CADTH

CADTH Common Drug Review

Clinical Review Report

RANOLAZINE (CORZYNA)

(KYE Pharmaceuticals Inc.)

Indication: Stable angina pectoris, adults

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Abbreviations

ANCOVA	analysis of covariance
CD	controlled delivery
CI	confidence interval
ECG	electrocardiogram
ER	extended release
FAS	full analysis set
ICC	intraclass correlation coefficient
LOCF	last observation carried forward
LS	least squares
MCS	mental component score
MID	minimal important difference
NYHA	New York Heart Association
PCS	physical component score
ROLE	Ranolazine Open Label Experience
SAQ	Seattle Angina Questionnaire
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Ranolazine (Corzyna) 500 mg and 1,000 mg extended-release tablets for oral administration
Indication	As add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium-channel blockers
Reimbursement request	As per indication
Health Canada approval status	Approved
Health Canada review pathway	Priority review
Notice of Compliance date	December 30, 2020
Sponsor	KYE Pharmaceuticals Inc.

Introduction

Coronary or ischemic heart disease is a leading cause of premature mortality and disability in Canada.[1] An estimated 2.4 million Canadian adults have been diagnosed with coronary heart disease, with 1.9% of adults self-reporting angina.[1,2] Angina symptoms, such as retrosternal discomfort or heaviness, occur when myocardial oxygen demand exceeds oxygen supply. For those with stable angina, symptoms are precipitated by exertion and resolve with rest or nitroglycerin.[3] Health-related quality of life may be severely affected for patients with angina pectoris that is refractory to medical management or reperfusion procedures.[4] Patients with recurrent and sustained angina pain have poor general health status, psychological distress, impaired functioning, and activity restriction that may affect their ability to complete activities of daily living.[4]

Ranolazine underwent priority review by Health Canada and was approved for use as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium-channel blockers.[5,6] It is available as 500 mg and 1,000 mg extended-release (ER) tablets, with a recommended initial dosage of 500 mg twice daily, which may be increased to 1,000 mg twice daily, as needed, based on clinical symptoms.[5]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of ranolazine 500 mg and 1,000 mg ER tablets as an add-on therapy for the treatment of stable angina pectoris in adults who are inadequately controlled or intolerant to first-line antianginal therapies.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

No patient groups provided input for this submission.

Clinician Input

Given the advances in the management of coronary artery disease, an increasing number of patients in Canada have ongoing symptoms of angina owing to disease that is not amenable to percutaneous coronary intervention or coronary artery bypass graft surgery. In these patients, symptoms may be managed with beta-blockers, calcium-channel blockers, and/or long-acting nitroglycerin; however, adverse effects that limit the use of at least 1 antianginal therapy are not unusual, resulting in dissatisfaction with either the adverse effect profile of the medication or ongoing angina when the medication is discontinued. For some patients, further up-titration of medical therapy is not possible due to the patient's hemodynamics. Thus, there is a substantial unmet need from patients who are not able to tolerate medical therapy and those who have maximized medical therapy and still have ongoing symptoms of angina.

According to the clinical experts consulted, ranolazine would likely be used as an add-on to standard treatments in patients with refractory angina despite maximal medical therapy, or in patients who were intolerant to antianginal therapies. Response to therapy would include a decrease in the frequency of angina or dyspnea symptoms, improvement in quality of life, or improvement in functionality. Ideally, this would be an improvement of at least 1 class on the Canadian Cardiovascular Society Angina scale, but it could include a report that a patient is now able to perform a specific task that they previously could not perform without the development of angina. In clinical practice, response is evaluated subjectively, based mainly on discussion between the patient and physician, and would vary depending on the individual patient's treatment expectations and desired activity levels. The experts stated that a 2- to 4-week trial of the medication would generally be sufficient to determine who would respond to ranolazine. Treatment would be discontinued if there was no relevant improvement in symptoms, or if the patient developed adverse effects that impact the patient's well-being.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The systematic review included 2 pivotal trials[7,8] and 6 other randomized trials.[9-14]

The 3 key studies (ERICA, CARISA, and TERISA) were multi-centre, randomized, double-blind, placebo-controlled, parallel design trials.[7,8,12] The ERICA study enrolled 565 adults with coronary artery disease and stable angina who reported at least 3 angina episodes per week while receiving amlodipine 10 mg daily (with or without long-acting nitrates).[7] Patients were randomized to ranolazine 1,000 mg twice daily or placebo, as an add-on to amlodipine. The primary outcome was the weekly average frequency of self-reported angina episodes over the 6-week double-blind treatment period.

The CARISA study included 823 patients with coronary artery disease and exertional angina despite receiving treatment with atenolol 50 mg daily or diltiazem controlled delivery (CD) 180 mg daily or amlodipine 5 mg daily.[8] Patients enrolled had limited exercise capacity

and experienced angina or ischemic ST-segment depression within 3 to 9 minutes during a modified Bruce protocol exercise test. Eligible patients were randomized to ranolazine 750 mg, ranolazine 1,000 mg, or placebo twice daily for 12 weeks in addition to background anginal treatments (atenolol, diltiazem CD, or amlodipine). The primary outcome was exercise duration at trough drug levels (12 hours after dose). CADTH has reported the results of the ranolazine 1,000 mg group as this dose was consistent with the Canadian product monograph.

The TERISA study enrolled 949 patients with coronary artery disease, type 2 diabetes, and stable angina who experienced at least 1 angina episode per week, and an average of 1 to 28 angina episodes per week during a 4-week run-in period.[12] Patients were randomized to receive 8 weeks of ranolazine 1,000 mg twice daily or placebo as add-on to 1 or 2 background antianginal drugs. The primary outcome was the average frequency of self-reported angina episodes over the last 6 weeks of treatment.

For these 3 studies, the mean age of patients enrolled ranged from 61.3 (standard deviation [SD] = 9.0) to 64.2 (8.4) years (per treatment group). Most of the patients enrolled in these trials were male (61% to 80%) and White (≥ 98%), with a history of myocardial infarction (56% to 82%), heart failure (28% to 52%), unstable angina (20% to 36%), and diabetes (19% to 100%).

Five other included studies had study design, population, sample size, outcome measures, or other sources of bias that limited the utility or robustness of the findings.[9-11,13,14] Due to these limitations, only a brief summary of the findings has been included in this report. The 5 studies included 1 open-label[11] and 4 double-blind randomized trials.[9,10,13,14] Three trials used a parallel design[9-11] and 2 were randomized crossover studies.[13,14] The studies enrolled 29 to 2,651 patients with stable angina who received ranolazine 500 mg to 1,500 mg twice daily compared with placebo or usual care (add-on to background antianginal drugs in 4 trials,[9-11,14] monotherapy in 1 trial[13]). The treatment duration ranged from 1 week[13] to 1.8 years.[10]

Efficacy Results

The frequency of angina episodes was lower among patients who received ranolazine 1,000 mg twice daily versus placebo in the 3 key trials, with differences that were statistically significant in the ERICA and TERISA studies (Table 2). During the 6-week treatment period in the ERICA study, the average number of angina episodes per week was reduced from a baseline trimmed mean of 5.6 or 5.7 events per week, to 2.9 (standard error [SE] = 0.19) events per week in the ranolazine group, compared with 3.3 (SE = 0.22) events per week in the placebo group (P = 0.028). In the TERISA study, the least squares (LS) mean weekly number of angina episodes was 6.6 and 6.8 at baseline, and during the 6-week treatment period it was 3.8 (95% confidence interval [CI], 3.6 to 4.1) and 4.3 (95% CI, 4.0 to 4.5) episodes per week for the 1,000 mg ranolazine and placebo groups, respectively (P = 0.008). The CARISA study reported that patients, at baseline, experienced an average of 4.4 and 4.6 angina episodes per week, and the mean number of angina episodes per week during the treatment period was 2.1 (SE = 0.24) and 3.3 (SE = 0.30) in the ranolazine 1,000 mg and placebo groups, respectively (between-group difference P < 0.001). Because the P value for this outcome was not controlled for type I error rate, these data should be considered supportive evidence for the effect of ranolazine in the overall population.

Nitroglycerin use was also lower during treatment with ranolazine versus placebo, with 2.0 (SE = 0.20) versus 2.7 (SE = 0.22) trimmed mean doses per week in the ERICA study (P = 0.014), and 1.7 (95% CI, 1.6 to 1.9) versus 2.1 (95% CI, 1.9 to 2.3) mean weekly doses (P = 0.003) for ranolazine versus placebo, respectively, in the TERISA study (Table 2). In the CARISA study, the mean weekly frequency of nitroglycerin use was 1.8 (SE = 0.28) doses and 3.1 (SE = 0.38) doses in the ranolazine 1,000 mg and placebo groups, respectively (P < 0.001). Data from the CARISA study can be considered supportive evidence only, as this outcome was not controlled for multiplicity of testing.

In the TERISA study, the differences between ranolazine and placebo in both the percentage of angina-free days (67% versus 64%, P = 0.068) and the percentage of patients with at least a 50% reduction in angina episodes (47% versus 42%; P = 0.034) were not found to be statistically significant according to the multiple testing procedure.

The change from baseline in exercise duration measured at trough drug levels (12 hours after dose) was the primary outcome in the CARISA study. Exercise duration improved for both groups, with an LS mean difference versus placebo of 24.0 seconds (SE = 11.0; P = 0.03) (Table 2). The between-group difference in exercise duration was similar at peak drug levels (LS mean difference = 26.1 seconds; SE = 10.8; P = 0.02) and can be considered supportive evidence as this outcome was not controlled for multiplicity of testing.

The between-group differences of approximately 0.4 to 0.5 angina events per week (ERICA and TERISA) and 24 seconds on an exercise test (CARISA) were considered clinically relevant by some but not all clinical experts consulted for this review. Both the FDA and the National Institute for Health and Care Excellence concluded that the observed improvements in angina frequency and exercise duration were modest, and of unclear clinical significance.[15,16]

Two studies reported data on health-related quality of life using the Seattle Angina Questionnaire (SAQ) and Short Form (36) Health Survey (SF-36). In the TERISA study, the change from baseline in SF-36 physical component score (PCS) (ranolazine, 2.9 points; placebo, 1.9 points) was not statistically significant according to the statistical testing procedure. No differences were found in the change from baseline in SF-36 mental component score (MCS) (ranolazine, 1.0; placebo, 1.1 points). However, the SF-36 may be less sensitive to change compared with the SAQ in patients with angina. The ERICA study found no statistically significant differences between groups in the physical limitation, angina stability, disease perception/quality of life, or treatment satisfaction domains of the SAQ. An LS mean difference of 4.1 points (SE = 1.55) was found between ranolazine and placebo (P = 0.008) for the angina frequency domain of the SAQ. This difference did not exceed the minimal important difference (MID) of 10 points reported in the literature. In addition, the study's authors stated that the SAQ was not linguistically or culturally validated for the Eastern European countries where the study was conducted, raising major concerns with the validity of these results.

None of the key trials were designed to assess the impact of ranolazine on major cardiovascular events or mortality, although this drug was not expected to affect these outcomes. No clear evidence of gender-related heterogeneity in treatment effects was found based on the subgroup data available.

The results of the 5 other randomized controlled trials that met the inclusion criteria for the systematic review are summarized below.

The open-label study by Saha et al.[11] found statistically significant lower angina frequency at 6 weeks among patients with exertional angina and no obstructive coronary artery disease who received ranolazine 1,000 mg twice daily compared with usual care. No statistically significant differences in dyspnea symptoms or Duke Activity Score Index values were detected between groups. Some differences favouring ranolazine were observed for 4 of the SAQ domains, although these should be viewed as supportive evidence, as the type I error was not controlled for these outcomes. This trial was rated as low methodological quality, with multiple potential sources of bias and a limited sample size (N = 65).

The 14-week study by Willis et al.,[9] which enrolled 29 patients with coronary artery disease and stable angina, reported no statistically significant difference between ranolazine 1,000 mg twice daily and placebo in the change from baseline in SAQ quality of life domain. Similarly, the 2-week crossover study by Bairey Merz et al.[14] (N = 128) found no statistically significant difference between ranolazine (500 mg twice daily for 1 week followed by 1,000 mg twice daily for the second week) and placebo in SAQ domains, angina frequency, nitroglycerin use, and SF-36 energy and emotional domains. This trial enrolled patients with ischemic symptoms but no coronary artery disease.

The 1-week crossover MERISA study reported that monotherapy with ranolazine 500 mg twice daily increased exercise duration by 24 seconds (SE = 7.9; P = 0.003), and ranolazine 1,000 mg twice daily increased exercise duration by 34 seconds (SE = 8.0; P < 0.001), relative to placebo, in patients with coronary artery disease and stable angina who were previously responding to beta-blockers, calcium-channel blockers, and/or long-acting nitrates (N = 191).[13]

The RIVER-PCI study[10] enrolled 2,651 patients with chronic angina who had incomplete revascularization after percutaneous coronary intervention completed within the previous 14 days. This study found no statistically significant difference between ranolazine 1,000 mg twice daily and placebo in the time to first occurrence of ischemia-driven revascularization or hospitalization, or in secondary outcomes: time to sudden cardiac death, cardiovascular death, and myocardial infarction (median follow-up of 1.8 years). No differences were found between groups in angina frequency and treatment satisfaction domains of the SAQ in a RIVER-PCI substudy.[17]

Harms Results

All 3 key trials were of short duration (6 to 12 weeks) and reporting of harms data was incomplete, thus the published reports provided limited information on safety. Among those enrolled in the CARISA, TERISA, and ERICA trials, 27% to 40% of those who received ranolazine 1,000 mg and 22% to 35% of those who received placebo experienced adverse events during the studies (Table 2). Nausea, dizziness, and constipation occurred more frequently among those who received ranolazine compared with those who received placebo in all 3 studies.

The frequency of withdrawals due to adverse events was low (1% to 2%) and similar between groups in the ERICA and TERISA studies. In the CARISA study, more patients in the ranolazine 1,000 mg group withdrew due to adverse events than in the placebo group (9% versus 5%).

Serious adverse events were reported in 3.4% of patients in the ranolazine and 4.2% of those in the placebo group in the TERISA study, and in 1.8% versus 2.1% in the ranolazine 1,000 mg group versus placebo in the ERICA study. The CARISA study did not report the

overall frequency of serious adverse events, but an integrated safety review of phase II and III trials conducted by the FDA reported serious adverse events in 5.4% of patients who received ranolazine (56 of 1,030 patients) compared with 3.0% who received placebo (22 of 738 patients).[15]

During the 3 key trials 5 deaths were reported among patients who received ranolazine 1,000 mg and 6 deaths among those who received placebo (≤ 1.1% per group). Most of the deaths were cardiovascular-related. Limited data were reported on arrythmias or cardiovascular events. No patients in the key studies reported torsades de pointes. The ERICA study reported that no more than 1.4% of patients in either group reported ventricular extrasystoles, sinus bradycardia, sinus tachycardia, tachycardia, or first-degree atrioventricular block.

