The implantable cardioverter-defibrillator (ICD) has been shown to be an effective therapy for the prevention of sudden cardiac death (1), an entity that remains a significant public health problem. However, because device implantation carries risks and is costly, the challenge has been to identify patients most likely to derive benefit from ICD implantation, especially those patients who have not yet suffered a clinical event (i.e., a primary prevention cohort). Toward this end, a number of randomized clinical trials have evaluated the efficacy of ICD implantation, as assessed by improvements in overall survival.

Left ventricular dysfunction identifies a patient cohort at particularly high risk for sudden death. As a result, most of these variables are readily ascertained noninvasively in patients with a negative electrophysiology study (3). As a result, more recent trials have focused on the presence of left ventricular dysfunction, either alone or in combination with underlying New York Heart Association (NYHA) functional class II or III congestive heart failure (4,5). Because these trials still demonstrate the benefit of ICD implantation (albeit of a smaller magnitude), current practice guidelines recommend ICD implantation in patients with ischaemic heart disease who are at least 40 days removed from myocardial infarction, have an EF ≤30%, with NYHA functional class II or III heart failure symptoms while on optimal medical therapy (class I indication), or in patients with an EF ≥30% to 35% due to any origin and NYHA functional class II or III heart failure symptoms while on optimal medical therapy (class IIa indication) (6).

Therefore, more recently, investigators have sought to identify patients with left ventricular dysfunction who may not derive benefit from ICD implantation. For example, Buxton et al. (12) recently reported on the limitations of using EF alone for predicting arrhythmic death and overall mortality using data derived from MUSTT (the Multi-center Unsustained Tachycardia Trial). This trial enrolled patients with a previous documented myocardial infarction, an EF ≤40%, and nonsustained ventricular tachycardia; management was directed by the results of electrophysiologic testing. Using a cohort of 670 patients (either those in whom no ventricular arrhythmia was inducible or inducible patients randomized to no therapy) in whom data for NYHA heart failure functional class were available, the authors identified several variables that predicted overall mortality. These included EF, the presence of congestive heart failure, and noncardiac co-morbid conditions such as renal failure, chronic pulmonary disease, peripheral vascular disease, and diabetes occur frequently in patients currently undergoing ICD implantation and adversely affect prognosis (11).

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In this issue of the *Journal*, Goldenberg et al. (13) provide additional novel insights from MADIT (Multicenter Automatic Defibrillator Implantation Trial-II), which enrolled 1,232 patients with documented myocardial infarction and an EF ≤30%; patients were randomized in a 3:2 ratio to receive either an ICD or continue conventional medical therapy. The authors first identified a “very high risk” (VHR) population (representing 5% of the overall study cohort), defined by the presence of underlying renal dysfunction (blood urea nitrogen [BUN] ≥50 mg/dl and/or creatinine ≥2.5 mg/dl). It should be noted that, by design, patients with a BUN >70 mg/dl or a creatinine level >3.0 mg/dl were specifically excluded in the overall MADIT-II study.) As compared with non-VHR patients, VHR patients were older, had a lower EF, had more advanced heart failure, and a wider QRS duration. The crude 2-year mortality in VHR patients treated with medical therapy was nearly 50% and was not improved by ICD implantation.

For the non-VHR patients, using a multivariate proportional-hazards regression model, the authors identified 5 clinical variables that predicted all-cause mortality in patients assigned to conventional medical therapy. These included NYHA functional class congestive heart failure >II, the presence of atrial fibrillation (defined as the baseline rhythm at enrollment), a QRS duration >120 ms, age >70 years, and a BUN >26 mg/dl (and, by definition, <50 mg/dl). A single point was assigned to each of these 5 variables to create a risk score ranging from 0 to ≥3. Importantly, nearly one-third of the study population had none of these risk factors (a score of 0). These patients had a 2-year mortality of only 8%; ICD implantation did not further reduce mortality in this subset of patients. In contrast, patients with ≥1 risk factor had 4 times the mortality of patients with no risk factor; ICD implantation in patients with ≥1 risk factors was associated with a nearly 50% reduction in mortality. The benefit was most pronounced in patients with 1 or 2 risk factors, a cohort that represented half the overall study population and in whom sudden death predominated as the cause of death.

What implications do these findings have on the selection of patients who are appropriate candidates for ICD implantation? Certainly, these data are applicable only to patients with coronary artery disease, history of previous myocardial infarction, and left ventricular dysfunction. However, the 5 “high-risk” markers identified by Goldenberg et al. (13) appear to be consistent with findings in other clinical settings. For example, in a population comprising a predominantly secondary prevention cohort, Klein et al. (14) identified left ventricular dysfunction (EF ≤40%), permanent atrial fibrillation, and a QRS duration ≥150 ms as independent predictors of a recurrence of a ventricular tachycardia after ICD implantation.

In the context of findings reported by the MUSTT Investigators, the analysis of the MADIT-II data by Goldenberg et al. (13) confirms that a significant proportion of patients with an ischemic cardiomyopathy lack other risk factors for sudden death. These patients have a low absolute risk of death that is not further attenuated by ICD implantation. We must keep in mind, however, that data being reported are for 2-year mortality risk, which represents a relatively short period of follow-up. Whether these findings persist over longer follow-up periods remains unknown. Second, although a wide variety of markers have been used for risk stratification (e.g., signal-averaged electrocardiography, T-wave alternans, heart rate variability), it may be that variables readily obtainable in an in-office setting, such as age, the presence of atrial fibrillation, degree of heart failure, QRS duration, and degree of renal dysfunction, may effectively risk stratify patients with an ischemic cardiomyopathy. Of concern, however, is that these variables are not static. Rather, patients get older, go in and out of atrial fibrillation, have exacerbations of congestive heart failure, and often have varying renal function. The impact of this variability on patient outcome also remains undefined.

What is clear is that EF alone is likely not enough when making judgements regarding the need for ICD implantation in an individual patient with an ischemic cardiomyopathy. The challenge now before us, however, is to investigate these variables in a prospective manner. As a starting point, potential expansion of the ICD Registry (from the National Cardiovascular Data Registry) to include information on long-term mortality would be very useful in defining prospectively the prognostic utility of these proposed “high-risk” variables, especially because these variables are all captured within the database. Without having these types of data, practice guidelines will remain unchanged and it will be hard (if not impossible) to deny “eligible” patients the option of ICD implantation. It is not always easy to put the genie back into the bottle.

**REFERENCES**


