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EDITORIAL COMMENT

Ranolazine in Patients With Implantable Cardioverter-Defibrillators

Ready for Prime Time?*

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The advent of implantable cardioverter-defibrillator (ICD) therapy ushered in a major paradigm shift in our approach to the treatment of life-threatening ventricular arrhythmias and prevention of sudden cardiac death (SCD). Compared with traditional antiarrhythmic drugs, ICDs are more effective at reducing mortality in both secondary and primary prevention populations (1-3). Thus, ICDs have become the cornerstone of our therapy for life-threatening ventricular arrhythmias. Although ICDs are effective at terminating ventricular arrhythmias and preventing death, recurrent ventricular arrhythmias can still result in significant symptoms and/or hemodynamic compromise, even when treated successfully by an ICD. Although ventricular tachycardia (VT) can often be treated painlessly by antitachycardia pacing (ATP), ICD shocks are still required for arrhythmias where ATP is unsuccessful, particularly polymorphic and/or rapid ventricular arrhythmias. ICD shocks, especially when recurrent, can have a major negative impact on quality of life (4,5) and are associated with an increase in mortality (6). ATP may have adverse effects as well (7). Therefore, despite the benefits of the ICD, and perhaps partly because of it, there remains a pressing clinical need for therapies that will prevent recurrent ventricular arrhythmias in patients with ICDs.

In this issue of the *Journal*, Zareba et al. (8) take a novel approach to addressing this important and unmet clinical need in the RAID (Ranolazine Implantable Cardioverter-Defibrillator Trial), a National Institutes of Health-sponsored, double-blind, placebo-controlled randomized trial. This study tested whether ranolazine, a nontraditional antiarrhythmic agent, reduces the incidence of ventricular arrhythmias or death in patients with ICDs. Ranolazine was developed primarily as an antianginal agent but also possesses electrophysiological properties (9,10). It was previously found to reduce the incidence of supraventricular and ventricular arrhythmias detected on electrocardiogram monitoring within 7 days of an acute coronary syndrome in the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndromes) trial (11). These data led the authors to hypothesize that ranolazine might be effective in reducing ventricular arrhythmias in ICD patients.

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The RAID trial tested the efficacy of 1,000 mg of ranolazine orally twice daily versus placebo (1:1) in reducing time to ICD therapy for VT/ventricular fibrillation (VF) or death in 1,012 high-risk ICD patients with both ischemic and nonischemic cardiomyopathy receiving optimal medical therapy (1). Patients were enrolled at 95 centers in the United States and Canada. The initial enrollment included patients who had either received an ICD for secondary prevention (history of VT/VF) or primary prevention if high-risk clinical features were present (12). Enrollment criteria were subsequently broadened to include primary prevention patients who had previously received ICD therapies. Rigorous standardized device programming was used in both treatment arms with an additional VT zone tailored to the clinical tachycardia in patients with documented slower VT (<190 beats/min).

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The authors (8) clearly were successful in identifying a high-risk patient population. During a median follow-up of 27 months, 372 patients (36.8%) experienced the primary endpoint, and 270 (26.7%) patients received ICD therapy for VT/VF. This outcome is much higher than the annual 3% to 6% appropriate shock rate for unselected patients with primary prevention ICDs (1,13,14). In the primary intention-to-treat (ITT) analysis, those randomized to receive ranolazine had a nonsignificantly lower incidence of the primary composite endpoint of time to first ICD therapy for VT or VF or death than patients randomized to receive placebo (34.1% vs. 39.4%; hazard ratio: 0.84; 95% confidence interval: 0.67 to 1.05; $p = 0.12$). Although the study was not powered to detect a difference in the individual components of the primary endpoint, when examined separately, the time to VT requiring ATP was found to be significantly lower (23.3% vs. 18%; hazard ratio: 0.73; 95% CI: 0.55 to 0.98; $p = 0.04$), whereas time to VT/VF requiring ICD shock and death did not differ. In a pre-specified secondary analysis, the risk for recurrent VT/VF events requiring ICD therapy was 30% lower in patients randomized to receive ranolazine compared with placebo (433 vs. 650 total ICD therapies; $p = 0.03$). There was no difference in any of the other secondary endpoints, which included combinations of appropriate and inappropriate ICD shocks, cardiovascular and heart failure hospitalizations, 6-min walk test, quality of life, and death.

The results from secondary analyses in trials need to be interpreted cautiously, particularly when the overall trial result is negative. However, the observed reduction in recurrent ICD therapies for VT events in patients randomized to receive ranolazine (8) raises the possibility that the drug may exert a potentially useful antiarrhythmic action in this high-risk population. This antiarrhythmic effect seems to be more modest than that exerted by traditional antiarrhythmic drugs or ablation (15,16) but still could be clinically useful. In comparison, amiodarone plus a beta-blocker was associated with a significant 70% reduction in risk of appropriate ICD shocks in the OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) trial (17), and in experienced centers, VT ablation for scar-related VT has been associated with 65% to 70% reductions in initial (18) and recurrent (19) VT events. Therefore, ranolazine is unlikely to serve as a replacement for these established therapies from an efficacy standpoint. However, as many as 50% of patients treated with amiodarone will experience side effects requiring termination (20), and multiple relative and absolute contraindications exist for current antiarrhythmic drug options (21). Similarly, many patients are not considered good candidates for VT ablation due to the absence of a scar-related VT mechanism or multiple comorbidities. Even in experienced centers, ~6% of patients undergoing VT ablation experience procedural-related complications (19,22). Thus, there could be a potential role for ranolazine in circumstances when other therapies result in intolerable side effects or are not viable options.

A major limitation of the RAID trial, which was recognized by the authors (8), is the high level of nonadherence to the study drug. Almost one-half of the patient population ($n = 452$ [45%]) discontinued the study drug, and 149 (15%) withdrew from the study altogether. As noted by the authors, this degree of noncompliance and dropout significantly reduces the power to detect a significant positive treatment effect, and a true benefit of ranolazine on the primary endpoint could have been missed in the pre-specified ITT analysis. However, it should also be noted that noncompliance decreases the ability to demonstrate adverse treatment effects in the ITT analysis as well, particularly when compliance is unbalanced (23,24). The rates of study drug discontinuation and withdrawal were significantly higher in the ranolazine arm, with the largest differences occurring within the first 12 months of the study. The reasons for discontinuation and dropout were unknown in the majority, leaving open the possibility that the true side effect profile of ranolazine may be greater than what was documented. Patients who discontinued treatment also had more high-risk features and, in aggregate, were more likely to experience the primary outcome than compliers (48% vs. 28%) (Online Table 3 [8]). Thus, we cannot rule out that adverse effects might have occurred if these sicker patients had continued taking the study drug. As pointed out by the authors, rates of ICD-treated polymorphic VT and mortality were reassuringly similar between treatment groups. However, given the noncompliance in the trial and the known QT-prolonging effect of ranolazine (9), it would be prudent to appropriately monitor ICD patients treated with ranolazine for proarrhythmia, particularly if used in combination with other antiarrhythmic agents.

Because the probability of complying with therapy was not random in the RAID trial, the authors