Four of the 5 other trials contributed little information on the safety of ranolazine.[9,11,13,14] In the RIVER-PCI study, 40% and 36% of patients stopped treatment in the ranolazine and placebo groups, respectively, including 14% and 11% of patients who stopped treatment due to adverse events.[10] Eleven percent of patients per group experienced a major adverse cardiovascular event, and 3% of patients per group died during the trial (median follow-up of 1.8 years). The adverse events reported more frequently in the ranolazine group versus placebo were dizziness (19% versus 9%), constipation (13% versus 6%), nausea (10% versus 5%), hypotension (5% versus 2.5%), vomiting (4% versus 2%), asthenia (4% versus 2%), syncope (4% versus 2%), and vertigo (3% versus 1%).[10]

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies

	ERICA[a]		CARISA[b]		TERISA[c]	
	Placebo N = 281	Ranolazine 1,000 mg N = 277	Placebo N = 258	Ranolazine 1,000 mg N = 261	Placebo N = 465	Ranolazine 1,000 mg N = 462
Angina frequency (events per week) (FAS)						
Baseline mean (SE)	5.7 (0.26)[d]	5.6 (0.21)[d]	4.6 (0.36)	4.4 (0.34)	—	—
Treatment mean (SE)	3.3 (0.22)[d]	2.9 (0.19)[d]	3.3 (0.30)	2.1 (0.24)	—	—
Baseline LS mean (95% CI)	—	—	—	—	6.8 (6.4 to 7.2)	6.6 (6.3 to 7.0)
Treatment LS mean (95% CI)	—	—	—	—	4.3 (4.0 to 4.5)	3.8 (3.6 to 4.1)
P value		0.028		< 0.001[e]		0.008
Nitroglycerin consumption (doses per week) (FAS)						
Baseline mean (SE)	5.0 (0.33)[d]	4.4 (0.26)[d]	4.1 (0.43)	3.7 (0.45)	—	—
Treatment mean (SE)	2.7 (0.22)[d]	2.0 (0.20)[d]	3.1 (0.38)	1.8 (0.28)	—	—
Baseline LS mean (95% CI)	—	—	—	—	4.5 (4.1 to 5.0)	4.1 (3.7 to 4.6)
Treatment LS mean (95% CI)	—	—	—	—	2.1 (1.9 to 2.3)	1.7 (1.6 to 1.9)
P value		0.014		< 0.001[e]		0.003
Exercise duration (seconds) at trough drug levels (12 hours after dose) (FAS)						
Baseline mean (SE)	NR	NR	418.3 (6.3)	414.7 (6.3)	NR	NR
Change from baseline, LS mean (SE)			91.7 (8.3)	115.8 (8.2)		

	ERICA[a]		CARISA[b]		TERISA[c]	
	Placebo N = 281	Ranolazine 1,000 mg N = 277	Placebo N = 258	Ranolazine 1,000 mg N = 261	Placebo N = 465	Ranolazine 1,000 mg N = 462
Difference from placebo, LS mean (SE)				24.0 (11.0)		
P value				0.03		
Harms, n (%) (safety population)	**N = 283**	**N = 281**	**N = 269**	**N = 275**	**N = 474**	**N = 470**
Adverse events	100 (35)	112 (40)	71 (26)	90 (33)	105 (22)	126 (27)
SAEs	6 (2.1)	5 (1.8)	NR	NR	20 (4.2)	16 (3.4)
WDAEs	4 (1.4)	3 (1.1)	13 (4.8)	24 (8.7)	11 (2.3)	9 (1.9)
Deaths	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)	2 (0.4)	3 (0.6)

CI = confidence interval; FAS = full analysis set; LS = least squares; SAE = serious adverse event; SE = standard error; NR = not reported; WDAE = withdrawal due to adverse event.

[a] ERICA angina frequency and nitroglycerin use based on Cochran-Mantel-Haenszel mean score test using rank scores stratified by geographic area for last 6 weeks of treatment period.

[b] CARISA exercise duration at 12 weeks based on ANOVA model adjusted for pooled site, background therapy, and baseline exercise treadmill time (last observation carried forward for missing data). Angina frequency and nitroglycerin use (over the 12-week treatment period) were based on a non-parametric ranked ANOVA model adjusted for pooled site, background therapy, baseline covariate.

[c] TERISA angina frequency and nitroglycerin use were based on a generalized linear model with a negative binomial distribution and log person-time offset adjusted for log baseline angina rate, and baseline stratification factors: average number of weekly angina episodes (1 to < 3; or 3 to 28), number of background antianginal drugs (1 or 2), and geographic region (Russia, Ukraine, and Belarus versus other countries). Estimates based on last 6 weeks of treatment period with no imputation for missing data.

[d] Trimmed mean (excluded highest and lowest 2% of values).

[e] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Stone et al. (2006),[7] Chaitman et al. (2004),[8] Kosiborod et al. (2013),[12] FDA Medical Review,[15] FDA Statistical Review.[18]

Critical Appraisal

There were major and significant gaps in the reporting of study methodology, statistical analysis plan, patient characteristics, disposition, and results in the ERICA and CARISA studies, which made it difficult to assess their internal and external validity. As the submission for this drug was based on third-party data, the sponsor was unable to supply the clinical study reports. There were issues with the statistical methods used to analyze angina frequency and nitroglycerin use data in the ERICA study. The analyses did not adjust for the baseline frequency of events that could have potentially biased the nitroglycerin use results in favour of ranolazine, as baseline use was lower in the active drug group than in the control. Also, the statistical methods were modified after reviewing the data, which contained extreme outliers. The 3 key trials included statistical testing procedures to control the risk of type I error; however, in the CARISA trial, type I error was controlled for the primary outcome only, and the secondary outcomes that reported statistically significant differences are therefore at an inflated risk of type I error and should be viewed as supportive evidence for the effect of ranolazine in the overall population.

Limitations of the other 5 trials included the following: unclear methods used to randomize patients and conceal allocation,[9,11,13,14] or to maintain blinding;[9,13,14] open-label design;[11] small sample size;[9,11] carry-over of effects between treatment periods in 1 crossover study;[13] short treatment duration (1 to 14 weeks);[9,11,13,14] and incomplete reporting of methods and results.[9,11]

Because the control treatment in all trials was placebo or usual care, data comparing ranolazine to other antianginal treatment options are lacking. As none of the key trials included a 500 mg dosage group, efficacy data are lacking for 1 of the dosage regimens that is being sought for approval. Longer-term efficacy is unclear, due to the short duration of the key trials (up to 12 weeks). Reporting of harms was incomplete in all trials. Only 1 trial (RIVER-PCI) provided longer-term safety data.

External validity was limited by several factors. Because the pivotal trials were conducted between 1999 and 2005, and most patients in the ERICA and TERISA studies were from Eastern Europe, management of patients with stable angina may not have been optimized according to current clinical standards. Moreover, most patients were White and male, and they may not be reflective of racial and gender distributions in Canada. The TERISA study enrolled an enriched population that was adherent to the study drug and outcome reporting. Background therapies were limited to 1 or 2 drugs, and, in the TERISA study, patients who were taking more than 2 antianginal drugs at baseline were required to stop additional therapies. Consequently, these trials may have included patients whose symptoms could have been controlled with standard therapies. As the population included in the RIVER-PCI trial[10] was more reflective of an acute coronary syndrome population, its generalizability to the indication under review may be limited.

Indirect Comparisons

No indirect treatment comparisons were submitted by the sponsor and no relevant published reports were identified in the literature search conducted by CADTH.

Other Relevant Evidence

The Ranolazine Open Label Experience (ROLE) study[19] was a long-term extension study that provided information on the safety and tolerability of ranolazine in patients with chronic angina who completed the CARISA or MARISA trials.[8,13]

A total of 746 patients were enrolled in the ROLE program: 603 from the CARISA trial and 143 from the MARISA trial, which represents 73% to 75% of the patients enrolled in the original trials. The patients included in the ROLE study were predominantly male (78%) and White (97%), and the majority (52%) were less than 65 years of age. The patients had a history of hypertension (64%), myocardial infarction (58%), prior revascularization (35%), heart failure (29%), unstable angina (23%), and diabetes (23%).

Patients received open-label ranolazine at a dosage of 500 mg or 1,000 mg ER twice daily in addition to background therapies. The mean exposure time to ranolazine was 2.8 years (range: 6 days to 6.5 years), and during follow-up 39% of patients discontinued therapy. Of those discontinuations, 13% were due to adverse events, 13% were due to elective withdrawal, and 8% were due to death.

The most common adverse events reported were angina pectoris (15%), dizziness (12%), constipation (11%), and peripheral edema (8%). In terms of mortality, 68 deaths were reported during the 2,372 patient-years of follow-up in the ROLE program, which corresponds to an annual mortality rate of 2.8 deaths per patient-year. No data were reported on the number of serious adverse events.

Limitations of the ROLE study include potential selection bias, lack of blinding, lack of comparator group, and lack of systematic follow-up after discontinuation of the ROLE program.

Conclusions

In patients with coronary artery disease and stable angina pectoris, ranolazine 1,000 mg ER twice daily as an add-on to 1 or 2 standard antianginal drugs reduced angina frequency and nitroglycerin consumption in the short-term, relative to placebo plus standard treatments. Short-term treatment with ranolazine as add-on therapy also improved exercise duration on a modified Bruce protocol exercise test compared with placebo plus standard treatments. The between-group differences in angina frequency and exercise duration were modest and may not be clinically important to patients.

The impact of ranolazine on health-related quality of life is uncertain. None of the key trials was designed to evaluate the effect of ranolazine on cardiovascular events or mortality in patients with stable angina. Data are lacking on the efficacy of the 500 mg dose of ranolazine and for ranolazine compared with other antianginal treatments.

Ranolazine was associated with increased frequency of nausea, constipation, and dizziness relative to placebo. Safety data were limited by the quality of the reporting in the published trials and the short duration of the key randomized controlled trials.

The findings of the key trials may not be representative of the broader Canadian population with stable angina. Given the time frame and the countries where the trials were conducted, the management of coronary artery disease may have been suboptimal, according to current Canadian practice standards. In addition, 1 study enrolled an enriched population that was adherent to treatment and outcome reporting.

Introduction

Disease Background

Coronary or ischemic heart disease is a leading cause of premature mortality and disability in Canada.[1] An estimated 2.4 million Canadian adults have been diagnosed with coronary heart disease, with 1.9% of adults self-reporting angina.[1,2] Angina symptoms, such as retrosternal discomfort or heaviness, occur when myocardial oxygen demand exceeds oxygen supply. For those with stable angina, symptoms are precipitated by exertion and resolve with rest or nitroglycerin.[3] Stable ischemic heart disease may be diagnosed based on a history of angina pectoris among those with risk factors or known atherosclerotic cardiovascular disease, and may include stress testing, cardiac imaging, or invasive coronary angiography.[3,20] Health-related quality of life may be severely affected in patients with angina that is refractory to medical management or reperfusion procedures.[4] Patients with recurrent and sustained pain have poor general health status, psychological distress, impaired functioning, and activity restriction that may affect their ability to complete activities of daily living.[4]

Standards of Therapy

Treatment of coronary artery disease resulting in angina is focused on 2 different aspects: avoiding disease progression or further manifestation of the disease and minimizing symptoms.[20] In the former category are medications such as statins, icosapent ethyl, sodium glucose cotransporter-2 inhibitors, antiplatelet medications, low-dose rivaroxaban, and blood pressure medications. Treatment may also include revascularization procedures, although the COURAGE trial[21] and the ISCHEMIA trial[22] indicate that revascularization does not improve the length of life for most patients.

In terms of symptom relief, options primarily include coronary revascularization via percutaneous coronary intervention or coronary artery bypass graft surgery. Commonly used medications for the treatment of angina include nitroglycerin, calcium-channel blockers (verapamil, diltiazem, and amlodipine), beta-blockers, and off-label use of ivabradine. These medications all alter myocardial oxygen demand, increasing the threshold of activity required to produce symptoms. They do not fundamentally change the course of coronary artery disease. Other symptomatic treatments that the clinical experts stated were used rarely include allopurinol, amiodarone, and spinal stimulation. The goals of antianginal therapy are to reduce the frequency and severity of symptoms or increase the exertion required to produce symptoms while remaining at least neutral in terms of adverse effects and mortality.

Drug

Ranolazine underwent priority review by Health Canada and was approved for use as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium-channel blockers.[5,6] The sponsor has requested reimbursement as per the indication.

Ranolazine is available as 500 mg and 1,000 mg ER tablets and the recommended initial dosage is 500 mg twice daily, which may be increased to 1,000 mg twice daily, as needed,

based on clinical symptoms.[5] The mechanism of action of its antianginal effect is not known.[5]

Ranolazine was approved in the US in 2006 for the treatment of chronic angina, with a recommended dose of 500 mg or 1,000 mg twice daily.[23] In Europe, ranolazine was approved for use in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).[24] It is available as 375 mg, 500 mg, and 750 mg prolonged-release tablets, with a recommended dosage of 375 mg to 750 mg twice daily.[24]

Table 3: Key Characteristics of Ranolazine

	Ranolazine
Mechanism of action	Piperazine derivative; mechanism of action is unknown
Indication[a]	As add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies, including beta-blockers and calcium-channel blockers
Route of administration	Oral
Recommended dose	500 mg or 1,000 mg twice daily
Serious adverse effects or safety issues	Dose-related QT-interval prolongation: • the magnitude of QTc prolongation with ranolazine at therapeutic doses is predicted to be large • the indicated patient population considered to be at high risk of torsades de pointes, and cases of torsades de pointes and ventricular fibrillation have been reported in post-marketing surveillance • ranolazine is a substrate sensitive to CYP 3A4 and therefore prone to large increases in plasma concentrations in the presence of these metabolic inhibitors Monitor renal function in patients with renal impairment (CrCL < 60 mL/min) as ranolazine has been associated with acute renal failure Contraindicated in patients with moderate or severe hepatic impairment, severe renal impairment (i.e., eGFR ≤ 30 mL/min/1.73 m^2) and those taking inducers of CYP 3A4, strong inhibitors of CYP 3A4, or class IA or III antiarrhythmics Dose reductions may be required if used concurrently with moderate inhibitors of CYP 3A4 (e.g., diltiazem, verapamil, erythromycin, and fluconazole), P-glycoprotein inhibitors (e.g., cyclosporine and verapamil), and CYP 2D6 inhibitors (e.g., digoxin) or in patients who are poor metabolizers of CYP 2D6; metformin dose should not exceed 1,700 mg/day in patients receiving ranolazine 1,000 mg twice daily
Other	Post-marketing reports of QT-interval prolongation, torsades de pointes, and ventricular fibrillation; nervous system adverse events such as abnormal coordination, diplopia, gait disturbance, myoclonus, paresthesia, and tremors; hypoglycemia in patients with diabetes receiving antidiabetic medications; rhabdomyolysis in patients receiving simvastatin; hallucinations; dysuria and urinary retention; angioedema, pruritus, and rash; and intentional overdose resulting in fatal outcomes

CrCl = creatinine clearance; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate.

[a] Health Canada–approved indication.

Source: Corzyna product monograph.[5]

Stakeholder Engagement

Patient Group Input

No patient groups submitted input for this review.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise on the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the ranolazine review, a panel of 4 clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where gaps in the evidence can be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented below.

