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Ranolazine: A Contemporary Review

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Ranolazine, a piperazine derivative sold under the trade name Ranexa, is a well-tolerated medication that selectively inhibits the late sodium current. Additionally, ranolazine has beneficial metabolic properties and does not affect heart rate or blood pressure. Ranolazine is currently approved in the United States and Europe as a second-line agent in the management of chronic stable angina pectoris (CSAP). It is not currently approved for use by Health Canada and requires an application through the Special Access Programme.

CSAP is estimated to affect >7 million North Americans, and is associated with significant morbidity.[1] Several randomized controlled trials (RCTs) have supported the use of ranolazine in this population. This evidence has been incorporated in North American and European guidelines.[2–4] In addition, the benefit of ranolazine in acute coronary syndrome (ACS), microvascular coronary dysfunction (MCD), arrhythmias, and glycemic control has been evaluated. We present a comprehensive review of the pharmacology, guidelines, and studied uses of ranolazine.

Pharmacology

Pharmacodynamics

Ranolazine is *N*-(2,6-dimethylphenyl)-4(2-hydroxy-3-[2-methoxyphenoxy]-propyl)-1-piperazine acetamide dihydrochloride. At clinically therapeutic levels, ranolazine inhibits sodium and potassium ion channel currents. Inhibition of the late phase of the inward sodium current during cardiac repolarization has been well studied.[5] In disease states, enhanced sodium–calcium exchange due to augmented late phase of the inward sodium current activity leads to increased cytosolic calcium concentration.[6] Intracellular calcium overload is believed to be critical to the mechanism of decreased left ventricular relaxation caused by ischemia and reperfusion. Elevated left ventricular diastolic wall tension compromises myocardial blood flow even further. Additionally, calcium overload has adverse effects on myocardial electrical activity predisposing to ventricular tachycardia.[7] While this mechanism has been well studied primarily in rats, the anti-ischemic effect of ranolazine as a result of late Na channel inhibition improving myocardial perfection lacks data to support this mechanism in patients with ischemic heart disease.

Ranolazine also inhibits the delayed rectifier potassium current (IKr) at clinically therapeutic concentrations, which prolongs the ventricular action potential duration.[8] The net effect of ranolazine on action potential duration is a balance between the effects of rectifier potassium current and late phase of the inward sodium current inhibition, which is generally a prolongation of QTc by 2 to 6 ms.[9]

Additional mechanisms of ranolazine activity have been studied such as adrenergic receptor binding and fatty acid oxidation inhibition. Ranolazine has α_1- and β_1-adrenergic antagonist activity in animal models, classically without negative chronotropic, dromotropic, or inotropic activity at rest or exercise.[10] However, a recently reported effect on both heart rate and rate pressure product has been observed in human subjects during stress.[11] Inhibition of fatty acid oxidation by ranolazine was initially proposed as the main anti-ischemic mechanism.[12] However, further evaluation using the therapeutic doses of ranolazine disproved this theory.[13] Currently, the mechanism of action as an anti-anginal medication is not yet understood.

In summary, ranolazine inhibits the late phase of the inward sodium current in ventricular myocardial cells, which reduces intracellular calcium overload and associated diastolic contractile dysfunction. The recently reported effect of ranolazine on heart rate and rate pressure product in humans is novel and will need further evaluation.[11]

Pharmacokinetics

Initial studies used immediate-release ranolazine capsules; however, the short half-life and variable interindividual absorption led to development of an extended-release

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J Am Heart Assoc. 2016;5:e003196 doi: 10.1161/JAHA.116.003196.

formulation.[14] Peak plasma concentration is obtained 2 to 6 hours after administration and steady state within 3 days of twice-daily dosing. The half-life of ranolazine at steady state is ≈7 hours. Ranolazine undergoes extensive hepatic metabolism by cytochrome P450 and is primarily renally excreted (75%).[14] Age, sex, and congestive heart failure do not influence pharmacokinetics.[14]

Tolerability

Extended-release ranolazine has been well tolerated in both short-term and long-term data sets.[15] In 746 patients followed during a mean follow-up of 2.82 years, the most frequent adverse events reported were dizziness (11.8%), constipation (10.9%), and peripheral edema (8.3%).[16] Plasma levels increase up to 50% to 60% in patients with moderate hepatic or renal impairment.[2] Therefore, ranolazine should be used with caution in these groups and is contraindicated in patients with creatinine clearance of ≤30 mL/min, dialysis, or cirrhotic patients.

