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EDITORIAL COMMENT

Understanding Implantable Cardioverter-Defibrillator Shocks and Mortality*

On Trial

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As a result of large randomized clinical trials, the implantable cardioverter-defibrillator (ICD) is now well established for its life-saving role in the prevention of sudden death in patients at risk with a history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or those with heart failure and severe left ventricular dysfunction (1–3). The ability of the ICD to deliver high-voltage therapy to terminate lethal ventricular arrhythmias—an ICD shock—is what saves lives. Nonetheless, in real-world ICD recipients, the issue of inappropriate or unnecessary ICD therapy for nonlethal arrhythmias is troubling. Approximately 10% to 17% of patients receive an inappropriate ICD shock within the first few years of implantation of the device (4–6).

See page 1674

Additionally, data from clinical trials have consistently shown an association between ICD shocks and subsequent cardiovascular events. In MADIT II (Multicenter Automatic Defibrillator Trial II), the risk of death over an average of 21 months of follow-up in those who survived appropriate ICD therapy was more than 3-fold greater than in those who survived without receiving ICD therapy (7). The excess mortality was driven by an abundance of heart failure and nonsudden cardiac death events in the group that received successful ICD therapy, suggesting the possibility that ICD therapy may be a marker of a more severe cardiomyopathic process. In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), the risk of mortality for those who survived >24 h after a first appropriate ICD shock was 3 times that of those who did not receive a shock over a median 45.5 months of follow-up (5). Certainly, patients who develop ventricular arrhythmias necessitating an ICD shock may be a priori at higher risk for cardiovascular events, which would explain a large part of this association. Additionally, these patients, having survived what could have been a terminal arrhythmic event without the ICD, are subsequently at risk for competing causes of both cardiovascular and noncardiovascular mortality. However, in the SCD-HeFT trial, a first inappropriate shock was also associated with a 1.6-fold increase in mortality (5). In the MADIT II study, there was a 2.3-fold increased risk of mortality with an inappropriate shock (4). These findings have fueled a debate as to whether the adverse cardiovascular outcomes after an ICD shock are related to the underlying cardiac arrhythmia or are a harmful effect of the shock itself.

In this issue of the *Journal*, Powell et al. (8) report the results of a large ICD patient remote monitoring database. In the ALTITUDE Survival by Rhythm Study, 3,809 patients who survived a first ICD shock for an appropriate or inappropriate cause were matched to control patients who had not had an ICD shock and followed up over a mean of 2.1 years. The majority of first shocks were appropriate and largely for monomorphic VT. However, 41% were inappropriate due to supraventricular tachyarrhythmias, such as atrial fibrillation/atrial flutter (AF/AFL), sinus tachycardia, or other supraventricular tachycardia, or nonarrhythmic causes that included lead noise, artifact, or oversensing. Mortality was significantly increased for patients with first shocks for monomorphic VT (hazard ratio [HR]: 1.65, $p < 0.0001$), polymorphic VT/VF (HR: 2.10, $p < 0.0001$), or AF/AFL (HR: 1.61, $p = 0.003$). However, there was no increased risk of mortality for those patients with inappropriate first shocks related to lead noise, artifact, or oversensing (HR: 0.91, $p = 0.76$) or for rhythms such as sinus tachycardia or supraventricular tachycardia (HR: 0.97, $p = 0.86$). Notwithstanding the limitations, acknowledged by the authors regarding the limited clinical data available from this observational study and precluding adjustment for patient comorbidities and medication use, these data support the hypothesis that "the adverse prognosis after first shock appears to be more related to the underlying arrhythmia than to an adverse effect from the shock itself." This was an unresolved question from the ICD clinical trials due to the small sample of patients receiving shocks for nonarrhythmic causes in both the SCD-HeFT trial and MADIT II; the large number of both appropriate and inappropriate ICD therapies in the ALTITUDE study allowed this issue to be examined in detail.