Unmet Needs

Given the advances in the management of coronary artery disease, an increasing number of patients in Canada have ongoing symptoms of angina due to disease that is not amenable to percutaneous coronary intervention or coronary artery bypass graft surgery. In these patients, symptoms may be managed with beta-blockers, calcium-channel blockers, and/or long-acting nitroglycerin. However, adverse effects that limit the use of at least 1 antianginal therapy are not unusual, resulting in dissatisfaction with either the adverse effect profile of the medication or ongoing angina when the medication is discontinued. For some patients, further up-titration of medical therapy is not possible due to the patient's hemodynamics. Additional antianginal therapies are needed by both patients who are not able to tolerate medical therapy and those who have maximized medical therapy and still have ongoing symptoms of angina.

Place in Therapy

The clinical experts stated that ranolazine would likely be used as add-on therapy in patients with refractory angina despite maximal medical therapy, or in patients who were intolerant to antianginal therapies. Ranolazine would be used to reduce symptoms, not to address the underlying disease process. Although the mechanism of action of ranolazine is unknown, it belongs to a different drug class than other antianginal therapies and may be used in patients with low blood pressure or a low heart rate as the drug does not affect these parameters.

According to the clinical experts, ranolazine is unlikely to cause a shift in the current treatment paradigm as the present guideline-recommended medications (nitroglycerin, beta-blockers, and calcium-channel blockers) are cost-effective and most patients can tolerate the adverse effect profile well. There is a large body of experience using these medications, and in some populations, there is evidence for additional benefit (e.g., beta-blockers in patients with heart failure and angina, amlodipine in patients with hypertension). Moreover, the adverse effects associated with ranolazine are not insignificant.

Patient Population

The clinical experts stated that ranolazine is best suited for patients with refractory angina despite maximal medical therapy or those who cannot tolerate additional medical therapy either owing to adverse effects, heart rate, or blood pressure. This would include patients in whom epicardial revascularization cannot be safely performed or those with a microvascular component to their symptoms. Patients who are suitable for ranolazine treatment would be identified based on clinician judgment. Patients generally voice dissatisfaction with their symptoms of angina, and this is an area of focused questioning by physicians treating those who are suspected or known to have coronary artery disease. No additional tests would be required, other than an electrocardiogram (ECG) or measurements of digoxin levels.

Ranolazine would not be suitable for patients with long QT syndrome, those with liver cirrhosis, or those who are receiving medications contraindicated for use with ranolazine. Caution may be warranted in patients receiving metformin and digoxin, or other medications with clinically important drug interactions. The experts stated that standard antianginal therapies should be selected as first-line therapies over ranolazine for patients who have adequate hemodynamics and no contraindications to beta-blockers, calcium-channel blockers, or long-acting nitrates.

Assessing Response to Treatment

In clinical practice, response is evaluated subjectively, based mainly on discussions between the patient and physician, and would vary depending on the individual patient's treatment expectations and desired activity levels. Response to therapy would include a decrease in the frequency of angina or dyspnea symptoms, improvement in quality of life, or improvement in functionality. Ideally, this would be an improvement of at least 1 class in the Canadian Cardiovascular Society Angina scale but could include a report that a patient is now able to perform a specific task that they previously could not perform without the development of angina.

The experts stated that a brief trial of the medication lasting 2 to 4 weeks would generally be sufficient to determine who would respond to therapy with ranolazine. The frequency of subsequent evaluations may be determined by the patient's health status and may be affected by the availability of specialists or other resource constraints. The outcome measures used in clinical trials, such as at the SAQ or time to development of objective measures of myocardial ischemia on a stress test, are not routinely employed in clinical practice.

Discontinuing Treatment

Treatment would be discontinued if there was no relevant improvement in symptoms, or if the patient developed adverse effects that affect patient well-being. Adverse events of concern include QT prolongation or life-threatening arrhythmia.

Prescribing Conditions

The clinical experts stated that input from a cardiologist is necessary for the diagnosis and treatment of patients with coronary artery disease and stable angina, including the prescribing of ranolazine. Ranolazine is suitable for use in community, hospital, or specialty clinic settings.

Clinical Evidence

The clinical evidence included in the review of ranolazine is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of ranolazine 500 mg and 1,000 mg ER tablets as add-on therapy for the treatment of stable angina pectoris in adults who are inadequately controlled or intolerant to first-line antianginal therapies.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists) Subgroups: • Gender
Intervention	Ranolazine 500 mg or 1,000 mg ER twice daily as add-on therapy to standard angina treatments (e.g., beta-blockers, nitrates, calcium-channel blockers)
Comparators	Standard therapies (with or without placebo) such as: beta-blockers, nitrates, calcium-channel blockers
Outcomes	**Efficacy outcomes:** • Symptoms (e.g., angina frequency, nitroglycerin consumption) • Functional status (e.g., exercise tolerance) • Health-related quality of life (e.g., SAQ) • Cardiovascular events (e.g., myocardial infarction, stroke, need for revascularization procedure) • Mortality (cardiovascular and all-cause) **Harms outcomes:** AEs, SAEs, WDAEs, notable harms (arrhythmias, renal failure–related AEs, digoxin-related AEs)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; ER = extended release; RCT = randomized controlled trial; SAE = serious adverse event; SAQ = Seattle Angina Questionnaire; WDAE = withdrawal due to adverse event.

Note: No input from patient groups was received for this submission.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).[25]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was ranolazine. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform search portal.

A study design filter was used to limit search results to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on September 15, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on January 20, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters)[26] Health technology assessment (HTA) agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials registries, and databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Eight studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5, Table 6, and Table 11.

The Health Canada submission was based on third-party data and the sponsor was unable to supply clinical study reports to CADTH.

A list of excluded studies is presented in Appendix 2.

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Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

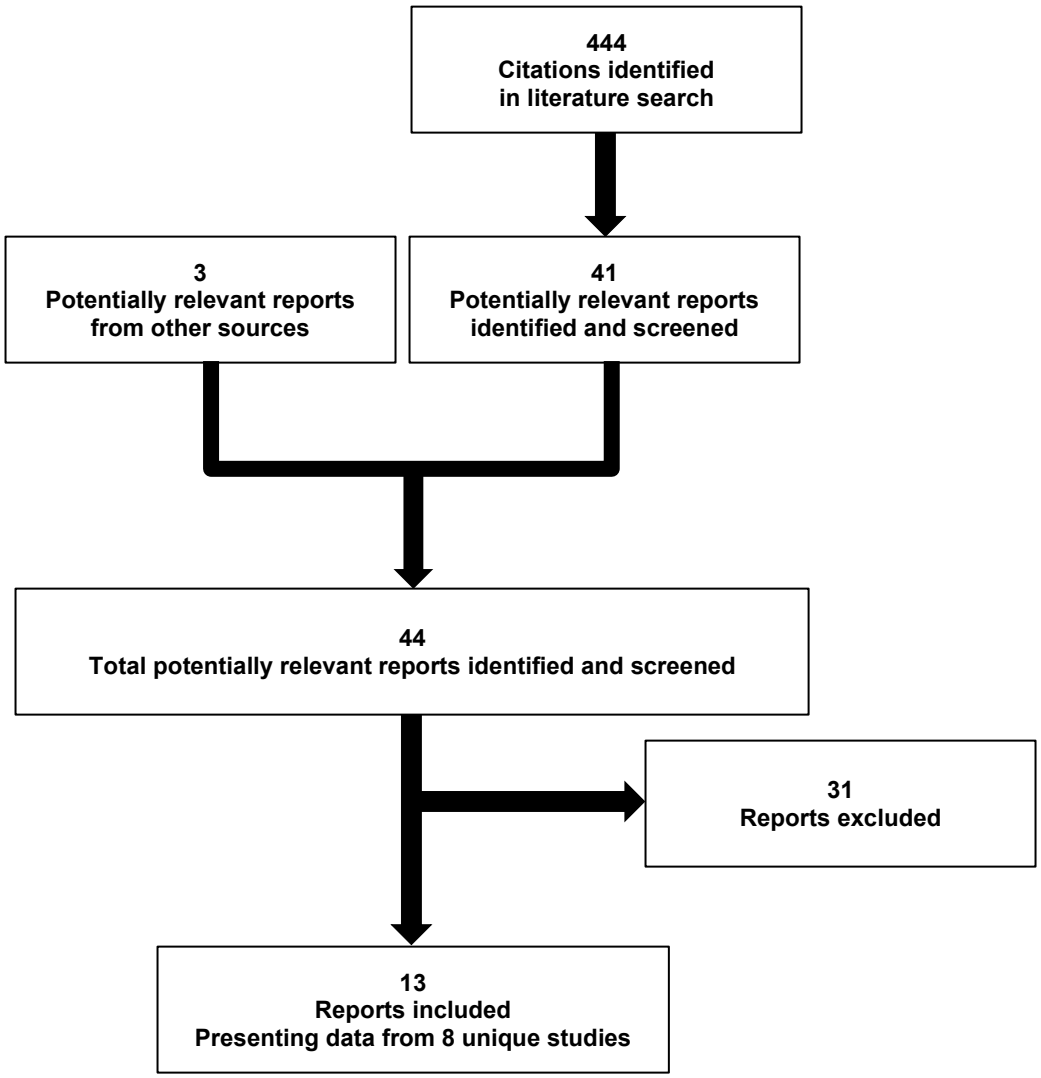

Table 5: Details of Pivotal Studies

		ERICA	CARISA
Designs and Populations	**Study design**	DB, parallel RCT	DB, parallel RCT
	Locations	Eastern Europe, US, Canada	Europe, Canada, US, New Zealand, Israel
	Randomized (N)	565	823
	Inclusion criteria	• Adults ≥ 18 years with history of CAD (≥ 60% stenosis of at least 1 major coronary artery, prior MI, and/or a stress induced reversible perfusion defect on radionuclide or echocardiographic imaging) • Chronic stable angina ≥ 3 months with ≥ 3 episodes of angina per week during a ≥ 2-week qualification period while receiving treatment with 10 mg amlodipine daily	• Patients with CAD (confirmed by angiography, prior MI, or diagnostic stress myocardial imaging study) • History of exertional angina ≥ 3 months • Receiving atenolol 50 mg daily, diltiazem CD 180 mg daily, or amlodipine 5 mg daily; (other antianginal medications were withdrawn) • At screening, had reproducible angina, ischemic ST-segment depression of at least 1 mm and limited exercise capacity of 3 to 9 minutes on a modified Bruce protocol testing
	Exclusion criteria	• NYHA class IV heart failure • MI or unstable angina within past 2 months • Active acute myocarditis, pericarditis, hypertrophic cardiomyopathy, or uncontrolled hypertension • History or torsades de pointes, those receiving drugs that prolong QTc interval or patients with QTc interval > 500 ms at study entry • Treated with CYP3A4 inhibitors, clinically significant hepatic disease, creatinine clearance < 30 mL/min • Receiving digoxin, perhexiline, trimetazidine, beta-blockers, or calcium-channel blockers other than amlodipine.	• NYHA class III or IV heart failure • Patients with factors that interfere with interpretation of ECG (e.g., resting ST-segment depression, left bundle branch block, digoxin therapy) • Acute coronary syndrome or revascularization procedure within the prior 2 months
Drugs	**Intervention**	Ranolazine 500 mg ER twice daily for first week then 1,000 mg ER twice daily plus amlodipine 10 mg daily	Ranolazine 750 mg SR twice daily or ranolazine 1,000 mg SR twice daily plus atenolol 50 mg daily or diltiazem 180 mg CD daily, or amlodipine 5 mg daily
	Comparator(s)	Placebo plus amlodipine 10 mg daily	Placebo plus atenolol 50 mg daily or diltiazem 180 mg CD daily, or amlodipine 5 mg daily
Duration	**Phase**		
	Qualifying/run-in	2 weeks	Duration NR[a]
	Initial	1 week (dose titration)[b]	NA
	Double-blind	6 weeks	12 weeks
	Follow-up	NR	14 days
Outcomes	**Primary end point**	Average frequency of self-reported angina episodes over 6 weeks	Exercise duration at trough drug levels (12 hours after dose)
	Secondary and exploratory end points	• Average weekly nitroglycerin consumption • Change from baseline in 5 dimensions of SAQ • Harms	• Exercise duration at peak drug levels (4 hours after dose) • Time to angina and 1 mm ST-segment depression at peak and trough drug levels • Frequency of angina attacks • Nitroglycerin use

		ERICA	CARISA
			• Harms
Notes	**Publications**	Stone et al. (2006)[7]	Chaitman et al. (2004)[8]

CAD = coronary artery disease; CD = controlled delivery; CYP = cytochrome P450; DB = double-blind; ECG = electrocardiogram; ER = extended release; MI = myocardial infarction; NA = not applicable; NR = not reported; NYHA = New York Heart Association; RCT = randomized controlled trial; SAQ = Seattle Angina Questionnaire; SR = sustained release.

[a] Single-blind placebo qualifying stage during which baseline exercise tests and angina frequency were measured. The duration of the qualifying stage was not reported.

[b] First week after randomization, where patients received a lower dose of study drug. This period was not included in the efficacy assessments.

Note: Three additional reports were included: FDA Medical Review,[15] FDA Statistical Review,[18] and CADTH Common Drug Review Submission.[6]

Source: Stone et al. (2006)[7] and Chaitman et al. (2004)[8].

Table 6: Details of Non-Pivotal Studies

		TERISA
Designs and Populations	**Study design**	DB RCT parallel design
	Locations	Eastern Europe, US, Canada, Israel
	Randomized (N)	949

	Inclusion criteria	• Adults ≥ 18 years with history of CAD (defined as 1 of the following: ≥ 50% stenosis of at least 1 major coronary artery, prior MI, cardiac imaging study or exercise test diagnostic for CAD, or history of coronary revascularization procedure)
		• Chronic stable angina for ≥ 3 months triggered by physical effort and relieved by rest or sublingual nitroglycerin
		• Treatment with 1 or 2 antianginal drugs (beta-blocker, CCB or long-acting nitrate) at a stable dose for at least 2 weeks
		• Type 2 diabetes
		• Criteria for treatment phase:
		  ○ ≥ 85% adherent to electronic diary data entry during run-in phase
		  ○ Average of 1 to 28 angina episodes per week, with at least 1 event each week
		  ○ ≥ 80% adherent to placebo
		  ○ No coronary revascularization procedure during run-in

	Exclusion criteria	• NYHA class III or IV heart failure • Acute coronary syndrome within the prior 2 months or planned revascularization procedure during trial • Stroke or TIA within 6 months • QTc > 500 ms • Uncontrolled hypertension, SBP < 100 mm Hg • Clinically significant hepatic impairment or receiving renal replacement therapy • Receiving a prohibited medication (see Intervention section)
Drugs	**Intervention**	Ranolazine 500 mg ER twice daily for first week then 1,000 mg ER twice daily plus 1 or 2 antianginal treatments (beta-blockers, CCBs, or long-acting nitrates)
	Comparator(s)	Placebo plus 1 or 2 antianginal treatments (beta-blockers, CCBs, or long-acting nitrates)
Duration	**Phase**	
	Run-in	4 weeks[a]
	Double-blind	8 weeks
	Follow-up	14 days

		TERISA
Outcomes	**Primary end point**	Average weekly angina frequency over last 6 weeks of treatment
	Secondary and exploratory end points	• Average weekly sublingual nitroglycerin use over last 6 weeks of treatment • Angina-free days over last 6 weeks • Proportion with at least a 50% reduction in angina frequency • Change from baseline in SF-36 MCS and PCS • Change from baseline in RDS, daily dyspnea score, SAQ domains, PGIC, PGA VAS • Harms
Notes	**Publications**	Kosiborod et al. (2013)[12]

CAD = coronary artery disease; CCB = calcium-channel blocker; DB = double-blind; ER = extended release; MCS = mental component score; MI = myocardial infarction; NR = not reported; NYHA = New York Heart Association; PCS = physical component score; PGA VAS = Physician's Global Assessment Visual Analogue Scale; RCT = randomized controlled trial; RDS = Rose Dyspnea Scale; SAQ = Seattle Angina Questionnaire; SBP = systolic blood pressure; PGIC = Patient's Global Impression of Change; SF-36 = Short Form 36 Health Survey; TIA = transient ischemic attack.