Interactions/Precautions

Ranolazine undergoes hepatic metabolism by CYP3A4 and to a lesser extent CYP2D6. Several interactions with medications and herbal products have been described. Ranolazine is contraindicated with potent inhibitors of the CYP3A4 pathway including certain antifungals (ketoconazole and other azole class), antibiotics (macrolides, clarithromycin), HIV protease inhibitors, diltiazem, and grapefruit products. Co-administration of ranolazine with drugs that inhibit CYP2D6 often does not necessitate dosage adjustment, with the exception of tricyclic antidepressants and some antipsychotics.[3]

Ranolazine prolongs the cardiac action potential duration and QT interval by 2 to 6 ms. An increased risk of torsade de pointes has not been described;[17] however, it is recommended that an ECG be performed 1 to 2 weeks after initiation.

Label Approval

Ranolazine was approved by the U.S. Food and Drug Administration in 2006 in 500 mg and 1000 mg extended-release doses, advising 500 mg BID as a starting dose and 1000 mg BID as maximum dose.[18] The European Medicine Agency approved ranolazine in 2008 in 3 different extended-release doses (375–500–750 mg), advising 375 mg BID as a starting dose and 750 mg BID as a maximum dose. Up titration was recommended after 2 to 4 weeks.[19] Despite the recognized burden of refractory angina in the Canadian population,[20] ranolazine has not been approved for use. Physicians must apply through the Special Access Program through Health Canada for use.

Guidelines

The American College of Cardiology Foundation and the American Heart Association published the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease in 2012. Ranolazine was recommended for patients with stable ischemic heart disease if unable to use acceptable doses of β-blockers (Class of recommendation IIa, Level of Evidence B).[3]

The European Society of Cardiology 2013 guidelines recommend ranolazine among agents for second-line symptomatic treatment for angina, without evidence of benefit on prognosis (Class of recommendation IIa and Level of Evidence B).[2]

Lastly, the Canadian Cardiovascular Society issued a position statement regarding management options for patients with refractory angina pectoris in 2009. Using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) convention, the use of ranolazine for patients unable to tolerate optimal doses of conventional anti-anginal agents received a weak recommendation based on moderate-quality evidence.[4]

Studied Uses

Refractory CSAP

Refractory CSAP is defined as the persistence of symptoms resistant to conventional treatments for coronary artery disease (CAD) including revascularization and anti-anginal medication.[4] CSAP is seen in up to 25% of patients and can result in severely impaired health-related quality of life.[1,21] Several randomized controlled trials (RCTs) have examined the role of ranolazine in CSAP.[22–28] The main outcomes evaluated in these trials included exercise stress test performance (duration, time to angina, time to ST-segment depression)[22–25,27] quality of life,[26] and frequency of angina with need for nitroglycerin.[21,22,26,28]

Initial studies showed conflicting results. Thadani et al published a double-blind RCT comparing the effects of 3 doses of immediate-release ranolazine (30, 60, and 120 mg TID) versus placebo with respect to change from baseline exercise stress test (EST) and angina frequency.[22] Approximately 30% of patients enrolled had a history of myocardial infarction (MI) and ≈20% had a history of coronary artery bypass graft (CABG). The changes observed with all doses were not superior to placebo. Pepine et al evaluated higher doses of immediate-release ranolazine (400 mg BID, 276 mg

TID, and 400 mg TID) in 312 patients with CSAP.[23] Forty-three percent of patients enrolled had a history of MI and 32% had a history of CABG. Thirty-four percent were already on a β-blocker and 24% were already on a calcium channel blocker. All 3 doses significantly improved exercise tolerance at peak concentrations of ranolazine. In comparison to the currently approved extended-released doses by the U.S. Food and Drug Administration (500–1000 mg BID) and European Medicine Agency (375–750 mg BID), the total daily doses evaluated by Pepine et al were within these ranges. Therefore, in this study using higher doses of immediate-release formulation, ranolazine was effective and well tolerated in CSAP.

Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) was the first study to investigate the effect of ranolazine monotherapy.[22] Previous studies included patients on nitroglycerine tablets,[22] β-blockers, and calcium channel blockers.[23] This double-blind RCT enrolled 191 patients with CSAP who received ranolazine extended-release at doses of 500, 1000, and 1500 mg BID for 1 week. Fifty-two percent of patients had a history of MI, 27% a history of CABG, and 32% had prior coronary angioplasty. The primary end point was total exercise duration at trough (estimated to be 12 hours after medication dosing). Other end points included time to angina onset and time to 1 mm ST-depression at peak and trough. Adverse events increased substantially with higher doses of ranolazine, specifically dizziness, nausea, asthenia, and constipation. All side effects were more common with the 1500 mg BID dose (34.2%) than with doses of 1000 mg BID (21.7%), 500 mg BID (16%), or placebo (15.6%). Early withdrawal due to adverse events also occurred most often in the 1500 mg BID dosing (11 patients compared to 4 patients in all other groups and placebo combined). Compared to placebo, a significant dose-dependent improvement was found in the primary and secondary end points, without clinically significant changes in heart rate or blood pressure. Exercise duration increased with all 3 doses of ranolazine by 94, 103, and 116 s, respectively, which were all significantly greater than the 70-s increase with placebo ($P<0.005$).

In the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial, 823 patients receiving antianginal therapy at enrollment were evaluated for EST performance, angina frequency, and nitroglycerin use.[25] Patients were stratified according to antianginal therapy (atenolol 50 mg, diltiazem 180 mg, or amlodipine 5 mg daily) and randomized to receive ranolazine extended-release 750 mg, 1000 mg, or placebo BID. Each treatment arm had similar background antianginal medications. After 12 weeks of therapy, both doses increased exercise capacity, with exercise duration increased by 115.6 s (pooled from both doses) versus 91.7 s in the placebo group ($P=0.01$). Angina frequency and nitroglycerin use was reduced by ≈1 per week as compared to placebo ($P<0.02$).

CARISA supported a benefit of ranolazine as an add-on therapy in CSAP. However, patients were not on the maximum recommended doses of antianginals, which may influence the external validity of the results. This was addressed in the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. Five hundred sixty-five patients were randomized to extended-release ranolazine 500 mg BID or placebo.[26] All patients were taking 10 mg of amlodipine and were allowed to continue long-acting nitrates. Eighty percent of patients had a history of MI, 11% had a history of previous CABG, and 10% had a history of previous percutaneous coronary intervention (PCI). The primary end point was the frequency of self-reported angina episodes during the 6-week treatment phase. Secondary outcomes included weekly nitroglycerin use and change in the Seattle Angina Questionnaire (SAQ). Ranolazine significantly improved the primary end point compared to placebo (2.88±0.19 versus 3.31±0.22; $P=0.028$) as well as the frequency of nitroglycerin use (2.03±0.20 versus 2.68±0.22; $P=0.014$).

The RAN080 trial compared immediate-release ranolazine with atenolol 100 mg daily and placebo.[27] One hundred fifty-eight patients were treated for 1 week and evaluated in 3 different parameters of EST. Fifty-six percent of patients had a history of MI. Both ranolazine and atenolol significantly improved exercise duration, time to angina onset, and time to ST-depression. Patients had significantly longer total exercise duration during therapy with ranolazine as compared to atenolol (mean difference 21.1 s, 95% CI: 6.2–36; $P=0.006$), whereas the differences observed in time to angina onset and ST-depression were not statistically significant. Ranolazine did not decrease blood pressure, heart rate, or rate–pressure product.