The excess of heart failure events and mortality seen in the patient population surviving after an ICD shock has been referred to as a "paradox" (9) because the same therapy previously proven to extend survival has been argued by

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some to be potentially deleterious and even hasten the demise of certain patients. Animal studies and small studies in humans have implicated high-voltage shocks in causing myocardial damage, as evidenced by troponin release or transiently impaired contractile function (10,11). Some have suggested that these effects explain the increase in adverse cardiac outcomes seen in ICD shock recipients, although this belies the long-term survival benefit seen with primary ICD therapy over extended follow-up in MADIT II (12) and the SCD-HeFT trial (13). Now, in light of the ALTITUDE study results, the alternative explanation is more reasonable: the occurrence of morbid arrhythmias, specifically ventricular arrhythmias and AF, identifies a high-risk patient population. The findings of this study add to the consistent association previously identified between shocks for VT, VF, or AF and subsequent mortality. In the case of VT/VF, it is not difficult to conclude that the connection between these arrhythmias and a destabilizing milieu such as myocardial ischemia or progressive heart failure explains the increased risk of mortality. In the case of AF, not only has it been consistently identified as an independent risk factor for mortality in heart failure (14), but the rapid ventricular response in AF that results in an ICD shock was postulated by the authors to be a marker for inadequate beta-blockade or increased sympathetic neurohormonal activation in heart failure (8). The ICD shock in either case is the innocent bystander in the equation and not the guilty suspect.

Unfortunately, modern-day ICD therapy is still imperfect. ICD intervention rates in real-world primary prevention patients are as high as 30% per year, with a considerable percentage of these either inappropriate or "appropriate" therapies delivered unnecessarily for self-terminating arrhythmias such as nonsustained VT (15). The issue of ICD programming is important to discuss. The ALTITUDE study contained a mixture of primary and secondary prevention ICD recipients, and the programming of ICD therapy zones was not standardized because devices were managed according to each physician's practice. Recently, results from a large randomized trial of primary prevention ICD programming, MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy), demonstrated that programming ICDs to only treat arrhythmias $\geq$200 beats/min, was associated with a significant reduction in all-cause mortality as compared with conventional programming (16). The reduction in mortality with the high-rate strategy paralleled a significant reduction in the incidence of ICD therapies in this group, driven by a profound decrease in the burden of antitachycardia pacing (ATP). Some of these ATP episodes were inappropriate ATP for atrial arrhythmias that were subsequently converted into ventricular arrhythmias by the ATP. Others were ATP episodes for VT that might have self-terminated without the need for ICD therapy, as evidenced by the lower incidence of appropriate ICD therapy in the less aggressive programming arms. Further analysis of the study data is needed to clarify the reasons for the increased mortality observed in the ICD programming arm that received conventional 2-zone therapy for VT and VF. Although ATP has been an attractive solution for electrophysiologists to replace shocks with a "painless" alternative to ICD therapy, the results of MADIT-RIT have called into question the routine practice of empiric ATP programming in patients without known monomorphic VT.

When used and programmed appropriately, the ICD reprises its role as the Good Samaritan, providing the best line of defense against sudden death in patients at risk for lethal ventricular arrhythmias. It is important to note that most patients who received a shock for VT or VF in the ICD clinical trials were alive at the end of each study (12,13). The fact that all patients do not survive should not come as a surprise. Ventricular arrhythmias may represent a final common pathway in otherwise terminal conditions such as end-stage heart failure or multiorgan failure. In any case, the debate as to whether an ICD shock carries an additional risk to the patient from shock-induced myocardial damage becomes a futile exercise, because the patient would have died either without or despite the shock. We still should seek to decrease ICD shocks, primarily to reduce unnecessary ICD therapy and to alleviate the adverse psychological effects associated with inappropriate ICD shocks in patients. However, in the case of the increased risk after ICD shock, it is the associated arrhythmia in a vulnerable patient that explains the increased cardiovascular risk and not the shock in isolation. In the meantime, as the effect of ICD discharges on subsequent mortality continues to be debated, may the results of the present study allow the defense to rest its case on a preponderance of evidence and recommend a verdict of "not guilty."

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JACC Vol. 62, No. 18, 2013
October 29, 2013:1680–2

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Key Words: atrial fibrillation ■ cardiac resynchronization therapy ■ implantable cardioverter-defibrillator ■ ventricular tachycardia.