[a] Single-blind placebo-controlled run-in period. Patients recorded angina episodes and nitroglycerin consumption using a handheld electronic diary.

Source: Kosiborod et al. (2013).[12]

Description of Studies

Two studies submitted by the sponsor were identified as pivotal trials: (1) Efficacy of Ranolazine in Chronic Angina (ERICA); and (2) Combination Assessment of Ranolazine in Stable Angina (CARISA).[7,8] Both were multi-centre, randomized, double-blind, placebo-controlled, parallel-design trials.

The objective of the ERICA trial[7] was to assess the impact of ranolazine on angina frequency in patients with persistent angina symptoms despite receiving maximum daily doses of amlodipine. This 6-week study enrolled 565 patients with coronary artery disease and chronic stable angina. Patients were randomized to ranolazine ER 1,000 mg twice daily or placebo (1:1) as add-on therapy to amlodipine 10 mg daily. Prior to randomization, patients underwent a 2-week qualifying period and were required to self-report at least 3 angina episodes per week while receiving amlodipine therapy. Eligible patients were randomized centrally with no stratification (no details on randomization methods were provided). During the first week after randomization, patients in the active treatment group received ranolazine ER 500 mg twice daily, with subsequent doses increased to 1,000 mg twice daily. Efficacy and safety assessments were conducted 6 weeks after the start of the full-dose treatment period. The study was conducted in 2004 and 2005 at 48 sites, including 45 sites in Eastern Europe, 2 sites in the US, and 1 site in Canada.[7,27]

The CARISA study[8] was designed to assess the effects of ranolazine versus placebo on treadmill exercise duration in patients with chronic angina and coronary artery disease who were receiving antianginal therapy. The study randomized 823 patients (1:1:1) to placebo, ranolazine 750 mg ER twice daily, or ranolazine 1,000 mg ER twice daily as add-on therapy to atenolol 50 mg daily, amlodipine 5 mg daily, or diltiazem CD 180 mg daily. The computer-generated block randomization was stratified by the 3 background antianginal drugs (with a block size of 6). Sealed envelopes with the treatment allocation were distributed to study sites for each patient randomized. The trial consisted of a single-blind placebo qualifying phase, during which baseline exercise tests were conducted, and a 12-week double-blind treatment phase. The CARISA study was conducted at 118 centres in Europe, the US, Israel, New Zealand, and Canada (15 sites) between 1999 and 2001. This

report will focus on the findings of the ranolazine 1,000 mg group, as this dose is consistent with the Health Canada product monograph.

Six other trials met the inclusion criteria for the systematic review.[9-14] Five of these studies were assessed as having study design, population, sample size, outcomes measures, or other sources of bias that limited the utility or robustness of the findings.[9-11,13,14] These trials are summarized briefly in the Other Included Studies section, but are not the focus of this CADTH review. One trial, the TERISA study,[12] was summarized in detail.

The objective of the Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) study[12] was to determine the efficacy of ranolazine in reducing angina in patients who had type 2 diabetes, coronary artery disease, and chronic angina, and who were symptomatic despite treatment. This parallel design trial included a 4-week single-blind placebo run-in period and an 8-week double-blind treatment period. Those patients who kept a symptom diary, were adherent to the study drug, and experienced at least 1 angina episode per week (average of 1 to 28 angina episodes per week) during the run-in period were eligible for randomization. In total 949 patients were randomized to receive ranolazine 1,000 mg twice daily or placebo (1:1) as an add-on to 1 or 2 antianginal drugs. An interactive voice or web response system was used to allocate patients to treatment, with randomization stratified by the average number of weekly angina episodes (1 to < 3; or 3 to ≤ 28), number of background antianginal drugs (1 or 2), and geographic region (Russia, Ukraine, and Belarus versus other countries). The trial was conducted in 14 countries between 2011 and 2012 and included 3 patients from Canada.

Populations

Inclusion and Exclusion Criteria

The ERICA trial enrolled patients with a documented history of coronary artery disease and chronic stable angina of at least 3 months duration (Table 5). Those who experienced at least 3 angina episodes per week during the 2-week qualifying period, despite background therapy of amlodipine 10 mg daily, were eligible for randomization. The study excluded those with a history of myocardial infarction or unstable angina in the past 2 months, uncontrolled hypertension, New York Heart Association (NYHA) class IV heart failure, torsades de pointes, or with a prolonged QTc interval.

In the CARISA study, patients were eligible if they had confirmed coronary artery disease and at least a 3-month history of exertional angina despite antianginal therapy (Table 5). During the qualifying period, patients continued the protocol-selected antianginal treatments (atenolol, amlodipine, or diltiazem CD) and all other angina treatments were stopped. Patients underwent 2 treadmill exercise tests 1 week apart and those who had exercise-limiting angina and ECG ischemia (at least 1 mm ST-segment depression versus resting ECG) within 3 to 9 minutes on a modified Bruce protocol exercise test were randomized to ranolazine or placebo as an add-on to background therapy. Patients had to show angina and ischemia on both qualifying treadmill tests and the exercise duration could not differ by more than 1 minute or 20% between the 2 tests. Patients were excluded from the CARISA trial if they had NYHA class III or IV heart failure or had an acute coronary syndrome or revascularization procedure within the past 2 months.

The TERISA study included adults with type 2 diabetes, coronary artery disease, and chronic stable angina of at least 3 months. Eligible patients were experiencing angina with physical exertion despite treatment with 1 or 2 antianginal drugs (i.e., beta-blockers,

calcium-channel blockers, or long-acting nitrates) (Table 6). All patients underwent a 4-week run-in phase and those who were at least 85% adherent to electronic diary data entry experienced an average of 1 to 28 angina episodes per week with at least 1 event each week and were at least 80% adherent to placebo were randomized to the double-blind treatment period. The study excluded those with a history of acute coronary syndrome in the past 2 months, stroke or TIA within the past 6 months, uncontrolled hypertension, or NYHA class III or IV heart failure, as well as those receiving a prohibited medication.

Baseline Characteristics

In general, the patient characteristics appeared to be balanced between groups within studies at baseline. The mean age of patients enrolled was 61.3 (SD = 9.0) and 62.0 (SD = 8.7) years per treatment group in the ERICA study, 63.7 (SD = 8.9) and 63.9 (SD = 9.3) years in the CARISA study, and 63.2 (SD = 8.5) and 64.2 (SD = 8.4) years per group in the TERISA study. Most of the patients enrolled in all 3 studies were male (61% to 80%) and White (≥ 98%) (Figure 2, Figure 3, and Figure 4).

The patients in the ERICA study had a history of myocardial infarction (80%), heart failure (52%), unstable angina (36%), and diabetes (19%). Overall, 10% had previously undergone a percutaneous coronary intervention, and 11% had a previous coronary artery bypass graft (Figure 2).

In the CARISA study, 57% of patients in the placebo and ranolazine 1,000 mg groups had a history of myocardial infarction, 28% had heart failure, 22% had unstable angina, and 22% had diabetes. The proportion of patients who had undergone a percutaneous coronary intervention was 20% and 19% in the placebo and ranolazine 1,000 mg groups, respectively. Comparable figures for a coronary artery bypass graft were 13% and 20% (Figure 3).

All patients in the TERISA study had type 2 diabetes and 93% were receiving antidiabetic medications. Most patients had a history of myocardial infarction (74%), hypertension (96%), and dyslipidemia (80%). Overall, 41% of patients had undergone a prior angioplasty and 19% had a coronary artery bypass graft (Figure 4).

Figure 2: Summary of Baseline Characteristics for the ERICA Study

	Placebo + Amlodipine (n = 283)	Ranolazine + Amlodipine (n = 281)	p Value
Demographics			
Age (yrs), mean ± SD	61.3 ± 9.0	62.0 ± 8.7	0.36*
Gender (M/W), %	73/27	72/28	0.66†
Race, %			0.22†
White	99	98	
Black	1	1	
Asian	0	<1	
Geographic region, %			NC
Eastern Europe	97	97	
North America	3	3	
Concomitant use of LANs, %	43	46	0.72†
Baseline characteristics			
Weekly rate of angina attacks, trimmed mean ± SE	5.68 ± 0.26 (n = 281)	5.59 ± 0.21 (n = 277)	0.48‡
Weekly rate of NTG consumption, trimmed mean ± SE	5.02 ± 0.33 (n = 281)	4.43 ± 0.26 (n = 277)	0.18‡
SAQ score, mean ± SD			
Angina frequency	40.0 ± 14.9 (n = 281)	40.6 ± 13.2 (n = 277)	0.67*
Physical limitation	48.9 ± 17.3 (n = 276)	49.2 ± 17.4 (n = 271)	0.93*
Anginal stability	57.2 ± 17.7 (n = 281)	54.7 ± 18.0 (n = 277)	0.10*
Disease perception	41.5 ± 17.8 (n = 281)	41.6 ± 17.2 (n = 277)	0.89*
Treatment satisfaction	75.4 ± 14.0 (n = 281)	74.6 ± 14.3 (n = 277)	0.46*
Medical history, n (%)			
History of unstable angina	98 (35)	100 (36)	0.87†
History of congestive heart failure	145 (51)	146 (52)	0.58†
NYHA functional class I	38 (13)	32 (11)	0.69†
NYHA functional class II	86 (30)	99 (35)	
NYHA functional class III	21 (7)	15 (5)	
NYHA functional class IV	0	0	
Diabetes mellitus	54 (19)	52 19)	0.82†
Insulin-dependent	2 (1)	11 (4)	
Previous myocardial infarction	233 (82)	218 (78)	0.16†
Previous coronary artery bypass grafting	34 (12)	28 (10)	0.52†
Previous percutaneous coronary intervention	25 (9)	34 (12)	0.095†
Intermittent claudication	32 (11)	39 (14)	0.48†
Hypertension	257 (91)	246 (88)	0.33†

*Analysis of variance with effects for treatment and pooled site. †Cochran-Mantel-Haenszel test, stratifying by pooled site. ‡Cochran-Mantel-Haenszel mean scores test, using rank scores, stratifying by pooled site.

LAN = long-acting nitrate; NC = not calculated; NTG = nitroglycerin; NYHA = New York Heart Association; SAQ = Seattle Angina Questionnaire; SD = standard deviation; SE = standard error.

Source: Permission obtained from the publisher to use Table 1 from Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial, by Stone PH, Gratsiansky NA, Blokhin A, et al. (2006).[7]

Figure 3: Summary of Baseline Characteristics for the CARISA Study

Variables	Placebo (n = 269)	Ranolazine, mg Twice Daily 750 (n = 279)	Ranolazine, mg Twice Daily 1000 (n = 275)	*P* Value
Background antianginal drug once daily, No. (%)				
Atenolol, 50 mg	118 (43.9)	119 (42.7)	117 (42.6)	.69
Amlodipine, 5 mg	81 (30.1)	86 (30.8)	89 (32.4)	
Diltiazem, 180 mg	70 (26.0)	74 (26.5)	69 (25.1)	
Age, mean (SD), y	63.7 (8.9)	64.3 (9.3)	63.9 (9.3)	.73
Age, No. (%), y				
≥65	140 (52.0)	138 (49.5)	137 (49.8)	.80
<65	129 (48.0)	141 (50.5)	138 (50.2)	
Male, No. (%)	202 (75.1)	217 (77.8)	219 (79.6)	.45
Baseline electrocardiographic results, No. (%)				
Pathologic Q waves	45 (16.7)	59 (21.1)	55 (20.0)	.57
Major ST-T wave abnormalities†	39 (14.5)	41 (14.7)	35 (12.7)	
Minor ST-T wave abnormalities†	71 (26.4)	68 (24.4)	82 (29.8)	
No pathologic Q or ST-T waves	114 (42.4)	111 (39.8)	103 (37.5)	
Prior medical history, No. (%)				
Hypertension	173 (64.3)	177 (63.4)	177 (64.4)	.97
Unstable angina	54 (20.1)	58 (20.8)	65 (23.6)	.54
Myocardial infarction	150 (55.8)	166 (59.5)	158 (57.5)	.67
Congestive heart failure	77 (28.6)	87 (31.2)	78 (28.4)	.72
Coronary artery bypass graft surgery	36 (13.4)	53 (19.0)	56 (20.4)	.07
Percutaneous coronary intervention	53 (19.7)	46 (16.5)	53 (19.3)	.57
Diabetes mellitus	57 (21.2)	68 (24.4)	64 (23.3)	.67
Angina frequency, mean (SD), attacks/wk	4.6 (5.7)	4.3 (5.3)	4.5 (5.4)	.84
Nitroglycerin use, mean (SD), tablets/wk	4.0 (6.7)	4.0 (7.7)	3.7 (6.9)	.86

*Treatment comparison *P* values for continuous variables are from an analysis of variance with effects fitted for treatment and background therapy. Treatment comparison *P* values for categorical variables are based on a Cochran Mantel-Haenszel test, stratified by background therapy.
†Without pathologic Q waves.

Source: Permission obtained from the publisher to use Table 1 from Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial by Chaitman BR, Pepine CJ, Parker JO, et al. (2004).[8]

Figure 4: Summary of Baseline Characteristics for the TERISA Study

	Ranolazine (n = 462)	Placebo (n = 465)
Age, yrs	63.2 ± 8.5	64.2 ± 8.4
Men	283 (61.3%)	286 (61.5%)
White	456 (98.7%)	462 (99.4%)
Hypertension	438 (95.0%)	445 (95.9%)
Dyslipidemia	350 (79.4%)	355 (80.3%)
Current smoking	71 (15.4%)	77 (16.6%)
Prior myocardial infarction	346 (75.4%)	336 (72.7%)
Prior angioplasty	197 (42.7%)	180 (38.8%)
Prior bypass graft surgery	84 (18.2%)	88 (18.9%)
Duration of diabetes, yrs	7.2 ± 6.7	7.7 ± 7.0
HbA1c, %	7.3 ± 1.5	7.3 ± 1.5
Antidiabetic medication	431 (93.3%)	431 (92.7%)
Insulin	81 (17.5%)	96 (20.6%)
Antianginal medications		
On 1	259 (56.1%)	259 (55.7%)
On 2	203 (43.9%)	206 (44.3%)
Beta-blockers	418 (90.5%)	418 (89.9%)
Calcium-channel blockers	124 (26.8%)	143 (30.8%)
Long-acting nitrates	161 (34.8%)	151 (32.5%)
Statins	381 (82.5%)	383 (82.4%)
Antiplatelet agents	415 (89.8%)	402 (86.5%)
ACE-I/ARBs	407 (88.1%)	407 (87.5%)
Baseline heart rate (beats/min)	69.0 ± 8.0	70.0 ± 9.8
Baseline systolic blood pressure (mm Hg)	131.0 ± 11.0	131.0 ± 11.3
Baseline diastolic blood pressure (mm Hg)	79.0 ± 7.7	79.0 ± 7.8

Values are n mean ± SD or (%).
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Note: 98% of patients were White.[15]

Source: Permission obtained from the publisher to use Table 1 from Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) by Kosiborod M, Arnold SV, Spertus JA, et al. (2013).[12]

Interventions

For the ERICA study, patients were required to have started background therapy with amlodipine 10 mg per day at least 2 weeks prior to the start of the qualification period. Sublingual nitroglycerin was allowed, as needed, as was long-acting nitrates (provided they had been administered at a constant dose for at least 2 weeks prior to study entry). All other antianginal medications were prohibited and had to be stopped at least 4 weeks before initiation of the study drug. After the qualifying period, patients were randomized 1:1 to ranolazine 1,000 mg ER twice daily or placebo. Those randomized to receive ranolazine received a 500 mg ER tablet twice daily for the first week, after which doses were increased to 1,000 mg ER twice daily for 6 weeks.