In the Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial, 949 patients with diabetes and CSAP treated with 1 or 2 antianginal medications were assigned to ranolazine extended-release 1000 mg BID or placebo for 8 weeks.[28] A total of 56% of patients were treated with 1 antianginal agent, with the remaining patients receiving 2 agents. The majority of patients were treated with β-blockers (90%), with calcium channel blockers (29%) and long-acting nitrates (34%) less frequently used. Seventy-three percent of patients had a history of MI, 40% had a history of angioplasty, and 18% a history of CABG. There was a statistically significant decrease in angina frequency (3.8: 95% CI: 3.6–4.1 versus 4.3: 95% CI: 4.0–4.5; $P=0.008$), and in doses of weekly sublingual nitroglycerin use (1.7: 95% CI: 1.6–1.9 versus 2.1: 95% CI: 1.9–2.3; $P=0.003$) in patients treated with ranolazine over placebo.

A recently published systematic review of 7 RCTs concluded that ranolazine effectively improves EST parameters and reduces angina episodes and nitroglycerin use in patients with CSAP due to CAD.[1] All studies but Thadani

et al[22] showed a statistically significant improvement in angina symptoms, and this may be attributable to the lower doses used in this study. Certain important elements of study design varied significantly between trials. Ranolazine dosages ranged from 30 mg TID to 1500 mg BID. The immediate-release formulation was used in the Thadani et al,[22] Pepine et al,[23] and the RAN080 trial,[27] while the other trials used the extended-release formulation. The treatment phase lasted only 1 week in 3 studies.[23,24,27] EST outcomes were examined in 5 RCTs,[22–25,27] while 4 studies examined change in weekly frequency of angina and nitroglycerin use.[22,25,26,28] Only the ERICA trial used the SAQ questionnaire.[26]

Overall, these data have supported the above-noted American and European guidelines to recommend the use of ranolazine in the setting of CSAP in patients who have not derived sufficient benefit from first-line agents.

Incomplete Revascularization After PCI

Incomplete revascularization after PCI has been associated with poor prognosis.[29,30]

The use of ranolazine in this population was evaluated in the recent Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial, a multicountry, randomized, double-blind trial involving 2651 patients with a history of chronic angina and incomplete revascularization after PCI.[31] Incomplete revascularization was defined as the presence of at least one lesion with stenosis of 50% or more in a coronary artery with reference vessel diameter of 2 mm or more. Patients were randomized to placebo or increasing doses of ranolazine, starting at 500 mg PO BID to goal of 1000 mg PO BID if tolerated. Median follow-up period was 643 days. Primary end point was the time to first occurrence of ischemia-driven revascularization or hospitalization without revascularization, which occurred in 26% of the ranolazine group and 28% placebo (hazard ratio=0.95; 95% CI: 0.82–1.10; *P*=0.48).

At this time there is a lack of evidence to support the use of ranolazine in patients with chronic angina following incomplete PCI.

Acute Coronary Syndrome

The use of ranolazine in the acute non-ST-elevation ACS setting was evaluated in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation ACS (MERLIN)-Thrombolysis In Myocardial Infarction (TIMI) trial.[32] Six thousand five hundred sixty moderate to high-risk patients were enrolled within 48 hours of symptoms of myocardial ischemia at rest. Ranolazine was administered by intravenous bolus followed by an infusion for 12 to 96 hours. Patients were then transitioned to ranolazine extended-release 1000 mg BID. Median follow-up was 348 days. The primary outcome was a composite of cardiovascular death, myocardial infarction, or recurrent ischemia. Safety end points were death from any cause and documented arrhythmia. There was no significant benefit of ranolazine compared with placebo in the primary outcome (hazard ratio=0.92; 95% CI: 0.83–1.02; *P*=0.11) and no signal for adverse trends in death or arrhythmia. Based on these results, there is currently no role for ranolazine in addition to standard ACS therapy in this patient population.

