To be included in the trial, patients were required to be aged ≥18 years, with a history of PAF documented within the prior 12 months, and a dual-chamber programmable pacemaker with AF detection capabilities (implanted at least 3 months prior to screening).

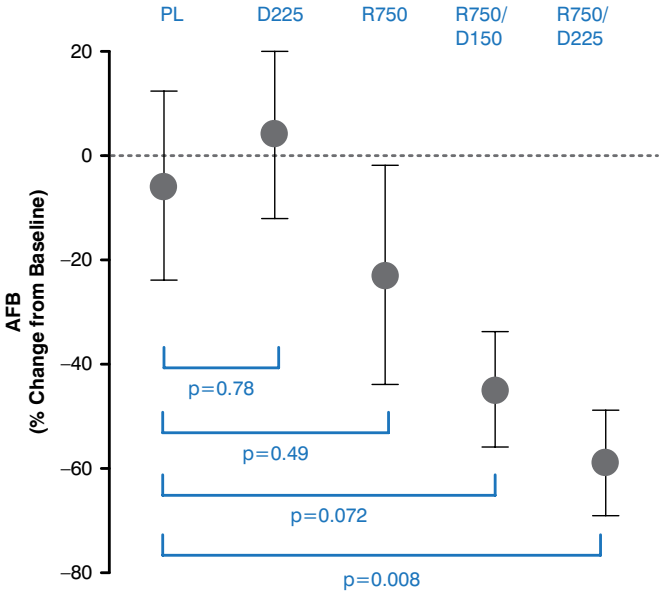
Exclusion criteria included persistent or permanent AF, a history of atrial flutter or atrial tachycardia without successful ablation, other acutely reversible causes of AF, a prior heart transplant, or a history of stroke 3 months prior to screening.

In total, 134 patients were enrolled and randomly assigned to five groups: placebo (n=26), ranolazine 750 mg twice daily (BID) (n=26), dronedarone 225 mg BID (n=26), ranolazine 750 mg and dronedarone 225 mg BID (n=27), or ranolazine 750 mg and dronedarone 150 mg BID (n=26).

The primary end points were the relative and absolute changes from baseline in AF burden (AFB) at 12 weeks. Secondary end points included the change in AFB at each study visit, the percentage of patients with a 50% reduction of AFB, and the safety and tolerability of dronedarone and ranolazine when used as monotherapy and/or in combination.

Compared with placebo, the patient group treated with ranolazine 750 mg and dronedarone 225 mg BID had a statistically significant reduction in AFB from baseline to 12 weeks (p=0.008; Figure 1). The reduction in AFB for those in the ranolazine group and in the dronedarone 150 mg BID and ranolazine 750 mg daily group was not statistically significant (p=0.072 and p=0.49, respectively). In addition, the patient group treated with dronedarone 225 mg BID showed no difference in percentage change in AFB when compared to placebo (p=0.78).

Figure 1. Percentage Change in AFB From Baseline to 12 Weeks



AFB=atrial fibrillation burden; D225=dronedarone 225 mg BID; R750=ranolazine 750 mg BID; R750/D150=ranolazine 750 mg and dronedarone 150 mg BID; R750/D225=ranolazine 750 mg and dronedarone 225 mg; PL=placebo.

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From baseline to 12 weeks, a ≥70% reduction of AFB occurred in 45% and 27% of patients in the ranolazine 750 mg–dronedarone 225 mg BID and ranolazine 750 mg–dronedarone 150 mg BID groups, respectively, compared to an 11% reduction in the placebo group. Neither ranolazine nor dronedarone 225 mg BID alone reduced AFB when compared with placebo (only 17% and 9%, respectively).

There were very few serious adverse events (AEs) reported in the treatment groups, and there was no dose relationship with respect to either serious AEs or those leading to treatment discontinuation. Dizziness and constipation were some of the most frequent serious AEs reported.

In summary, the HARMONY trial showed that ranolazine and dronedarone lowered AFB as compared to placebo or either agent when used as monotherapy. In addition, there was a dose–response relationship seen with the effects of dronedarone when used in combination with ranolazine.

Dr. Kowey concluded by noting that plans are now underway to further study these agents with 2 large Phase 3 trials. One trial plans to study the effects of dronedarone and ranolazine on the time to recurrent atrial fibrillation. The other trial will study the effects of dronedarone and ranolazine on cardiovascular death or hospitalization.

Favorable Phase 2 Data for Ranolazine in AF

Written by Nicola Parry

Gaetano De Ferrari, MD, Policlinico S Matteo and University of Pavia, Pavia, Italy, presented results of the Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion randomized trial [RAFFAELLO; NCT01534962], an international, double-blind, parallel, Phase 2, dose-ranging study testing three oral ranolazine doses. The results demonstrated safety and provided favorable findings with regard to efficacy for patients with atrial fibrillation (AF).

Although antiarrhythmic medications are widely used in managing patients with AF, with the aim of reducing mortality and hospitalizations, their use has been limited by a combination of toxicity and only modest efficacy. Ranolazine is a relatively new drug approved for the management of chronic angina that blocks late sodium currents, and although it also reduces supraventricular

arrhythmias, its use by patients with AF is poorly documented [Zimetbaum P. *Circulation* 2012].