In the CARISA study patients were randomized to 12 weeks of placebo, ranolazine 750 mg ER twice daily, or ranolazine 1,000 mg ER twice daily (1:1:1) in addition to antianginal therapy of atenolol 50 mg daily, diltiazem 180 mg CD daily, or amlodipine 5 mg daily. Patients were required to stop any other antianginal treatments at least 5 days before qualifying exercise tests. The selection of background therapy was at the discretion of the study investigator and doses were fixed during the trial. Other allowed medications included Aspirin, stable doses of angiotensin-converting enzyme inhibitors or diuretics, and sublingual nitroglycerin.[18]

In the TERISA study, patients who met the inclusion criteria were randomized to ranolazine 1,000 mg twice daily or matching placebo, as an add-on to background therapy that included 1 or 2 antianginal medications (i.e., beta-blocker, calcium-channel blocker, or long-acting nitrate). Patients in the ranolazine group received a 500 mg dose twice daily for the first week and then 1,000 mg twice daily if tolerated for the remaining 7 weeks. The maximum dosage of ranolazine in patients treated with verapamil or diltiazem CD was 500 mg twice daily. The dose of background therapies could not be increased during the trial but could be decreased if there were safety concerns. Patients who were receiving more than 2 antianginal drugs prior to enrolment were required to stop the additional treatments at least 2 weeks before the start of the run-in period. Patients were also prohibited from receiving trimetazidine, ivabradine, or nicorandil during the trial, and were required to stop these medications prior to the run-in. Other prohibited medications include strong inhibitors of CYP3A, CYP3A or P-glycoprotein inducers, CYP3A substrates with a narrow therapeutic range, simvastatin (if unable to switch statins or reduce dose to 20 mg daily), class I and III antiarrhythmics, and metformin (if unable to reduce the dose to 1,000 mg or lower per day).

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 7. These end points are further summarized subsequently. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 7: Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	ERICA	CARISA	TERISA[a]
Primary	Weekly average frequency of self-reported angina episodes over 6-week treatment period	Change from baseline in exercise duration at trough drug levels (12 hours after dose)	Average weekly frequency of self-reported angina episodes over last 6 weeks of treatment
Secondary	• Weekly average frequency of self-reported nitroglycerin use over 6-week treatment period • Change from baseline to week 6 in each of the 5 SAQ dimensions (angina frequency, physical limitation, angina stability, disease perception, treatment satisfaction)	• Change from baseline in exercise duration at peak drug levels (4 hours after dose) • Time to onset of angina at trough and peak drug levels • Time to 1 mm ST-segment depression at trough and peak drug levels • Angina frequency per week over 12-week treatment period • Nitroglycerin consumption per week over 12-week treatment period	• Average weekly sublingual nitroglycerin use over last 6 weeks of treatment • Angina-free days over last 6 weeks • Proportion with at least a 50% reduction in average weekly angina frequency • Change from baseline in SF-36 MCS • Change from baseline in SF-36 PCS

MCS = mental component score; PCS = physical component score; SAQ = Seattle Angina Questionnaire; SF-36 = Short Form 36 Health Survey.

[a] The TERISA study collected data on dyspnea symptoms and SAQ domains as exploratory outcomes but results for these end points were not reported by Kosiborod et al.[12]

Source: Stone et al. (2006)[7], Chaitman et al. (2004),[8] Kosiborod et al. (2013).[12]

In the CARISA study, patients underwent a modified Bruce protocol treadmill exercise test to measure exercise capacity. A central blinded ECG laboratory read all resting and exercise ECGs, and all exercise ECGs were analyzed using customized software. Post-treatment exercise tests were performed at trough drug levels (12 hours after dose) at 2, 6, and 12 weeks after randomization, and at peak drug levels (4 hours after dose) at weeks 2 and 12.

The ERICA study assessed angina symptoms and quality of life using the SAQ. The 19-item self-reported instrument includes 5 dimensions: angina frequency, physical limitation, angina stability, disease perception/quality of life, and treatment satisfaction, each assessed on an ordinal scale (range: 1 to 5 or 6), with lower numbers indicating lower level of functioning. Scores are summed across items within each of the 5 scales and transformed to a score between 0 and 100 by subtracting the lowest possible score for each respective scale, dividing this value by the range of the scale, and multiplying by 100. Higher scores indicate better health status. There is no summary score for the SAQ as each scale measures a unique dimension of coronary artery disease. Validity and test-retest reliability were determined to be acceptable, and the SAQ was sensitive to detect change over time in patients with coronary artery disease (see Appendix 4). The MID was estimated to be a change of 10 points in the SAQ score in patients with stable angina.[28]

The SF-36 is a general health status questionnaire that has been used in clinical trials in many disease areas to assess the impact of disease on health-related quality of life.[29] It is a self-reported patient questionnaire consisting of 8 health domains: physical functioning, mental health, social functioning, vitality, role physical, role emotional, general health, and bodily pain.[30] For each of the 8 categories, a subscale score is calculated. The SF-36 also provides 2 component summaries for the PCS and MCS, which are derived from aggregating the 8 domains according to a scoring algorithm. The PCS and MCS range from 0 to 100, with higher scores indicating better health status. The SF-36 is a validated

instrument that has demonstrated acceptable test-retest reliability in populations with angina but compared with the SAQ, the SF-36 appeared to be less sensitive to changes in health-related quality of life for populations with angina (see Appendix 4). The MID for either the PCS or MCS has been reported to be between 2.5 points and 5 points.[31-33] No MID was identified in populations with stable angina.

Statistical Analysis

ERICA

In the ERICA study the average weekly rate of angina episodes or nitroglycerin use were analyzed using a Cochran-Mantel-Haenszel mean score test using rank scores, stratified by pooled site data within geographic areas (North America; Bulgaria and Romania; Georgia; Moscow; St. Petersburg; other Russian cities). The authors state that the data were analyzed "using scores proportional to the sample ranks to reduce the influence of outlying data." Mean, median, and 25th and 75th quartile data were calculated for the post-treatment period. It is unclear which analysis was pre-planned as the primary outcome measure. Before unblinding, several extreme outliers were observed (i.e., 47 to 160 angina episodes per week) and, as a result, the analysis was amended to exclude the top and bottom 2% of values and to present the results as the trimmed mean. The assessment of angina frequency and nitroglycerin use were based on the last 6 weeks of the treatment period to allow for the study drug to reach steady-state levels at the maximum dose. All SAQ data were analyzed using an analysis of covariance (ANCOVA) model that included treatment, pooled centre, and baseline score covariates (Table 8).

Type I error rate was controlled through a statistical testing hierarchy, where testing of secondary outcomes was to proceed only if the prior outcome was statistically significant ($P < 0.05$). Outcomes were tested in the order shown in Table 8. A pre-planned subgroup by gender was conducted. Stone et al.[7] did not report power calculations or how missing data were handled. The FDA Statistical Review states the study had a 95% power to detect a 1.0 reduction in the weekly angina frequency relative to placebo with 225 patients enrolled per group, assuming an exponential distribution and placebo angina frequency of 3.3 episodes per week (2-sided alpha of 0.05).[18] The FDA Statistical Review also stated that angina frequency and nitroglycerin use were calculated using the partial diary data available for patients who withdrew early.[18]

CARISA

The change from baseline in exercise duration at trough was analyzed using an analysis of variance model adjusted for pooled site, background therapy, and baseline exercise duration. The last observation carried forward (LOCF) method was used for patients with missing data after randomization. Similar methods were used to estimate exercise duration at peak and for time to angina onset or ECG ischemia. An adjusted non-parametric ranked analysis of variance model was used to analyze angina frequency and nitroglycerin use during the treatment period. It is unclear how missing data were handled (Table 8).

The CARISA study had a 90% power to detect a 30-second difference in exercise duration (at trough drug levels) between each dose of ranolazine and placebo, assuming normally distributed data with an SD of 80 seconds. A sample size of 577 patients was calculated assuming a 20% dropout rate. An interim analysis was conducted to re-assess the sample size, when half on the patients had completed 12 weeks of follow-up. Based on an SD from this blinded analysis of aggregate data, the sample size was increased to 810 patients. A conservative sensitivity analysis was reported that estimated the increase in exercise

duration for patients with missing data in the placebo group and the decrease in duration among those with missing data in the ranolazine group that would be required for the results to be non-significant. (It is unclear if this was post hoc or pre-planned.) No information on planned subgroup analyses was reported by Chaitman et al.[8]

A 2-stage step-down procedure was used to control the type I error rate for the primary outcome in the CARISA study. The change from baseline in exercise duration at trough drug levels was tested first for the pooled ranolazine groups versus placebo. If significance was achieved, then each ranolazine dose was tested individually using a 2-sided alpha of 0.05 (the order of dose group testing was not reported). The other outcomes in the CARISA study were not controlled for the type I error rate.

TERISA

The average number of self-reported angina episodes per week over the last 6 weeks of the treatment period was estimated using a generalized linear model with a negative binomial distribution and log person-time offset adjusted for log baseline angina rate and baseline stratification factors: average number of weekly angina episodes (1 to < 3; or 3 to ≤ 28), number of background antianginal drugs (1 or 2), and geographic region (Russia, Ukraine, and Belarus versus other countries) (Table 8). The primary efficacy analysis was based on the last 42 days of the up-to-56-day treatment period for each patient in the full analysis set (FAS) population and excluded data after discontinuing the study drug. Days with missing diary data were excluded from the analysis. The same model was used to analyze nitroglycerin consumption. Sensitivity analyses for the anginal frequency outcome were conducted for the FAS population including data from days after drug discontinuation. Other sensitivity analyses were conducted based on a modified intention-to-treat population that did not require patients to be treated with at least 14 days of the study drug.

The proportion of patients with at least a 50% reduction in average weekly angina frequency was analyzed using the Cochran-Mantel-Haenszel test stratified by the number of concomitant anginal therapies, baseline angina frequency, and geographic region. Continuous outcomes were analyzed using an ANCOVA model adjusted for baseline values and stratification factors (number of concomitant anginal therapies, baseline angina frequency, geographic region).

With a planned sample size of 900 patients, the TERISA study had a 90% power to detect a 20% relative reduction in weekly angina frequency, assuming an average of 2.0 weekly angina events in the placebo group (2-sided alpha of 0.05).

There was a pre-planned subgroup analysis according to sex. The type I error rate for primary and secondary outcomes was controlled using a closed testing procedure with a Hochberg adjustment. If any step in the ordered testing procedure did not achieve statistical significance, then testing would proceed but significance would not be claimed.

Table 8: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analyses
ERICA			
Weekly average frequency of self-reported angina episodes over 6-week treatment period	Cochran-Mantel-Haenszel mean score test using rank scores	Stratified by geographic area (North America; Bulgaria and Romania; Georgia; Moscow; St. Petersburg; other Russian cities)	Adjusted for baseline frequency (unclear if post hoc or pre-planned)
Weekly average frequency of self-reported nitroglycerin use over 6-week treatment period			
Change from baseline to week 6 in each of the 5 SAQ dimensions (angina frequency, physical limitation, angina stability, disease perception, treatment satisfaction)	ANCOVA	Pooled centre and baseline score	NR
CARISA			
Change from baseline in exercise duration at trough drug levels (12 hours after dose)	ANOVA (LOCF)	Pooled site, background therapy, baseline exercise treadmill time	Threshold analysis (unclear if post hoc or pre-planned)
Change from baseline in exercise duration at peak drug levels (4 hours after dose)	ANOVA (LOCF)	Pooled site, background therapy, baseline exercise treadmill time	NR
Time to onset of angina or ECG ischemia at trough and peak drug levels	ANOVA (LOCF)	Pooled site, background therapy, baseline exercise treadmill time	NR
Angina frequency per week of treatment period	Non-parametric ranked ANOVA	Pooled site, background therapy, baseline covariate	NR
Nitroglycerin use per week of treatment period			
TERISA			
Average number of self-reported angina episodes per week over last 6 weeks of treatment period	Generalized linear model with a negative binomial distribution and log person-time offset	Log baseline angina rate, baseline stratification factors: average number of weekly angina episodes (1 to < 3; or 3 to 28), number of background antianginal drugs (1 or 2), and geographic region (Russia, Ukraine, and Belarus versus other countries)	FAS (minimum 14 days study drug) including data after discontinuing study drug mITT (all patients who took at least 1 dose of study drug)
Average weekly frequency of sublingual nitroglycerin use	Same as above	Same as above	NR
Number of angina-free days	ANCOVA	Baseline value, number of concomitant anginal therapies, baseline angina frequency, geographic region	NR
Proportion of patients with ≥ 50% reduction in average weekly angina frequency	Cochran-Mantel-Haenszel test	Stratified by number of concomitant anginal therapies, baseline angina frequency, and geographic region	NR
Change from baseline in SF-36 MCS and PCS	ANCOVA	Baseline value, number of concomitant anginal therapies,	NR

End point	Statistical model	Adjustment factors	Sensitivity analyses
		baseline angina frequency, and geographic region	

ANCOVA = analysis of covariance; ANOVA = analysis of variance; ECG = electrocardiogram; FAS = full analysis set; LOCF = last observation carried forward; MCS = mental component score; mITT = modified intention to treat; NR = not reported; PCS = physical component score; SAQ = Seattle Angina Questionnaire; SF-36 = Short Form (36) Health Survey.

Source: Stone et al. (2006)[7], Chaitman et al. (2004),[8] Kosiborod et al. (2013),[12] FDA Medical Review.[15]

Analysis Populations

Efficacy data in the ERICA study were analyzed based on the FAS that included all patients who received at least 1 dose of study medication and submitted any angina diary data during the 6-week treatment phase. The ERICA study did not define the safety population.

In the CARISA study, efficacy analyses were based on the FAS which included randomized patients who received at least 1 dose of study drug and had at least 1 post-baseline exercise test. Safety data were based on all randomized patients who received at least 1 dose of study drug.

In the TERISA study, efficacy analyses were based on the FAS that included all patients who received at least 14 days of study drug and had at least 1 post-baseline efficacy assessment for the primary outcome and did not have any major eligibility violations. The safety population included all patients who received at least 1 dose of the study drug, analyzed according to the treatment received.