In a subgroup analysis of the MERLIN-TIMI 36 trial, 914 patients with previous angina who were treated with PCI had a reduced risk of recurrent ischemia (hazard ratio=0.69; 95% CI: 0.51–0.92; *P*=0.01) and reduced cardiovascular death (hazard ratio=0.39; 95% CI: 0.55–0.91; *P*=0.01) when treated with ranolazine during a 1-year follow-up.[33] As mentioned above, the RIVER-PCI study further evaluated the use of ranolazine in patients with incomplete revascularization and did not find a benefit.[31]

Microvascular Coronary Dysfunction

MCD is defined as impaired vasodilation of arterioles, leading to inadequate increase in blood flow from rest to stress.[34] MCD is likely implicated in the pathogenesis of microvascular angina (MVA), which is defined as angina with myocardial ischemia, in the absence of myocardial disease and significant obstruction on angiography.[35] MVA is a diagnosis of exclusion. Although the long-term prognosis of patients with stable MVA is not as poor as patients with obstructive CAD,[36] patients often have an impaired quality of life due to persistent angina.[15] Treatment typically consists of standard anti-anginal medications including β-blockers and calcium channel blockers; however, 20% to 30% of patients remain symptomatic.[15] There is evidence that ranolazine may reduce mechanical compression of coronary microcirculation and thus improve mechanical dysfunction.[37,38]

Multiple techniques exist to evaluate microvascular function including coronary flow reserve using invasive testing and myocardial perfusion reserve using positron emission tomography or cardiac magnetic resonance imaging.[34]

Recent studies have evaluated the role of ranolazine in MVA. In a pilot study, Mehta et al randomized 20 women with evidence of ischemia but no obstructive CAD to ranolazine 500 to 1000 mg BID versus placebo.[39] There was a significantly higher (improved) SAQ score in patients on ranolazine for 4 weeks along with trend towards improved coronary flow reserve evaluated by cardiac magnetic resonance imaging. Villano et al investigated the effects of ivabradine and ranolazine in patients with MVA.[40] Forty-six patients (9 men and 37 women) were randomized including 15 in the ranolazine subgroup. Patients in this group received

ranolazine 375 mg BID for 4 weeks and were then reassessed. SAQ scores and EuroQoL VAS score were significantly improved in both groups with ranolazine more so than ivabradine, along with time to 1 mm ST-depression. Tagliamonte et al recently reported a significant improvement in transthoracic Doppler-derived coronary flow reserve in 58 patients with MVA.[41] After 8 weeks of ranolazine therapy, coronary flow reserve significantly increased in the ranolazine group but not the placebo group. The authors concluded that this benefit was primarily derived from an improvement in coronary autoregulation.

Results of the Angina Myocardial Ischemia (RWISE) trial were recently published.[11] Bairey Merz et al conducted a randomized trial evaluating the effect of ranolazine in 128 patients (96% female) with evidence of MCD. Patients were randomized to ranolazine 500 to 1000 mg BID as tolerated versus placebo for 2 weeks and evaluated for changes in SAQ, quality of life questionnaire and cardiac magnetic resonance imaging myocardial perfusion reserve index. None of the primary outcomes improved with ranolazine as compared to placebo and thus did not support findings of previous studies.

Variability in methodology among studies may contribute to the conflicting results observed. The main differences include patient population size (ranging from 20[39] to 128[11]), dose variability (ranging from 375 BID[40] to 1000 BID[11]), primary outcomes evaluated, and time to follow-up (2 weeks[11] to 8 weeks[41]). At this time, ranolazine can be considered in refractory cases or patients who do not tolerate other anti-anginals due to bradycardia and hypotension.

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.[42] 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 (<48 hours) evaluated the effect of amiodarone infusion (loading dose 5 mg/kg followed by maintenance of 50 mg/h) plus ranolazine (1500 mg 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 12 hours (52% versus 32%; P=0.021) in the ranolazine plus amiodarone infusion group was observed.[43]

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 750 mg BID, dronedarone 150 mg BID, dronedarone 225 mg BID, combination therapy, or placebo.[44] This moderate dose of ranolazine combined with the reduced-dose dronedarone (which is currently available as 400 mg) 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 750 mg BID/dronedarone 225 mg BID) compared with placebo. No significant reduction in AF burden was noted in the placebo, either drug alone, or combination therapy with dronedarone 150 mg BID groups.

