] has provided clinical evidence that after MI, analysis of the autonomic system in the form of baroreflex sensitivity, has a significant prognostic value independent of LVEF and ventricular arrhythmias, and that it significantly adds to the prognostic value of heart rate variability. However, this test has not been evaluated in a prospective ICD trial.

Some recent data suggest that T-wave alternans analysis could stratify patients meeting MADIT-II criteria by selecting those at very low risk of SCD in which ICD therapy may not be indicated[23].

It is remarkable that the two ICD trials (MADIT and MUSTT) that used a complex stratification protocol to select patients at high risk for SCD, including LVEF, Holter recording, EPS, and drug testing, showed the efficacy of ICD treatment with better NNT and cost-effectiveness ratio compared to the trials that used LVEF alone.

The Italian situation

From the data of the ICD Italian Registry (Proclemer A. Oral presentation, ANMCO National Congress 2004, Florence, Italy,) and from industry data, about 6000 ICDs were implanted in Italy in 2003 (corresponding to 100 per 1 million people). Of these only a very small number were implanted in post-MI patients for primary prevention of SCD.

Because of the recent progress in the treatment of acute MI, particularly the widespread use of primary percutaneous coronary intervention, it is difficult to estimate the number of post-MI patients with a low LVEF. Using a conservative estimate, if the ICD is implanted in all the patients meeting MADIT, MADIT-II, COMPANION and SCD-HeFT criteria, the number of ICD implantation per year would double.

The amount of expenditure of the health care systems varies in the different countries, but is always limited. Is Italian health care system able to deal with such an increase in expenditure, or will it be necessary to compare ICD treatment to other cardiological and non-cardiological treatments, in order to prioritize the allocation of healthcare resources?

The future paradigm for management of sudden cardiac death in the population at large

SCD is a major public health problem worldwide, but especially in the United States and Europe. Appropriately, SCD prevention has become one of today's most critical public health challenges. An acknowledged major limitation of management strategies of SCD is the fact that the majority of SCD occurs in the general asymptomatic public, where the incidence is low. The current management of SCD is directed at a relatively small percentage of the total population at risk and primarily at patients already known to be at increased risk by conventional criteria. In the last several years, there has been an accumulating body of evidence suggesting that there may be molecular, genetic, biophysical, and biochemical indicators of SCD. Based on this evidence, the future goals for risk stratification and management of SCD in the general public could be summarized as follows[24]:

• identification of novel clinical, biochemical, and genetic markers for SCD and assessment of the functional consequences of sequence variants identified in human genetic studies, as well as relevant environmental-genetic interactions;

• determination of the heritability of genetic risk factors for SCD, as well as the factors involved in ethnic specific differences in risk of SCD;

• identification of a battery of a relatively limited number of incrementally cumulative low-to-intermediate risk variants and development of a "signature" combination of clinical, biochemical, and genetic markers of SCD. However, we should not be surprised that the positive predictive value of some of the new risk factors, similar to conventional risk factors, will be relatively low, especially if they are applied to large populations that are at low risk. In fact, the true value

of risk stratification of SCD in the future may be to identify low-risk populations that do not warrant prophylactic intervention with therapy with demonstrated efficacy, e.g., the ICD. One approach is to target patients who receive the ICD for primary prophylaxis per approved criteria and concomitantly conduct studies within those cohorts to attempt to identify the low-risk patients;

• identification of novel pharmacologic and non-pharmacologic approaches for risk modification and prevention of SCD. A prime example is the recent interest in clinical prevention of SCD by n-3 polyunsaturated fatty acids. Although this relatively new diet-heart hypothesis that underlies this therapeutic modality has yet to catch the attention of the clinical community at large, experimental and clinical evidence points to the validity of this approach;

• wider collaboration among different academic and industrial institutions by sharing research results and resources such as clinical data, blood, and other tissues from biorepository centers. The ultimate goal is to identify novel methods for risk stratification, risk modification, and prevention of SCD that can be applied to the general public at large.

Conclusions

It is currently accepted that primary ICD prophylaxis is effective in saving lives when applied to well-defined populations at increased risk of SCD. For the present, this management strategy ought to be adopted in Italy, irrespective of costs. On the other hand, it is increasingly realized that a low LVEF should not be the sole arbiter for patient selection for primary ICD prophylaxis. Therapeutic decisions must be based on strong clinical evidence. It is hoped that the accelerating pace of basic and clinical research in this field will ultimately result in a universally accepted optimal management strategy for SCD.

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