Results

Patient Disposition

In the ERICA study, 10% of the 627 patients who entered the 2-week qualifying phase were excluded as they no longer met the inclusion criteria (7%) or had fewer than 3 angina episodes during qualifying phase (3%). Of the 565 patients randomized, 13 withdrew (2% per group) due to adverse events, withdrawal of consent or death (Table 9).

Few details were available on the disposition of patients in the CARISA study. In this trial, 823 patients were randomized, and 9%, 9%, and 13% withdrew in the placebo, ranolazine 750 mg, and ranolazine 1,000 mg groups, respectively (Table 9). The reasons for withdrawal were not reported by Chaitman et al.[8] but the FDA Statistical Review stated that 5% of patients in the placebo group and 7% to 9% of patients in the ranolazine groups withdrew due to adverse events.[18]

The TERISA study was the only trial to report the number of patients screened. In this trial, 96% of the 1,185 patients screened entered the qualifying phase. During the 4-week qualification period, 17% of patients were excluded, leaving 949 patients randomized to placebo or ranolazine. Eleven patients per group (2%) discontinued the study within the first 2 weeks and were excluded from efficacy analysis. Reasons for withdrawal were not reported (Table 9).

Table 9: Patient Disposition

	ERICA		CARISA			TERISA	
	Placebo	Ranolazine 1,000 mg	Placebo	Ranolazine 750 mg	Ranolazine 1,000 mg	Placebo	Ranolazine 1,000 mg
Screened, N	NR		NR			1,185	
Entered qualifying phase, N	627[a]		NR			1,142	
Randomized, N (%)	565 (90)		823			949 (83)	
	284[b]	281	269	279	275	476	473
Discontinued from study, N (%)	6 (2)	7 (2)	25 (9)	25 (9)	36 (13)	11 (2)	11 (2)
Reason for discontinuation, N (%)			NR	NR	NR	NR	NR
Adverse events	5 (2)	3 (1)	13 (5)[c]	20 (7)[c]	24 (9)[c]		
Death	1 (< 1)	1 (< 1)					
Withdrew consent	0	3 (1)					
Full analysis set, N (%)	281 (99)	277 (99)	258 (96)	272 (97)	261 (95)	465 (98)	462 (98)
Safety, N (%)	283 (99.6)[c]	281 (100)[c]	269 (100)	279 (100)	275 (100)	474 (99.6)	470 (99.4)

NR = not reported.

[a] Total of 62 patients were excluded: 42 no longer met inclusion criteria and 20 had fewer than 3 angina episodes per week during the qualifying phase.

[b] One patient withdrew on the randomization day prior to receiving any medication.

[c] Data from FDA.

Source: Stone et al. (2006)[7], Chaitman et al. (2004),[8] Kosiborod et al. (2013),[12] FDA Statistical Review.[18]

Exposure to Study Treatments

None of the published reports provided information about the duration of exposure or adherence to the study drugs.

In the ERICA study, the use of concomitant medications was generally similar between the placebo and ranolazine groups: long-acting nitrates (43% and 46%), Aspirin (86% and 87%), angiotensin-converting enzyme inhibitors (51% and 54%), statins (33% and 39%), diuretics (27% and 32%), and antidiabetic drugs (10% and 12%), respectively. Among patients receiving long-acting nitrates, the mean daily dose of isosorbide mononitrate was 45.4 mg per day and was reported to be similar between groups.

The CARISA study reported that 43% of patients were taking atenolol, 31% were receiving amlodipine, and 26% were receiving diltiazem CD as background therapy, and the proportion of patients on each drug were similar between groups (Figure 3). No information was provided on other concomitant medications.

In the TERISA study 56% of patients were receiving 1 background antianginal drug and 44% were receiving 2 drugs. These included beta-blockers (90%), calcium-channel blockers (29%), and long-acting nitrates (34%). Overall, 82% were taking statins, 88% were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 88% were on antiplatelet drugs (Figure 4), with a similar frequency between groups. The authors report that target doses of ranolazine were achieved by more than 95% of patients.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Angina Symptoms

Frequency of Angina Episodes

All 3 studies reported data on the frequency of angina episodes, which was the primary outcome in the ERICA and TERISA studies, and secondary outcome in the CARISA study.

In the ERICA study, the baseline trimmed mean frequency of angina attacks was 5.7 events per week (SE = 0.26) in the placebo group and 5.6 events per week (SE = 0.21) in the ranolazine group. During the 6-week treatment period, the weekly trimmed mean frequency of angina attacks was 3.3 (SE = 0.22) events per week in the placebo group, compared with 2.9 (SE = 0.19) events per week in the ranolazine group (P = 0.028) (Figure 5). The FDA reported that a sensitivity analysis, which adjusted for baseline angina frequency, yielded a P value of 0.005, but no further details were provided.

In the TERISA study, the LS mean weekly frequency of angina episodes was 6.8 events (95% CI, 6.4 to 7.2) for placebo and 6.6 (95% CI, 6.3 to 7.0) for the ranolazine group at baseline, and on treatment it was 4.3 (95% CI, 4.0 to 4.5) and 3.8 (95% CI, 3.6 to 4.1) for placebo and ranolazine, respectively (P = 0.008) (Figure 6). No results were reported for the planned sensitivity analyses.

The CARISA study reported that patients, at baseline, experienced on average 4.6 angina episodes per week (SE = 0.36) and 4.4 episodes per week (SE = 0.34) in the placebo and ranolazine 1,000 mg groups, respectively (Figure 7). During the treatment period, the mean number of angina episodes per week was 3.3 (SE = 0.30) and 2.1 (SE = 0.24) in the placebo and ranolazine 1,000 mg groups, respectively (between-group difference P < 0.001), and thus is considered supportive evidence as it was not adjusted for multiple comparisons.

Frequency of Angina Episodes: Subgroup Analysis

Pre-planned subgroup analyses of angina frequency based on sex (women: n = 155; men: n = 403) were reported for the ERICA study. During treatment, the trimmed mean weekly number of angina attacks in the placebo and ranolazine groups, respectively, was 3.5 (SE = 0.45) and 2.9 (SE = 0.41) in women (P = 0.33), and 3.2 (SE = 0.24) and 2.9 (SE = 0.23) in men (P = 0.026) (baseline data not reported). Additional data from the FDA showing the mean difference from placebo in weekly angina frequency for women and men are provided in Appendix 3, Figure 10. The point estimates in both subgroups favour ranolazine versus placebo, but with a 95% CI that includes the null.[15] Stone et al.[7] stated that the study was not powered to test treatment effects within subgroups, nor between subgroups, but the treatment by subgroup interaction did not provide evidence of differences.

The authors of the TERISA study reported that the treatment effects on angina frequency in men (n = 569) and women (n = 358) were similar (interaction P value = 0.46). The incidence density ratio for men and women favoured ranolazine over placebo, but with a 95% CI that excluded the null for women only (Appendix 3, Figure 11).

Nitroglycerin Consumption

Nitroglycerin use was reported as a secondary outcome in the 3 studies. In the ERICA study, there were imbalances between groups in nitroglycerin use at baseline, and data were highly skewed. The baseline trimmed mean consumption of nitroglycerin was 5.0 (SE = 0.33) and 4.4 (SE = 0.26) doses per week in the placebo and ranolazine groups, respectively, with 2.7 (SE = 0.22) and 2.0 (SE = 0.20) trimmed mean doses per week over the 6-week treatment period (P = 0.014) (Figure 5). Stone et al.[7] stated that a non-parametric analysis that adjusted for baseline nitroglycerin use also showed statistically significant differences between groups (P = 0.033), but no details were provided and it is unclear if the analysis was pre-planned or post hoc.

In the TERISA study the average weekly nitroglycerin consumption was 4.5 doses (95% CI, 4.1 to 5.0) and 4.1 doses (95% CI, 3.7 to 4.6) at baseline in the placebo and ranolazine groups, respectively. On treatment, the mean weekly nitroglycerin use was 2.1 doses (95% CI, 1.9 to 2.3) and 1.7 doses (95% CI, 1.6 to 1.9) for placebo and ranolazine (P = 0.003) (Figure 6).

In the CARISA study, the mean nitroglycerin consumption changed from 4.1 (SE = 0.43) and 3.7 (SE = 0.45) at baseline to 3.1 (SE = 0.38) and 1.8 (SE = 0.28) in the placebo and ranolazine 1,000 mg groups (P < 0.001), but the analysis did not control for type I error rate and the results should be viewed as supportive evidence only (Figure 7). The end-of-treatment analysis was missing data from 2.3% to 6.5% of patients in the placebo and ranolazine groups, respectively.

Other Angina Outcomes

In the placebo group of the TERISA study, the percentage of angina-free days was 64% (95% CI, 61% to 67%), and 67% (95% CI, 65% to 70%) for ranolazine (P = 0.068) (Figure 6). The percentage of patients with at least a 50% reduction in angina episodes was 42% (95% CI, 38% to 46%) for placebo and 47% (95% C, 43% to 51%) for ranolazine (P = 0.034). Based on the planned statistical testing procedures, these 2 outcomes did not achieve statistical significance.

Figure 5: Angina Frequency and Nitroglycerin Consumption in the ERICA Study — Full Analysis Set

	Placebo (n = 281)	Ranolazine (n = 277)	p Value*
Weekly angina frequency			
Trimmed mean ± SE	3.31 ± 0.22	2.88 ± 0.19	0.028
Arithmetic mean ± SE	4.30 ± 0.64	3.29 ± 0.26	
25th percentile	1.47	1.24	
Median	2.43	2.18	
75th percentile	4.17	3.66	
Weekly nitroglycerin consumption			
Trimmed mean ± SE	2.68 ± 0.22	2.03 ± 0.20	0.014
Arithmetic mean ± SE	3.57 ± 0.54	2.72 ± 0.38	
25th percentile	0.50	0.47	
Median	1.67	1.34	
75th percentile	4.00	2.48	

*Cochran-Mantel-Haenszel mean scores test using rank scores, stratifying by pooled site.
SE = standard error.

Source: Permission obtained from the publisher to use Table 3 from Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial by Stone PH, Gratsiansky NA, Blokhin A, et al. (2006).[7]

Figure 6: Clinical Outcomes in the TERISA Study — Full Analysis Set

	Ranolazine	Placebo	p Value
Efficacy endpoints*	n = 462	n = 465	
Primary endpoint			
Angina frequency, baseline, n/week	6.6 (6.3–7.0)	6.8 (6.4–7.2)	0.54
Angina frequency, on treatment, n/week	3.8 (3.6–4.1)	4.3 (4.0–4.5)	0.008
Secondary endpoints			
SL NTG use, baseline, n/week	4.1 (3.7–4.6)	4.5 (4.1–5.0)	0.27
SL NTG use, on treatment, n/week	1.7 (1.6–1.9)	2.1 (1.9–2.3)	0.003
Percentage of angina-free days, %	67 (65–70)	64 (61–67)	0.068
Subjects with ≥50% reduction in angina episodes, %	47 (43–51)	42 (38–46)	0.034
SF-36 mental component score, change from baseline	1.0 (0.2–1.8)	1.1 (0.3–1.9)	0.77
SF-36 physical component score, change from baseline	2.9 (2.3–3.5)	1.9 (1.3–2.5)	0.005
PGIC scale score	4.0 (3.8–4.2)	3.9 (3.7–4.1)	0.41
Diary compliance, %	98 (95–98)	98 (95–98)	0.46
Safety endpoints*	n = 470	n = 474	
Serious adverse events			
Serious adverse event	16 (3.4)	20 (4.2)	0.51
Death	3 (0.6)	2 (0.4)	0.69
Nonfatal myocardial infarction	1 (0.2)	3 (0.6)	0.62
Stroke/transient ischemic attack	1 (0.2)	4 (0.8)	0.37
Unstable angina or coronary revascularization	6 (1.3)	7 (1.5)	0.79
Notable nonserious adverse events			
Dizziness	17 (3.6)	6 (1.3)	0.019
Nausea	17 (3.6)	2 (0.4)	<0.001
Headache	7 (1.5)	9 (1.9)	0.63
Constipation	8 (1.7)	2 (0.4)	0.063
Hypoglycemia	3 (0.6)	0 (0.0)	0.12
Any adverse event	126 (26.8)	105 (22.2)	0.096

Values are least-squares mean (95% confidence interval), n (%), or median (interquartile range) (arithmetic means for angina frequency and SL NTG use are presented in Online Table 5). *Analytic sample for the safety dataset includes patients who took any dose of the study drug whereas analytic sample for the efficacy dataset includes patients who completed 14 days of the study drug.

PGIC = Patient's Global Impression of Change; SF-36 = Medical Outcomes Short Form-36; SL NTG = sublingual nitroglycerin.

Source: Permission obtained from the publisher to use Table 2 from Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) by Kosiborod M, Arnold SV, Spertus JA, et al. (2013).[12]

Figure 7: Angina Frequency and Nitroglycerin Consumption From the CARISA Study — Full Analysis Set

Variable	Placebo		Ranolazine ER 750 mg b.i.d.		Ranolazine ER 1000 mg b.i.d.	
	N	Reported Frequency	N	Reported Frequency	N	Reported Frequency
Angina Attacks/Week						
Mean (SE) at Baseline	258	4.63 (0.36)	272	4.37 (0.33)	261	4.44 (0.34)
Mean (SE) during Double-Blind Treatment	258	3.31 (0.30)	272	2.47 (0.23)	261	2.13 (0.24)
p-Value[a]				0.006		< 0.001
Nitroglycerin Consumption/Week						
Mean (SE) at Baseline	247	4.08 (0.43)	258	4.00 (0.49)	244	3.72 (0.45)
Mean (SE) during Double-Blind Treatment	252	3.14 (0.38)	262	2.11 (0.27)	244	1.76 (0.28)
p-Value[a]				0.016		< 0.001

b.i.d. = twice daily; ER = extended release; SE = standard error.

[a] Ranolazine versus placebo obtained from an analysis of variance model using ranked scores data adjusted for treatment, baseline covariate, pooled site, and background therapy.

Source: Reproduced from FDA Medical Review.[15]

Functional Status

The change from baseline in exercise duration measured at trough drug levels (12 hours after dose) was the primary outcome in the CARISA study. At 12 weeks 91% and 87% had complete data and 5% and 8% patients had data imputed (using LOCF) in the placebo and ranolazine groups, respectively. As the comparison of the pooled ranolazine groups versus placebo was statistically significant (P = 0.01) testing of the individual dosage groups was conducted, as per the statistical analysis plan.

For the placebo and ranolazine 1,000 mg groups, the baseline exercise duration at trough drug levels was 418.3 seconds (SE = 6.3) and 414.7 seconds (SE = 6.3), respectively. The LS mean change from baseline was 91.7 seconds (SE = 8.3) in the placebo group and 115.8 seconds (SE = 8.2) in the ranolazine 1,000 mg group, with an LS mean difference versus placebo of 24.0 seconds (SE = 11.0; P = 0.03) (Figure 8). The between-group difference in exercise duration was similar at peak drug levels (LS mean difference = 26.1 seconds (SE = 10.8; P = 0.02), which was not controlled for the type I error rate and should be viewed as supportive evidence for the effect of ranolazine compared to placebo in the overall population.