The RAFFAELLO trial conducted by Prof. De Ferrari and colleagues was the first study to prospectively examine the efficacy and safety of ranolazine in patients with persistent AF. To be included in the study, patients were required to be aged ≥18 years, have persistent AF of 7 days to 6 months in duration, and be suitable for direct-current cardioversion (DCC). Exclusion criteria included congestive heart failure (NYHA Class 3 or 4) and the use of Class 1 or 3 antiarrhythmic agents in the previous 3 days (or 2 weeks and 3 months in the cases of dronedarone and oral amiodarone, respectively).

The primary end point was median time from randomization to first documented AF recurrence. Secondary end points included time to first documented and confirmed AF recurrence and time to first documented AF recurrence in patients who remained in sinus rhythm 2 days after DCC.

During the 16-week study, electrocardiograms (ECGs) were performed daily and in the case of symptoms, using transtelephonic ECG (TT-ECG) devices. ECGs were then transmitted to a central core ECG laboratory for interpretation.

Intention-to-treat (ITT) analysis was performed on 238 study participants, who were randomly assigned 1:1:1:1 to ranolazine (RAN) 375 mg twice daily (BID) (n=65), 500 mg BID (n=60), or 750 mg BID (n=58), or placebo (n=55). The most common ECG interpretation was stable sinus rhythm (79.1%), followed by AF (11.5%), and the remaining 9.3% comprised poor-quality recordings that were unable to be assessed.

Overall safety was favorable, with a similar incidence of all treatment-emergent side effects in the RAN 375 (78.5%), RAN 500 (76.7%), RAN 750 (72.4%), and placebo (74.5%) groups. The incidence of drug-related side effects appeared to be dose dependent (10.8% vs 15.0% vs 22.4% vs 3.6%), was mostly mild, and involved dizziness, fatigue, constipation, and nausea. Severe side effects were rare, comprising pancreatitis (RAN 375; n=1), orthostatic hypotension (RAN 750; n=1), atrial flutter (RAN 750; n=1), and sudden cardiac death (placebo; n=1).

The primary efficacy endpoint of this study was not met, because no single dose of ranolazine significantly prolonged time to first AF recurrence. In a prespecified analysis of time to first AF recurrence, however, excluding patients who relapsed within the first 48 hours, there was a trend toward significance for the two higher doses of ranolazine (Figure 1).

An exploratory analysis of the different dose groups also showed that, whereas the 375-mg dose was ineffective, the two higher doses showed promising trends toward efficacy in freedom from AF (Figure 2).

The study did suggest very good safety and tolerability of ranolazine. In addition, combining data from the 500- and 750-mg-dose groups and comparing them with either placebo or the ineffective 375-mg-dose group suggested a 25% to 30% reduction in overall recurrence of AF, concluded Prof. De Ferrari.

These data show favorable findings that support further investigation in the use of ranolazine after cardioversion by patients with atrial fibrillation.

Figure 1. Prespecified Analysis of Time to First Atrial Fibrillation Recurrence

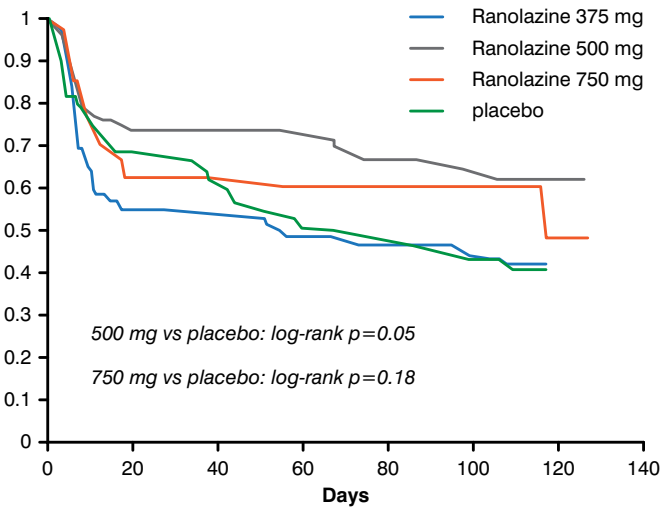

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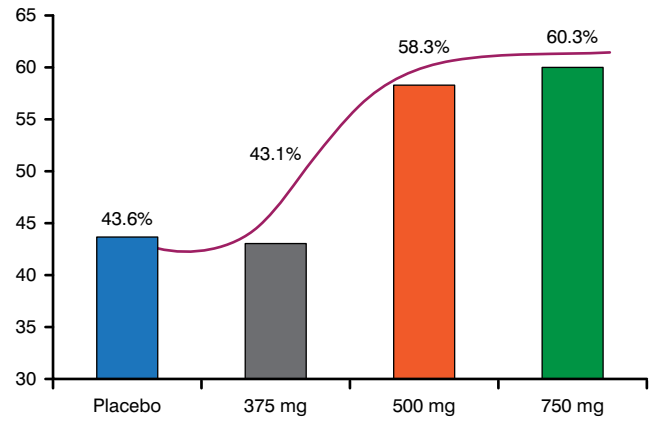
Figure 2. Freedom From Atrial Fibrillation



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