AF burden in the setting of CAD and ACS was evaluated in the MERLIN-TIMI 36 study.[5] Six thousand six hundred fifty patients with non-ST-segment elevation myocardial infarction were randomized to ranolazine 1000 mg 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[45] and observational study.[46] Most recently, the Ranolazine in Atrial Fibrillation Following an Electrical Cardioversion (RAFFAELLO) study, evaluated 241 patients with persistent AF after successful electrical cardioversion.[47] Patients were treated with dose-ranging ranolazine (375, 500, or 750 mg 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.[48] Retrospective studies have suggested a role for ranolazine in postoperative CABG patients.[49,50]

RCTs offer conflicting results. Tagarakis et al randomized 102 patients with new-onset AF after elective CABG standard postoperative therapy versus ranolazine 375 mg BID for

3 days prior to surgery until discharge.[51] 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 <48 hours.[52] 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 et al recently published an abstract of their results of a trial assessing 51 patients postoperatively following CABG and/or aortic valve replacement.[53] 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.[54] 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.[55] 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.[25,33] Patients with type 2 diabetes and chronic angina demonstrated a dose-dependent reduction in HbA1C in the CARISA trial.[25] 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.[32] These studies were not, however, prospectively designed to evaluate the effect on glycemic parameters. Additionally, patients were often on other antiglycemic medications.

Eckel et al 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.[56] 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

Table. Studies Examining the Use of Ranolazine in Various Cardiovascular Disease States

Disease State	Studies Supporting Benefit (First Author and Reference No.)	Studies Not Supporting Benefit (First Author and Reference No.)	Guideline Recommendation
Chronic stable angina	Pepine[23] Chaitman[24] Chaitman[25] Stone[26] Rousseau[27] Kosiborod[28]	Thadani[22]	CCS 2009: weak recommendation based on moderate-quality evidence ACCF/AHA 2012: class of recommendation IIa, level of evidence B ESC 2013: class of recommendation IIa, level of evidence B
Incomplete revascularization after PCI		Weisz[31]	Insufficient evidence to support regular use
Acute coronary syndrome		Morrow[32]	Insufficient evidence to support regular use
Microvascular coronary dysfunction	Mehta[39] Villano[40] Tagliamonte[41]	Bairey Merz[11]	Conflicting evidence; could consider use in refractory cases
New-onset and paroxysmal AF	Koskinas[43] Reiffel[44]	Scirica[5]	Insufficient evidence to support regular use
Chronic AF		De Ferrari[47]	Insufficient evidence to support regular use
Postoperative cardiac surgery AF	Tagarakis[51]	Bekeith[53]	Insufficient evidence to support regular use
Glycometabolic effect	Chaitman[25] Morrow[32] Eckel[56]		Insufficient evidence to support regular use

ACCF indicates American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention.

Diabetes Association as a reasonable goal for most patients with type 2 diabetes.[57] These results suggest a possible currently unrecognized option for patients with concurrent CSAP and type 2 diabetes.

Conclusions

Ranolazine, through inhibition of the late sodium current, has been well tolerated and effective in patients with CSAP. The Table provides a summary of studies reviewed in the current article. This evidence has been reflected in American and European guidelines where ranolazine is supported as a second-line agent in patients with refractory angina despite commonly used anti-anginals such as β-blockers, calcium channel blockers, and/or nitrates. At this time, ranolazine is not approved by Health Canada for use in CSAP and requires an application to Special Authority. We believe the evidence presented in this review supports the re-evaluation of the Canadian Cardiovascular Society guidelines for ranolazine use in CSAP. The evidence supporting a potential role for ranolazine in other areas, such as MCD, post-CABG AF, and glycemic control in type 2 diabetics, has also shown promise. Ranolazine has limited evidence thus far in other areas, such as ACS, incomplete revascularization post-PCI, and new or chronic AF.

Disclosures

None.

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Key Words: angina • cardiovascular diseases • coronary disease • drugs • pharmacology