A conservative sensitivity analysis supported the results of the primary analysis. The study would have failed to show efficacy if the 11 missing patients in the placebo group had increased their exercise duration by 92 seconds and if the 21 patients missing from the ranolazine group had a decrease from baseline of 40 seconds or more. Subgroup data by sex are reported in Appendix 3, Figure 12. The LS mean change from baseline in exercise duration (at trough) was 8.6 seconds (95% CI, −37.4 to 54.6) in women and 26.1 seconds (95% CI, 1.6 to 50.6) in men, for the ranolazine 1,000 mg group versus placebo (n = 51 women; n = 210 men).[15] No treatment by subgroup interaction P value was reported.

The CARISA study reported an LS mean difference in the time to angina onset of 26.0 seconds (SE = 12.2) at trough drug levels, and 37.9 seconds (SE = 12.6) at peak levels for ranolazine 1,000 mg versus placebo (both P values < 0.05) (Figure 8). The LS mean difference in the time to ECG ischemia for ranolazine 1,000 mg versus placebo was 21.1 seconds (SE = 12.4; P = 0.09) and 34.5 seconds (SE = 11.9; P = 0.004) at trough and peak levels, respectively. The type I error rate was not controlled for any of these outcomes and thus these data should be viewed as supportive evidence.

Figure 8: Treadmill Exercise Results in the CARISA Study — Full Analysis Set

Variables	Placebo (n = 258)	Ranolazine, mg Twice Daily 750 (n = 272)	Ranolazine, mg Twice Daily 1000 (n = 261)
Trough Ranolazine Levels			
Background antianginal drug once daily, No. (%)			
Atenolol, 50 mg	115 (44.6)	116 (42.7)	112 (42.9)
Amlodipine, 5 mg	77 (29.8)	86 (31.6)	86 (33.0)
Diltiazem, 180 mg	66 (25.6)	70 (25.7)	63 (24.1)
Exercise duration, mean (SE), s			
Baseline	418.3 (6.3)	416.4 (6.2)	414.7 (6.3)
Change from baseline	91.7 (8.3)	115.4 (8.0)	115.8 (8.2)
Difference from placebo		23.7 (10.9)	24.0 (11.0)
P value vs placebo		.03	.03
Time to onset of angina, mean (SE), s			
Baseline	326.7 (6.4)	324.7 (6.5)	326.7 (6.7)
Change from baseline	114.3 (9.2)	144.0 (8.9)	140.3 (9.1)
Difference from placebo		29.7 (12.1)	26.0 (12.2)
P value vs placebo		.01	.03
Time to ECG ischemia, mean (SE), s			
Baseline	298.9 (8.9)	310.0 (9.1)	301.6 (9.2)
Change from baseline	125.1 (9.2)	145.1 (9.0)	146.2 (9.3)
Mean difference from placebo		19.9 (12.2)	21.1 (12.4)
P value vs placebo		.10	.09
Peak Ranolazine Levels			
	(n = 256)	(n = 270)	(n = 255)
Exercise duration, mean (SE), s			
Baseline	466.5 (8.2)	464.8 (8.1)	470.4 (7.9)
Change from baseline	65.4 (8.1)	99.4 (7.8)	91.5 (8.1)
Mean difference from placebo		34 (10.7)	26.1 (10.8)
P value vs placebo		.001	.02
Time to onset of angina, mean (SE), s			
Baseline	389.2 (8.3)	387.8 (8.5)	383.6 (8.2)
Change from baseline	88.9 (9.4)	126.9 (9.1)	126.8 (9.4)
Mean difference from placebo		38.0 (12.4)	37.9 (12.6)
P value vs placebo		.002	.003
Time to ECG ischemia, mean (SE), s			
Baseline	404.3 (9.5)	410.5 (9.4)	400.4 (10.3)
Change from baseline	59.2 (9.0)	100.0 (8.7)	93.8 (8.9)
Mean difference from placebo		40.8 (11.8)	34.5 (11.9)
P value vs placebo		<.001	.004

ECG = electrocardiogram; SE = standard error.

Note: All values (except baselines, which are mean SE), are LS means (SEs) based on an analysis of variance model, including effects for baseline, pooled site, background therapy, and treatment. There were no significant differences between treatment groups in any baseline exercise time. Times to angina and to ECG ischemia substitute exercise duration when angina or ECG ischemia did not occur. Changes from baseline are to last observation carried forward.

Source: Permission obtained from publisher to use Table 2 from Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial by Chaitman BR, Pepine CJ, Parker JO, et al. (2004).[8]

Health-Related Quality of Life

The ERICA study analyzed the change from baseline in the SAQ domain scores as secondary outcomes. At baseline, the mean angina frequency score was 40.0 (SD = 14.9) in the placebo group and 40.6 (SD = 13.2) in the ranolazine group. The mean change from baseline was 18.5 (SD = 18.8) in the placebo group, compared with 22.5 (SD = 19.0) in the ranolazine group (P = 0.008).[7] The FDA reported a statistically significant LS mean difference of 4.1 points (SE = 1.55) for ranolazine versus placebo based on an ANCOVA model that included treatment, baseline score, and pooled site as covariates (Appendix 3, Figure 13).[18] No statistically significant differences were detected between groups in the change from baseline in physical limitation, anginal stability, disease perception, or treatment satisfaction domains of the SAQ (no details reported by Stone et al.[7]).

The TERISA study reported an LS mean change from baseline in the SF-36 PCS of 1.9 points (95% CI, 1.3 to 2.5) in the placebo group and 2.9 points (95% CI, 2.3 to 3.5) in the ranolazine group (P = 0.005). However, statistical significance could not be claimed according to the statistical testing procedure. The LS mean change from baseline in the SF-36 MCS was 1.1 points (95% CI, 0.3 to 1.9) in the placebo group and 1.0 points (95% CI, 0.2 to 1.8) in the ranolazine group (between-group difference P = 0.77) (Figure 6).

Cardiovascular Events

None of the 3 trials evaluated cardiovascular events as an efficacy outcome. Cardiovascular adverse events are discussed in the Harms section of this report.

Mortality

None of the 3 trials evaluated mortality as an efficacy outcome. Deaths during the trials are reported in the Harms section of this review.

Harms

Only those harms identified in the review protocol are reported below. See Figure 6 and Table 10 for detailed harms data.

Adverse Events

Among those enrolled in the CARISA, TERISA, and ERICA trials, 22% to 35% of those who received placebo and 27% to 40% of those who received ranolazine 1,000 mg experienced adverse events during the 6- to 12-week studies (Figure 6 and Table 10).

Nausea, dizziness, and constipation occurred more frequently among those who received ranolazine compared with placebo in all 3 studies.

Serious Adverse Events

The overall frequency of serious adverse events was not reported in the CARISA study.

In the ERICA study, 6 patients in the placebo group (2.1%) and 5 in the ranolazine group (1.8%) reported serious adverse events. Myocardial infarction was reported in 0.7% and 0.4% of patients in the placebo and ranolazine groups, respectively. No patients in either group reported a stroke or unstable angina. Cardiac adverse events were reported by 7.8% of those in the placebo group and 5.7% of patients in the ranolazine group. (It is unclear what proportion were serious adverse events.)

The frequency of serious adverse events was similar in the placebo (4.2%) and ranolazine groups (3.4%) in the TERISA study (Figure 6). In the placebo and ranolazine groups, respectively, 0.8% and 0.2% experienced a stroke or TIA, 0.6% and 0.2% reported a non-fatal myocardial infarction, and 1.5% and 1.3% reported unstable angina or coronary revascularization.

An integrated safety review of phase II and III studies conducted by the FDA reported serious adverse events in 5.4% of patients who received ranolazine (56 of 1,030 patients) compared with 3.0% who received placebo (22 of 738 patients).[15] Serious adverse events reported by 3 or more patients who received ranolazine included myocardial infarction (7 patients), syncope (4), dizziness (4), coronary artery disorder (4), pneumonia (3) and headache (3).[15]

Withdrawals Due to Adverse Events

The frequency of withdrawals due to adverse events was low (1% to 2%) and similar between groups in the ERICA and TERISA studies. Four and 3 patients in the placebo and ranolazine groups, respectively (1% per group), stopped the study due to adverse events in the ERICA study. In the TERISA study, 11 patients in the placebo group (2%) and 9 in the ranolazine group (2%) withdrew from the study due to adverse events. In the CARISA study, 5% of patients in the placebo group and 9% of those in the ranolazine group withdrew from the study due to adverse effects.

The FDA integrated safety review reported that 2.6% and 6.0% of patients who received placebo and ranolazine discontinued due to adverse events.[15]

Mortality

In total there were 6 deaths among patients who received placebo and 5 deaths among those who received ranolazine 1,000 mg across the 3 trials. In the ERICA study, 1 patient in the placebo group died due to acute myocardial infarction and 1 in the ranolazine group died due to pneumonia and cardiopulmonary arrest. In the ranolazine group of the TERISA study, 2 patients died due to myocardial infarction and 1 due to acute cardiac death. Acute cardiac failure and pulmonary embolism was the cause of death for 2 patients in the placebo group. The cause of death was not reported in the CARISA study.

Notable Harms

In the ERICA study, up to 1.4% of patients per group reported ventricular extrasystoles, sinus bradycardia, sinus tachycardia, tachycardia, or first-degree atrioventricular block. No patients in any study reported torsades de pointes. Five patients who received ranolazine 1,000 mg experienced syncope in the CARISA study. The study's authors stated that all patients recovered spontaneously with no signs or ECG evidence of ventricular tachycardia.

No data were provided in the TERISA study on digoxin-related toxicity. Patients receiving digoxin were excluded from the ERICA and CARISA trials. None of the trials reported renal-related adverse events or safety data for patients with end-stage renal disease.

Table 10: Summary of Harms for ERICA and CARISA Studies

	ERICA		CARISA	
	Placebo N = 283	Ranolazine 1,000 mg N = 281[a]	Placebo N = 269	Ranolazine 1,000 mg N = 275
Patients with ≥ 1 adverse event				
n (%)	100 (35.3)	112 (39.9)	71 (26.4)	90 (32.7)
Most common events, n (%)				
Constipation	5 (1.8)	25 (8.9)	≥ 0.7%	≤ 7.3%
Peripheral edema	8 (2.8)	16 (5.7)	NR	NR
Dizziness	7 (2.5)	11 (3.9)	≥ 0.7%	≤ 7.3%
Nausea	2 (0.7)	8 (2.8)	≥ 0.7%	≤ 7.3%
Headache	7 (2.5)	8 (2.8)	NR	NR
Asthenia	3 (1.1)	6 (2.1)	≥ 0.7%	≤ 7.3%
Patients with ≥ 1 serious adverse event				
n (%)	6 (2.1)	5 (1.8)	NR	NR
Patients who stopped study due to adverse events				
n (%)	4 (1.4)	3 (1.1)	13 (4.8)	24 (8.7)
Deaths				
n (%)	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)
Description of events	Acute myocardial infarction	Pneumonia and cardiopulmonary arrest	NR	NR
Notable harms				
Torsades de pointes, n (%)	0	0	0	0

NR = not reported.

Source: Stone et al. (2006)[7], Chaitman et al. (2004),[8] FDA Statistical Review.[18]

Critical Appraisal

Internal Validity

Major and significant gaps in the reporting of study methodology, statistical analysis plan, patient characteristics, disposition, and results in the ERICA and CARISA studies made it difficult to assess their internal and external validity. As this drug submission was based on third-party data, the sponsor was unable to supply the clinical study reports. Centralized randomization not stratified by site was used in the ERICA study; however, no further details were provided on the methods to conceal allocation or maintain blinding, thus the risk of bias is unclear. For sites with low enrolment, the lack of site stratification may result in within-site imbalances between groups. The methods used in the CARISA study included a computer-generated block randomization code provided in sealed envelopes, with drugs packaged by a central pharmaceutical company. A central blinded laboratory was used to read ECG data in the CARISA study. Based on this information, the risk of bias related to randomization, allocation concealment, and blinding is likely low. However, sealed envelopes have numerous known limitations and have been known to compromise allocation concealments in randomized controlled trials. With regards to patients' baseline characteristics, the CARISA study provided limited information, with no data on race, geographic region, or concomitant medications. Based on the information available, the characteristics of patients at baseline appear to be similar between groups within trials, with

the exception of nitroglycerin use in the ERICA study, and prior coronary artery bypass surgery in the CARISA trial, both of which are markers of or may influence, anginal symptoms. These differences suggest underlying differences in characteristics may have existed within the trials, and randomization was not as successful as intended. The number of patients who withdrew from the ERICA study was low (2% per group) and ranged from 9% to 13% in the CARISA study, with few details provided on the reasons for withdrawal. Both trials analyzed data based on the FAS, rather than the intention-to-treat, population, and the number of patients excluded was small (1%) for ERICA but up to 5% for the CARISA study. Given the magnitude of exclusions in the CARISA study, there is potential for the validity of the results to be affected by the lack of a true intention-to-treat analysis. According to the clinical experts consulted, the background therapies used in the trials were standard treatments used in clinical practice in Canada (ERICA: amlodipine 10 mg daily with or without long-acting nitrates; CARISA: amlodipine 5 mg daily, diltiazem CD 180 mg daily, or atenolol 50 mg daily).

The primary outcome of the ERICA study was the average weekly frequency of angina episodes during the 6-week full-dose treatment period, with nitroglycerin consumption as a secondary outcome. Patients used diaries to self-report angina episodes and nitroglycerin doses. This self-reported data may be limited by recall bias as well as patients' perceptions of angina symptoms (i.e., which events are cardiac versus non-cardiac). In addition, the weekly number of angina events may vary depending on activity level, which was not controlled for during the trial. However, these issues would be expected to affect all treatment groups equally, provided blinding was maintained. Stone et al.,[7] states that diary data were reviewed by study staff to ensure accuracy, but it is unclear what steps were taken to verify the angina and nitroglycerin use data and no information was provided on the extent of missing diary data, or how missing data were handled in the analysis. Stone et al.[7] states that "several data points were identified as extreme outliers (ranging from 47 to 160 angina attacks per week) before unblinding." Both the angina frequency and nitroglycerin use data were skewed, and the study's authors reported that the "conventional means were strongly influenced by the few outliers in data and may not be representative of the true treatment effect."[7] The published report states the data were analyzed using non-parametric methods, but does not state which analysis methods were pre-planned. The FDA Statistical Review indicates that the main analysis methods were modified due to the presence of outliers, and the decision to use trimmed means was made post hoc.[18] The outliers appear to be more common in the placebo group, with a larger difference observed between the raw data and the mean trimmed data in the placebo arm compared with the ranolazine arm. It is unclear what impact this may have had on the results. Another issue with the statistical analysis is that it did not adjust for baseline frequency. This was particularly of concern for the analysis of nitroglycerin use, as the baseline consumption was lower in the ranolazine group, which may have biased the results in favour of the active drug. Stone et al.[7] reported that the difference between groups in nitroglycerin use remained statistically significant in favour of ranolazine based on a secondary analysis that adjusted for baseline values, but did not provide any further details, nor a justification of why these methods were not selected for the primary analysis.

Stone et al.[7] did not report power calculations for the ERICA study. Type I error rate was controlled using a hierarchical testing procedure for the primary and secondary outcomes (nitroglycerin use and change from baseline in SAQ domains). Reporting of the SAQ domain data was incomplete, with Stone et al.[7] providing limited results for the first domain tested ($P < 0.05$). No results were provided for the other domains in the published report, but these data were found in the FDA Statistical Review. Stone et al.[7] stated that the SAQ

was not culturally or linguistically validated for the Eastern European countries where the study was conducted and, as a result, the validity of the SAQ results is a major concern.

