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Ranolazine After Incomplete Percutaneous Coronary Revascularization in Patients With Versus Without Diabetes Mellitus

RIVER-PCI Trial

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ABSTRACT

BACKGROUND Chronic angina is more common in patients with diabetes mellitus (DM) with poor glucose control. Ranolazine both treats chronic angina and improves glucose control.

OBJECTIVES This study sought to examine ranolazine's antianginal effect in relation to glucose control.

METHODS The authors performed a secondary analysis of the RIVER-PCI (Ranolazine in Patients with Incomplete Revascularization after Percutaneous Coronary Intervention) trial, a clinical trial in which 2,604 patients with chronic angina and incomplete revascularization following percutaneous coronary intervention were randomized to ranolazine versus placebo. Mixed-effects models were used to compare the effects of ranolazine versus placebo on glycosylated hemoglobin (HbA_{1c}) at 6- and 12-month follow-up. Interaction between baseline HbA_{1c} and ranolazine's effect on Seattle Angina Questionnaire angina frequency at 6 and 12 months was tested.

RESULTS Overall, 961 patients (36.9%) had DM at baseline. Compared with placebo, ranolazine significantly decreased HbA_{1c} by 0.42 ± 0.08% (adjusted mean difference ± SE) and 0.44 ± 0.08% from baseline to 6 and 12 months, respectively, in DM patients, and by 0.19 ± 0.02% and 0.20 ± 0.02% at 6 and 12 months, respectively, in non-DM patients. Compared with placebo, ranolazine significantly reduced Seattle Angina Questionnaire angina frequency at 6 months among DM patients but not at 12 months. The reductions in angina frequency were numerically greater among patients with baseline $HbA_{1c} \geq 7.5\%$ than those with $HbA_{1c} < 7.5\%$ (interaction $p = 0.07$).

CONCLUSIONS In patients with DM and chronic angina with incomplete revascularization after percutaneous coronary intervention, ranolazine's effect on glucose control and angina at 6 months was proportionate to baseline HbA_{1c}, but the effect on angina dissipated by 12 months. (J Am Coll Cardiol 2017;69:2304–13) © 2017 by the American College of Cardiology Foundation.

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More than 20% of patients with diabetes mellitus (DM) have coronary artery disease (CAD), and in patients with DM between 65 and 74 years of age, that proportion increases to 45% (1). Despite aggressive use of traditional secondary prevention medications, nearly 50% of adults with both DM and CAD have chronic angina, and those with poorer glucose control are more likely to have severe angina (2).

Ranolazine is an oral antianginal agent that acts to inhibit the late sodium ion current and, through that action, reduces calcium overload in the myocytes (3). Clinically, ranolazine has been shown to reduce angina frequency, particularly among patients with more frequent angina or DM (4–6). Unexpectedly, ranolazine has also been observed to reduce glycosylated hemoglobin (HbA_{1c}) in patients with and without DM (7). The hypothesized mechanism of ranolazine's effect on HbA_{1c} is through inhibition of sodium channels in pancreatic alpha cells (analogous to the myocardial action) but, in this case, resulting in reduced glucagon release (8). As patients with DM are particularly responsive to ranolazine's antianginal properties, interactions between ranolazine's effect on glucose and angina control are of particular interest (5,6).

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The randomized RIVER-PCI (Ranolazine in Patients with Incomplete Revascularization after Percutaneous Coronary Intervention) trial examined the utility of ranolazine in patients with a history of chronic angina that had incomplete revascularization following percutaneous coronary intervention (PCI) (9). Compared with placebo, ranolazine did not reduce the rate of the trial's primary endpoint, ischemia-driven revascularization or rehospitalization, nor did it improve measures of quality of life (QOL) or angina frequency. As part of the trial, glycometabolic parameters were prospectively collected from participants at baseline, 6 months, and 12 months to further understand the relationship between glucose control and antianginal efficacy. The results of this pre-specified substudy are reported here.

METHODS

The RIVER-PCI trial was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 245 centers in 15 countries; the design and primary results have been published, as have the effects on angina burden and QOL (6,9,10). Briefly, patients with a history of chronic angina who had undergone PCI with resultant incomplete revascularization were randomized to receive ranolazine 1,000 mg twice daily or placebo. Chronic angina was defined as ≥2 episodes of typical angina with episodes occurring on ≥2 separate days between 30 days and 1 year prior to PCI. Qualifying PCI could be due either to acute coronary syndrome (ACS) or stable angina, and patients could have additional angina within 30 days of their PCI. Incomplete revascularization was defined as the presence of at least 1 lesion with ≥50% diameter stenosis in a coronary artery ≥2.0 mm in diameter, in either a PCI-treated or nontreated vessel. In patients with prior coronary artery bypass graft surgery, incomplete revascularization was defined as at least 1 ≥50% diameter stenosis in a nonbypassed coronary artery ≥2.0 mm in diameter or at least 1 ≥50% diameter stenosis in a bypass graft supplying an otherwise nonrevascularized territory. The primary endpoint of the RIVER-PCI trial was the cumulative rate of ischemia-driven hospitalization or revascularization.

PATIENT POPULATION AND STUDY PROCEDURES. The RIVER-PCI trial randomized 2,651 patients, stratified by ACS versus non-ACS, and DM versus no DM. Among those randomized, 2,604 patients who had a qualifying PCI and received at least 1 dose of study drug were included in the full efficacy analysis. For analyses of the effect of ranolazine on glycometabolic parameters, we included all patients in the full analysis set: 1,317 patients were randomized to receive ranolazine and 1,287 were randomized to receive placebo. Analyses of angina frequency were performed on patients with DM who participated in the QOL substudy; this population included 864 patients, of

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

DM = diabetes mellitus

HbA_{1c} = glycosylated hemoglobin

PCI = percutaneous coronary intervention

QOL = quality of life

SAQ = Seattle Angina Questionnaire

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