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Risks in Risk Stratification: What Is Relevant in Practice?

To the Editor:

La Rovere et al published an excellent article on neuroautonomic measurements as predictors of life-threatening arrhythmias. The authors concluded that these measures could be used to identify patients who might benefit from an implantable cardioverter-defibrillator (ICD). However, because the study was based on an observational design, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study results are also influenced by certain biases that make this conclusion arguable.

When searching for predictors of arrhythmic death, we should bear in mind that the only therapeutic option, an ICD, is expensive. With the current indications for ICD implantation, 30% to 50% of the patients receive appropriate shocks. This level of accuracy is considered cost-effective. This fact implies that, in prophylactic ICD therapy, the positive predictive accuracy (PPA) of the test should exceed 30% and be combined with reasonable sensitivity. La Rovere et al do not report the PPA of the variables in their study. On the basis of the data presented, the PPA seems to be around 15% with the best combination of tests, indicating a relatively low accuracy in terms of the need to implant an expensive device.

Optimal therapy may be important for the prediction of arrhythmic death. Only 20% of the patients were on β-blocking medication in the ATRAMI study. Because the majority of the patients were not treated according to the current guidelines, it is difficult to know the impact of these variables among patients with optimal medical therapy after a myocardial infarction. This is important because β-blocking medication may affect the measured risk variables. A combined end point of sudden death or sustained ventricular tachycardia was used in the ATRAMI study. This combination causes an end-point bias without specificity as to the exact mode of death. Many conditions other than arrhythmias that evolve rapidly may lead to sudden death. In this respect, it remains uncertain whether the variables used in the study really predicted the occurrence of life-threatening arrhythmias that were preventable with an ICD.

There are various other risk markers for life-threatening arrhythmias, but we do not know which one would be the most useful. Despite the promising ATRAMI results, we need further observational studies with multiple risk indices in patients with optimal therapy and well-defined end points. After that, randomized prospective clinical trials with intervention will be of pivotal importance to resolve the everlasting dilemma of the prediction and prevention of sudden arrhythmic deaths.

“Prediction is difficult, especially of the future.” These were the words of the Nobel Prize winner Dr Bohr, who studied the movements of electrons around atoms. At the moment, we face a similar problem in the prediction of sudden cardiac deaths.

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Response

Because of space limitations, we can address only the main comment by Mäkikallio and Huikuri, which is based on the “current indications” for internal cardioverter-defibrillator (ICD) implantation in primary prevention—namely, the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT). Our study did not question the indications emerging from MADIT. We expressed concern that the likely success of MADIT II and of Sudden Cardiac Death in Heart Failure: Trial of prophylactic amidarone versus implantable defibrillator therapy (SCD-HeFT), which randomized patients solely on the basis of a depressed left ventricular ejection fraction (LVEF), would lead to a large increase in the number of ICD implants. Zipes did the same in an editorial on the cost-effectiveness ratio of the ICD, calling for “careful patient selection.” Thus, the figure of a minimum of 30% positive predictive accuracy (PPA) is just a technical device to develop a thesis, and it has the potential to mislead readers. A high PPA cannot be expected when the rate of events is low and arrhythmic mortality is progressively shrinking.

It may interest the readers to see the practical implications, for both arrhythmic deaths and total cardiac mortality, of the strategy for risk prediction emerging from our study. A combined score of an LVEF ≤35% and a depressed baroreceptor reflex sensitivity (BRS) was observed in 52 patients, 8 of whom had an arrhythmic death, for a PPA of 15%. If the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study population had been stratified according to the MADIT II criteria, with 157 patients with LVEF ≤35% and 11 who died, there would have been a PPA of only 7%. Thus, using the MADIT II criteria, 3 more lives could be saved (37%), but this would be achieved at the cost of implanting 105 more ICDs, an increase of 202%. Looking at total cardiac mortality, among the same 52 patients in ATRAMI, there were 11 deaths, for a PPA of 21%. If one considers patients with an LVEF ≤35% and either depressed BRS or nonsustained ventricular tachycardia (NSVT), there would be 70 patients with 14 deaths and a PPA of 20%. By contrast, among the 157 patients with just a depressed LVEF, there were 18 deaths, for a PPA of only 11%.

How do all these numbers translate in terms of cost-effectiveness? Assuming the current cost of $22 000 US for an ICD (just the hardware), the cost for a life saved (arrhythmic mortality), considering all patients with an LVEF ≤35% and a depressed BRS at risk, would be $770 000 US (105×22 000/3). In the case of total mortality, the cost for a life saved, considering all patients with an LVEF ≤35% at risk instead of using our combination with


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BRS or NSVT, would be $478 500 (87×22 000/4). Improved selection of patients with newer tests will help to maximize the cost-effectiveness of the ICD.

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