Current status of ranolazine in clinical practice

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Arrhythmias

New-Onset and Paroxysmal Atrial Fibrillation

The mechanism of action of ranolazine has been proposed to reduce atrial excitability and prolong the atrial refractory period. ShryockJC,Cardiovasc Res.2013;99:600–611.) The role of ranolazine as an adjunctive anti-arrhythmic agent for atrial fibrillation (AF) has been evaluated in several studies. A randomized study of 121 patients with recent onset AF (<48hours) evaluated the effect of amiodarone infusion (loading dose 5mg/kg followed by maintenance of 50mg/h) plus ranolazine (1500mg single dose) versus amiodarone infusion alone for conversion to sinus rhythm. A significantly higher conversion rate at 24 hours (87% versus 70%, respectively;P=0.024) and at 12hours (52% versus 32%;P=0.021) in the ranolazine plus amiodarone infusion group was observed.(KoskinasKC,.2014;16:973–979.)

In the recent Combined Ranolazine and Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism (HARMONY) trial, 134 patients with paroxysmal AF and implanted pacemakers were randomized to ranolazine 750mg BID, dronedarone 150mg BID, dronedarone 225mg BID, combination therapy, or placebo.(Reiffel JA, Circ Arrhythm Electrophysiol. 2015;8:1048–1056.) This moderate dose of ranolazine combined with the reduced-dose dronedarone (which is currently available as 400mg) was hypothesized to have complementary electrophysiological properties with a potential increased safety and tolerability profile. After 12 weeks of treatment, a significant 59% reduction (P=0.008) in AF burden was observed in the combination therapy group (ranolazine 750mg BID/dronedarone 225mg BID) compared with placebo. No significant reduction in AF burden was noted in the placebo, either drug alone, or combination therapy with dronedarone 150mg BID groups.

AF burden in the setting of CAD and ACS was evaluated in the MERLIN-TIMI 36 study.(Scirica BM, Circulation.2007;116:1647–1652.) Six thousand six hundred fifty patients with non-ST-segment elevation myocardial infarction were randomized to ranolazine 1000mg PO BID versus placebo and followed with continuous ECG for a median of 6.8 days. New-onset AF developed in 1.7% in the ranolazine group versus 2.4% in the placebo group, which was not statistically significant (P=0.08). There was, however, a significant reduction in all supraventricular arrhythmias observed (44.7% versus 55%, P<0.001).

At this time there is no strong evidence for the addition of ranolazine to standard anti-arrhythmic therapy in patients with new-onset AF.

Chronic AF

The role of ranolazine as an adjunctive anti-arrhythmic agent in chronic AF has been evaluated in a small case series (Murdock DK, Indian Pacing Electrophysiol J. 2008;8:175–181.) and observational study. (Murdock DK,..2012;35:302–307.) Most recently, the Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion (RAFFAELLO) study, evaluated 241 patients with persistent AF after successful electrical cardioversion.(De Ferrari Heart Rhythm. 2015;12:872–878.)

Patients were treated with dose-ranging ranolazine (375, 500, or 750mg BID) or placebo 2 hours after cardioversion and followed by transtelephonic electrocardiographic monitoring during a 4-month follow-up period. No dose of ranolazine significantly prolonged time to AF recurrence.

Postoperative Cardiac Surgery AF

AF following surgery (CABG) is associated with increased morbidity and mortality (Circulation. 2011; 124:2610–2642.) Retrospective studies have suggested a role for ranolazine in postoperative CABG patients. (Miles RH, Am J Cardiol.2011;108:673–676.)(Hammond DA,..2015;104:410–417)

RCTs offer conflicting results. Tagarakis etal randomized 102 patients with new-onset AF after elective CABG standard postoperative therapy versus ranolazine 375mg BID for 3 days prior to surgery until discharge.(Tagarakis GI, Curr Vasc Pharmacol. 2013;11:988–991.) A significant reduction in the incidence of postoperative AF was noted in the ranolazine group (8.8% versus 30.8%,P<0.001). Another randomized study evaluated 41 patients after CABG with postop AF of <48hours. (Simopoulos V,Angiology. 2014; 65:294–297.) Treatment with ranolazine plus IV amiodarone followed by PO amiodarone versus amiodarone alone was evaluated for time to sinus rhythm conversion. The amiodarone plus ranolazine group had a significantly shorter time to sinus rhythm conversion compared to amiodarone alone. Bekeith etal recently published an abstract of their results of a trial assessing 51 patients postoperatively following CABG and/or aortic valve replacement. (Bekeith S, Circulation.2015;132:A13387.)

Patients received either ranolazine 1000 mg daily or placebo and were followed for up to 30 days. A 38% reduction in incidence of AF was noted during the 14-day postoperative follow-up; however, it was not statistically significant (P=0.530).

At this time, these studies offer conflicting evidence for the benefit of ranolazine in this postoperative patient population.

Glycometabolic Effect

It is well recognized that diabetes and CAD, while separate disease processes, have overlapping metabolic pathophysiology. (Lüscher TF, Circulation. 2003;108:1655–1661.) A recent analysis of 1957 adults with CAD in the National Health and Nutrition Examination Survey (NHANES) cohort reported that 28% also had a diagnosis of diabetes. (Wong ND,.. 2014;63:A1538.) Among these, 44% had angina, supporting a significant comorbid profile. It would therefore be of benefit to have a medication that offers simultaneous treatment of both conditions.

Ranolazine has been associated with significant reductions in glycosylated hemoglobin (HbA1C) in large RCTs. (Chaitman BR, JAMA. 2004;291:309–316.) (Gutierrez JA, Clin Cardiol. 2015;38:469–475.)

Patients with type 2 diabetes and chronic angina demonstrated a dose-dependent reduction in HbA1C in the CARISA trial. In the MERLIN-TIMI 36 trial, this effect was also noted along with a reduction in the incidence of newly elevated HbA1C in normoglycemic patients. These studies were not, however, prospectively designed to evaluate the effect on glycemic parameters. Additionally, patients were often on other antiglycemic medications.

Eckel etal recently published a randomized, double-blind, placebo-controlled study evaluating the effect of ranolazine monotherapy on glycemic control in 465 patients with type 2 diabetes. Eckel RH, Diabetes Care. 2015;38:1189–1196.) The primary end point was a change in HbA1C at 24-week follow-up. Ranolazine lowered HbA1C by a mean difference of –0.56% with almost twice as many subjects achieving a HbA1C <7.0%, which is accepted by the American Diabetes Association as a reasonable goal for most patients with type 2 diabetes. (Williamson C,.. 2014;126:145–160.)

These results suggest a possible currently unrecognized option for patients with concurrent CSAP and type 2 diabetes.