Randomized clinical trials have clearly shown that the implanted cardiac defibrillator (ICD) saves lives and that cardiac resynchronization therapy (CRT) and combined ICD and CRT devices reduce both heart failure and mortality. However, during long-term follow-up of patients with these implanted devices, only a minority will use appropriate ICD therapy for life-threatening ventricular tachyarrhythmic events. For example, in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), only 35% of the patients in the ICD arm received appropriate ICD therapy (shock or antitachycardia pacing) during 3-year follow-up. The challenge facing the medical profession is how to better identify and select patients who will benefit from implanted ICD or combined ICD and CRT devices so as to achieve greater therapeutic efficacy without losing patients. During recent years, several noninvasive and invasive electrophysiological tests have been evaluated, including signal-averaged ECG, heart rate variability, heart rate turbulence, T-wave alternans, and programmed electrophysiological testing, but the risk-stratification results from these tests have not been very encouraging. Recently, Goldenberg et al demonstrated that the ICD:conventional therapy hazard ratio in patients with advanced renal disease (blood urea nitrogen >50 mg/dL) and in good-risk patients without adverse clinical factors such as heart failure, atrial fibrillation, older age, and wide QRS complex, renal dysfunction was close to 1.0 in 35% of the ICD-treated patients, with no evident benefit from the ICD. The remaining 65% of the at-risk ICD-treated patients received considerably enhanced benefit from the ICD, with a 50% or greater reduction in mortality. These findings are encouraging, but we should be able to do better.

A thoughtful and innovative approach for analyzing risk-benefit considerations for patients treated with the ICD is presented in the article by Koller et al in the current issue of Circulation. In the introduction, the authors point out the obvious: patients who die before the first appropriate ICD therapy and ICD patients who never sustain a ventricular tachyarrhythmia during follow-up will not benefit from an ICD. With this as background, the authors evaluate the probability of appropriate ICD therapy versus death without prior appropriate ICD therapy in 442 patients enrolled and followed in their prospective single-center ICD registry from 1994 to 2006. A competing risk methodology (cumulative incidence function) was used to evaluate the competing events over time with predefined covariates included in the model. The study, the approach, and the findings are of considerable interest. In brief, the authors conclude that the risk of death before appropriate ICD therapy was substantial, especially in patients with advanced heart failure. If this very high-risk, non–ICD-firing subgroup could be accurately identified, patients belonging to this subgroup could be excluded from implantation of an ICD device because they do not receive antitachycardia therapy before death.

Let us take a closer look at this study. From a methodological point of view, the authors applied an accepted competing-risk approach to study the processes of benefit and loss in ICD-treated patients, an actuarial approach that has been used in evaluating time-related fatal and nonfatal events after prosthetic valve replacement. In the Koller et al study, appropriate ICD therapy was dominated by termination of ventricular tachycardia, either by antitachycardia pacing or shock. However, it is more appropriate to focus on ventricular fibrillation–terminated events. The key finding is that the cumulative incidence of appropriate ICD therapy for lifesaving ventricular fibrillation events was 13% (23 patients) during a median follow-up of 3.6 years, during which time 23% (57 patients) died, largely from heart failure, without prior ICD therapy. Diuretic use at the time of ICD placement, a surrogate marker for baseline heart failure, was associated with a 4-fold increased risk of death before ICD therapy during follow-up. It should be noted that only 16% of the 442 patients had a resynchronization combined ICD and CRT device, which has been shown to reduce heart failure and death.

This study comes with several interesting caveats. Appropriate ICD therapy was twice as likely in patients with a secondary as opposed to a primary indication for implantation of the ICD. Appropriate ICD-therapy increased by 20% for each 10% decrease in ejection fraction. Older patients received more appropriate ICD therapy (benefit) than younger patients, a finding that is in accord with the recent study by Huang et al. The occurrence of appropriate ICD therapy progressively decreased over time with no first ICD therapies for ventricular fibrillation observed during the 6- to 8-year interval after device implantation. This latter finding raises questions about the benefit to be achieved with device replacement in those who have never had a device firing at the end of battery life at 4 to 5 years after ICD implantation. As in any good study, a few issues can be pointed to that raise concern. Only baseline clinical risk factors were used in the competing risk approach, yet recent data indicate that...
time-dependent risk factors such as interim heart failure during follow-up are the major risk factors for appropriate device therapy. The failure of Koller et al to include interim (postenrollment) time-dependent covariates such as heart failure, coronary events, and interim drug changes and usage in the risk analysis weakens the interpretation of the findings. Programming of ICD and combined ICD and CRT devices was not standardized or uniform, and information is not provided about the specifics of antitachycardia pacing and shock detection therapy zones used. The rate at which the ventricular back-up pacing was set would be important to know because ventricular pacing can affect heart failure. Also, the authors fail to provide any information about the frequency of inappropriate ICD therapy. Because postmortem device interrogation was not routinely performed, it may be that some of the deaths without documented prior ICD therapy may have been a failure of the device to terminate the first fatal ventricular fibrillation episodes.

Many advances have taken place in device technology and in clinical electrophysiological practice since patient enrollment began in the Koller registry in 1994. Nevertheless, the competing-risk approach used in the study opens a new chapter in the application of risk stratification to implanted electrotherapeutic devices. The authors are to be commended for focusing on ways to save lives.

Disclosures
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Arthur J. Moss

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