Azimilide: Another Effort to Prevent Implantable Cardioverter-Defibrillator Shocks and Their Sequelae

Why it Is Important and How it Works*

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Over the past decade, a series of randomized clinical trials using the implantable cardioverter-defibrillator (ICD) have demonstrated a reduced mortality compared with that of the best medical therapy in selected populations with ejection fraction (EF) <40%. Only patients with a low EF due to recent acute myocardial infarction or recent coronary bypass surgery do not benefit as seen in prior trials. Subsequent ICD shocks remain of great interest to investigators since device therapies are associated with significant patient morbidity and mortality.

Patients with ICDs receive frequent shocks from their devices. In the AVID (Antiarrhythmic Versus Implantable Defibrillator) trial, there was a 46% incidence of shocks at 1 year (1). In the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study, during the 17.2-month follow-up of 719 subjects, 169 (24%) received appropriate and 83 (11.5%) received inappropriate ICD therapy (2,3). ICD shocks have a negative impact on quality of life including anxiety, panic, depression, and decreased physical and sexual activity. A meta-analysis shows that psychological intervention reduces anxiety and depression (4). It is not surprising that the impact of ICD shocks is related to a patient’s personality type and social network (5).

The MADIT II study evaluated the effect of placebo versus ICD on total mortality in patients with coronary artery disease and an EF ≤30% (6). At 2 years, the total mortality was reduced 31% by the ICD compared with that seen with medical therapy. A retrospective analysis of the MADIT II study population showed that during the 2 years of the trial 21% of patients were hospitalized for congestive heart failure (CHF) (7). A higher number of patients in the ICD group required hospitalization (23%) compared with the conventionally treated group (17%, p = 0.02). The occurrence of an appropriate shock was a significant predictor of both CHF hospitalization and subsequent death. The effect of antitachycardia pacing (ATP) was not separately analyzed. The occurrence of an ICD shock and resultant CHF thus mitigated the mortality benefit of the ICD in the MADIT II study. Possible explanations for this finding include prolongation of life by effective ICD therapy allowing more time for CHF to occur or, conversely, that cardiac muscle and function are damaged by the ICD shock and cause CHF.

It is essential to minimize ICD shocks for patient comfort even if a mortality benefit is uncertain. One-third of ICD patients are treated with antiarrhythmic drugs after insertion. A recent meta-analysis showed that amiodarone is more effective than a beta-blocker in reducing ICD shocks (8). Sotalol is no better than a beta-blocker (9). No antiarrhythmic drug is approved by the Food and Drug Administration specifically as a therapy to reduce ICD shocks. Lipid-lowering agents also reduce ICD shocks (10).

Sophisticated programming of ICDs reduces shocks. Aggressive ATP for ventricular tachycardia rates over 200 beats/min will reduce the number of shocks by 80% (11). Extending the number of intervals to detect a ventricular arrhythmia before delivering defibrillating therapy reduces shocks because many arrhythmias self-terminate. Cardiac ablation as first-line prophylactic therapy to reduce shocks in ICD populations is surprisingly effective. The SMASH-VT (Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia) trial showed that patients randomized to primary ablation after device insertion had appropriate ICD shocks reduced from 33% to 15% (12).

Azimilide is an investigational class III antiarrhythmic drug with effects on the IKr and IKs potassium channels; IKr block exhibits reverse use dependence (13). It has no known effect on cardiac hemodynamics. The current study by Dorian et al. (14) in this issue of the Journal re-examines the original SHIELD (Shock Inhibition Evaluation With Azimilide) study population. In the SHIELD study, 633 ICD patients were randomized to determine if 75 or 125 mg of azimilide reduced symptomatic ventricular arrhythmias and ICD therapy compared with that in placebo (15). Azimilide reduced all appropriate therapies inclusive of ATP and shocks. In the current study, the data is reanalyzed to determine if azimilide reduced emergency department (ED) visits and hospitalizations. The authors found that the 75 mg dose of azimilide significantly reduced “cardiac-related ED/hospitalizations” by 37% (Table 2 of Dorian et al. [14]). Azimilide in a dose of 125 mg reduced this...
measure by only 15%. However, the 125 mg dose of azimilide reduced what are called—in a separate category in Table 2 of Dorian et al. (14)—“arrhythmic-related ED/hospitalizations” by 31%, and the 75 mg dose reduced this measure by 47%. It is difficult in the study to clarify whether the ED visits and hospitalizations were for arrhythmias only, for CHF only, or for both.

The definitions used do not appear to be clearly specified. Table 3 of Dorian et al. (14) states that only 21% of the ED visits were for nonarrhythmic events. Are we to presume this means for CHF alone without an arrhythmia? Overlapping or incomplete definitions hamper our understanding of the data.

In this and other studies of ICD populations, the risk factors for hospitalization or death include the presence of advanced heart failure and atrial fibrillation. Other studies have identified advanced renal failure, dual- versus single-chamber device, and right ventricular pacing as contributing to an increased mortality risk in ICD patients. These factors are not considered here. It is unclear why azimilide has a beneficial effect on any heart failure measure as it neither eliminates ICD shocks (in a statistically significant fashion) nor reduces the incidence of atrial fibrillation: either of these effects might reduce ED visits for any cardiac cause. Azimilide does reduce the incidence of ATP; while this may be surrogate therapy for an ICD shock in this study, there are no details about the specifics of this therapy that make comparisons with published series possible. Azimilide had no effect on mortality in the trial, although the follow-up was only for 1 year.

The reasons for the differing clinical effects of 75 mg versus 125 mg of azimilide are clear neither in the study by Dorian et al. (14) nor in the initial SHIELD study. Is there any reason we should expect a difference between 75 and 125 mg of azimilide on CHF given the known mechanisms of action of azimilide?

This study is an interesting snapshot in the history of our attempt to decrease ICD shocks and their impact on clinical outcomes. It confirms the importance of ICD therapy as a possible contributor to poor patient outcomes and shows that azimilide has a positive clinical effect albeit for unclear reasons. Perhaps, ultimately, the early application of cardiac resynchronization therapy at the time of an initial clinical shock or ATP episode will modify the now recognized and disastrous short-term outcome of the ICD patient receiving device therapy (16).

**REFERENCES**


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