The primary outcome in the CARISA study (change from baseline to week 12 in exercise duration at trough drug levels) was analyzed using a statistical model adjusted for baseline exercise duration and used LOCF for missing data. There were more patients in the ranolazine group who were excluded from the analysis or had imputed 12-week data (5% and 8%) compared with the placebo group (4% and 5%). However, the authors conducted a conservative sensitivity analysis that suggests the results of the primary analysis were robust. FDA reviewers noted that many patients do not achieve trough drug levels at 12 hours and therefore the primary outcome may not be fully representative of a trough analysis. Type I error rate was controlled for testing of the multiple dosage groups for the primary outcome only, thus the statistically significant differences detected in exercise duration at peak levels and time to angina or time to ECG ischemia should be viewed as supportive evidence for the overall effect of ranolazine versus placebo, given the potential inflated risk of type I error. Non-parametric analysis methods were used to analyze angina frequency and nitroglycerin use data because the data were not normally distributed. Other than stating that patients used diaries to report angina episodes and nitroglycerin use, no details were provided on methods to ensure the completeness or accuracy of the data collected. As it is unclear how missing diary data were handled in the analysis and the type I error rate was not controlled for these outcomes, they should be viewed as supportive evidence only.

The TERISA study used an interactive voice or web response system with a stratified randomization code to assign patients to treatments and conceal allocation, which CADTH rated as presenting a low risk of bias. Placebo tablets were visually indistinguishable to the active drug and in identical packaging to maintain blinding. Because there were no notable differences in the adverse event profile, the risk of unblinding due to adverse effects seems to be low. The baseline characteristics appear to be similar between groups, and only 2% of patients per group withdrew from the study prematurely. The published report does not describe the reasons for withdrawal. The trial enrolled an enriched population that was adherent to the study drug and electronic symptom diary use.

The statistical analyses were adjusted for baseline values and randomization stratification factors, and the primary outcome (angina frequency) also included adjustment for follow-up time. The efficacy analysis was based on the FAS population, which required patients receive at least 14 days of the study drug and have no major eligibility violations. The analysis excluded any days with missing diary data and excluded outcome data after treatment was stopped. While this was not a true intention-to-treat analysis, the proportion of patients excluded (2%) was small in both treatment groups and the authors reported that 98% of all patient days for both groups had a diary entry. The protocol listed several sensitivity analyses conducted to explore the impact of missing data, but results of these analyses were not reported. The trial used a closed testing procedure to control the type I error rate for the primary and secondary outcomes. Exploratory outcomes of interest to this review (e.g., SAQ) were not reported by Kosiborod et al.[12]

For all 3 trials, subgroup data based on gender were reported for the primary outcome. While the US label suggests that ranolazine may be less effective in women, the subgroup data have a number of limitations. None of the trials stratified randomization based on gender, thus there may be imbalances in prognostic factors between groups at baseline. Fewer women than men were enrolled, and the numbers of women in the subgroup

analyses were small (51 to 79 women per treatment group in the pivotal trials, and 179 women per group in the TERISA study). None of the studies were powered or designed to test for differences in treatment effects between genders and there was no control of the type I error rate. As a result, these subgroup data should be interpreted as supportive evidence only.

All trials were short duration (6 to 12 weeks), and reporting of harms data was incomplete, thus the published reports provided limited information on safety. The trials were not designed to assess the impact of ranolazine on major cardiovascular events or mortality, although this drug was not expected to impact these outcomes. Data comparing ranolazine to other treatment options is lacking because the control treatment in all trials was placebo. None of the key trials included a 500 mg dose group, thus efficacy data are lacking for 1 of the dosage regimens that is being sought for approval.

External Validity

External validity was limited by several factors. All 3 trials were conducted primarily in Europe, with 97% of patients in the ERICA study and 70% of patients in the TERISA study from Eastern Europe. Most patients (> 98%) were White, and male (61% to 80%), therefore they do not reflect the racial diversity or gender balance in Canada. Moreover, the pivotal trials took place between 1999 and 2005, and the management of coronary artery disease may not reflect current clinical practice. This is reflected in the low proportion of patients who had previously undergone revascularization procedures (9% to 20% for percutaneous coronary intervention and 10% to 20% for coronary artery bypass graft). Moreover, Stone et al.[7] stated that patients in the ERICA trial may not have been optimally managed, as only 36% were receiving statins during the trial. Background therapies were limited to 1 or 2 drugs, and in the TERISA study, patients who were taking more than 2 antianginal drugs at baseline were required to stop additional therapies. Consequently, these trials may have included patients whose symptoms could have been controlled with standard therapies.

In addition, the TERISA study enrolled an enriched population that was adherent to study drug and met angina frequency criteria, excluding 20% of patients who were screened. Both the ERICA and CARISA studies had a run-in phase that excluded patients who did not meet specific angina frequency or exercise duration criteria. This may affect the generalizability of the results to the broader population of patients with stable angina.

The key trials addressed short-term outcomes that are relevant to patients, but longer-term efficacy is unclear.

Other Studies Included in the Systematic Review

Description of Studies

Five other studies met the inclusion criteria for the systematic review. These included 1 open-label[11] and 4 double-blind randomized trials.[9,10,13,14] Three trials used a parallel design[9-11] and 2 were randomized crossover studies.[13,14] The studies enrolled 29 to 2,651 patients with stable angina who received ranolazine 500 mg to 1,500 mg twice daily compared with placebo or usual care (add-on to background antianginal drugs in 4 trials,[9-11,14] monotherapy in 1 trial[13]). The treatment duration ranged from 1 week[13] to 1.8 years.[10] Three studies were conducted at 1 or 2 clinical sites;[9,11,14] the others were multi-centre trials.[10,13]

Results

Efficacy

A summary of the key results identified in the review protocol is reported in Table 11.

The open-label study by Saha et al.[11] found statistically significant lower angina frequency at 6 weeks among patients with exertional angina and no obstructive coronary artery disease who received ranolazine compared with usual care. No statistically significant differences in dyspnea symptoms or Duke Activity Score Index values were detected between groups. Some differences favouring ranolazine were observed for 4 of the SAQ domains, although the type I error was not controlled for these outcomes and therefore should be viewed as supportive evidence only. This trial was rated as of low methodological quality, with multiple potential sources of bias and limited sample size (N = 65).

The 14-week study by Willis et al.,[9] which enrolled 29 patients with coronary artery disease and stable angina, reported no statistically significant difference between ranolazine and placebo in the change from baseline in SAQ quality-of-life domain. Similarly, the 2-week crossover study by Bairey Merz et al.[14] (N = 128) found no statistically significant difference between ranolazine and placebo in SAQ domains, angina frequency, nitroglycerin use, and SF-36 energy and emotional domains. This trial enrolled patients with ischemic symptoms but no coronary artery disease.

The 1-week crossover MERISA study reported that monotherapy with ranolazine 500 mg twice daily increased exercise duration by 24 seconds (SE = 7.9; P = 0.003), and ranolazine 1,000 mg twice daily increased exercise duration by 34 seconds (SE = 8.0; P < 0.001), relative to placebo, in patients with coronary artery disease and stable angina who were previously responding to beta-blockers, calcium-channel blockers, and/or long-acting nitrates (N = 191).[13]

The RIVER-PCI study[10] enrolled 2,651 patients with chronic angina who had incomplete revascularization after percutaneous coronary intervention completed within the previous 14 days. This study found no statistically significant difference between ranolazine and placebo in the time to first occurrence of ischemia-driven revascularization or hospitalization, or secondary outcomes, time to sudden cardiac death, cardiovascular death, and myocardial infarction. No differences were found between groups on angina frequency and treatment satisfaction domains of the SAQ in a RIVER-PCI substudy.[17]

Harms

Chaitman et al. (2014)[13] reported that 8% of patients discontinued the study due to adverse events. The percentages of patients who experienced an adverse event were 16%, 16%, and 22% during the placebo, ranolazine 500 mg, and 1,000 mg dosage periods, respectively. The adverse events reported included dizziness, nausea, angina, asthenia, constipation, headache, and sweating.[13]

In the study by Bairey Merz et al.,[14] 21% of patients receiving ranolazine decreased their dose to 500 mg due to adverse events, compared with 14% receiving placebo. Serious adverse events were reported in 4%, 0%, and 2% of patients during the ranolazine, placebo, and washout periods, respectively. The frequency of non–serious adverse events was 5%, 5%, and 2% during ranolazine, placebo, and washout periods.[14]

In the RIVER-PCI study, 40% and 36% of patients stopped treatment in the ranolazine and placebo groups, respectively, including 14% and 11% of patients who stopped treatment

due to adverse events.[10] Eleven percent of patients per group experienced a major adverse cardiovascular event, and 3% of patients per group died during the trial (median follow-up of 1.8 years). The adverse events reported more frequently in the ranolazine group versus placebo were dizziness (19% versus 9%), constipation (13% versus 6%), nausea (10% versus 5%), hypotension (5% versus 2.5%), vomiting (4% versus 2%), asthenia (4% versus 2%), syncope (4% versus 2%) and vertigo (3% versus 1%).[10]

Two studies did not report any data on harms.[9,11]

Table 11: Summary of Other Included Studies

Study name, author, year	Study design, duration	Population, N	Intervention, comparators	Outcomes
Saha (2017)[11]	OL RCT, single centre 6 weeks	Adults with angina or dyspnea symptoms on exertion with abnormal exercise stress test and no obstructive CAD N = 65 Mean age 49 years; 42% male	RAN 1,000 mg b.i.d.[a] plus usual care versus usual care angina treatments	At 6 weeks angina symptoms were reduced in the RAN group versus usual care (60% versus 87%) (P = 0.02). No difference detected in dyspnea symptoms (P = 0.79) or DASI scores (P = 0.39) At 6 weeks SAQ physical functioning, angina stability, angina frequency and quality of life domains were all higher for RAN versus usual care (P < 0.05)[b] SAQ treatment satisfaction was lower for RAN versus usual care (P < 0.05)[b]
Willis (2019)[9]	DB RCT, single centre 14 weeks	CAD with stable angina (> 3 months) and > 3 episodes per week N = 29 Mean age 67.4 (SD = 8.3) and 69.2 (SD = 11.2) years; 66% male	RAN 1,000 mg b.i.d[a] versus placebo; all patients completed 12-week cardiac rehabilitation exercise program	At 14 weeks, no statistically significant difference between RAN and placebo in the change from baseline in SAQ quality of life domain Mean change from baseline to 14 weeks (SD) RAN: 13.0 (18) Placebo: 19.2 (21), P = not statistically significant
Bairey Merz (2016)[14] (Birkeland [2017][34])	DB randomized crossover study, 2 clinical sites 2-week treatment with 2-week washout	Patients with ischemic symptoms; no obstructive CAD, preserved ejection fraction and abnormal coronary reactivity testing N = 128 Mean age 55.2 years (SD = 9.8); 4% male	RAN 500 mg b.i.d. for 1 week then 1,000 mg b.i.d. for 1 week versus placebo (plus prior anti-angina treatments)	No statistically significant difference between RAN and placebo in SAQ domains, angina frequency, or nitroglycerin use, SF-36 energy or emotional domain Substudy on activity levels (N = 30)[34] Mean steps per day were statistically significantly lower for RAN versus placebo (mean difference, −837 steps; 95% CI, −1,465 to −209; P = 0.01)[b]

Study name, author, year	Study design, duration	Population, N	Intervention, comparators	Outcomes
MERISA Chaitman (2004)[13]	DB randomized crossover study, multicenter 1-week treatment with no washout	CAD with at least a 3-month history of effort angina responding to beta-blockers, CCB, and/or long-acting nitrates. N = 191 Mean age 64.3 years (SD = 9.4), 73% male	RAN 500 mg b.i.d., RAN 1,000 mg b.i.d, and RAN 1,500 mg b.i.d. versus placebo All patients discontinued anti-anginal treatment during the study (except sublingual nitroglycerin)	All doses of RAN showed statistically significant increases in exercise duration on a modified Bruce protocol with mean differences ranging from 23.8 sec (SE = 7.9; P = 0.003) for RAN 500 mg dose, to 33.7 sec (SE = 8.0; P < 0.001) for RAN 1,000 mg at trough drug levels Statistically significant differences in time to angina and time to 1 mm ST-segment depression were detected for RAN 500 mg and 1,000 mg doses versus placebo[b]
RIVER-PCI Weisz (2016)[10] (Alexander [2016][17])	DB RCT, multi-centre Median duration 643 days	Adults with history of chronic angina who had incomplete revascularization after PCI (randomized within 14 days of PCI) N = 2,651 Mean age 63.4 (SD = 10.5); 80% male	RAN 1,000 mg b.i.d.[a] versus placebo (plus standard treatments)	No statistically significant difference found in the time to first ischemia-driven revascularization or hospitalization (HR = 0.95; 95% CI, 0.82 to 1.10; P = 0.48), sudden cardiac death (HR = 0.67; 95% CI, 0.24 to 1.69; P = 0.40), cardiovascular death (HR = 1.07; 95% CI, 0.58 to 1.99; P = 0.82) or myocardial infarction (HR = 0.97; 95% CI, 0.75 to 1.26; P = 0.81) HRQoL substudy[17] N = 2,389 (90%): • SAQ angina frequency: LS mean difference = 1.0, 95% CI –0.2 to 2.2, P = 0.11 • SAQ treatment satisfaction: LS mean difference = −0.1; 95% CI, –1.1 to 0.8; P = 0.80 • DASI: LS mean difference = −0.4; 95% CI. −1.3 to 0.4; P = 0.34

b.i.d. = twice daily; CAD = coronary artery disease; CCB = calcium-channel blocker; CI = confidence interval; DASI = Duke Activity Status Index; DB = double blind; HR = hazard ratio; HRQoL = health-related quality of life; LS = least squares; OL = open label; PCI = percutaneous coronary intervention; RAN = ranolazine; RCT = randomized controlled trial; SAQ = Seattle Angina Questionnaire; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a] Initial dose was ranolazine 500 mg b.i.d. for 1 week, or 2 weeks in Saha et al. (2017), then increased to 1,000 mg b.i.d.

[b] No control for type I error rate.

Source: Saha et al. (2017),[11] Willis et al. (2019),[9] Bairey Merz et al. (2016),[14] Birkeland et al. (2017),[34] Chaitman et al. (2004),[13] Weisz et al. (2016),[10] Alexander et al. (2016).[17]

Critical Appraisal

These trials had several limitations that affect internal or external validity. The methods to randomize patients and conceal allocation were unclear in 4 studies.[9,11,13,14] Although 4 studies were reported to be double-blind, 3 studies provided no information on the methods to maintain blinding.[9,13,14] One study was open-label.[11] Knowledge of the study drug received may influence the use of co-interventions and reporting of subjective outcomes, such as angina frequency and health-related quality of life, potentially biasing the results. Baseline characteristics were generally similar between treatment groups, but the sample size was small in 2 studies (29 and 65 patients).[9,11] Therefore, there may be residual imbalances as randomization may not have been effective at balancing the groups. The rate of attrition ranged from 2%[10] to 21%[9] (no information for Saha et al.[11]), and although the withdrawal rate was generally similar between treatment groups within trials, the high attrition rate in some studies may affect the validity of the results. In the crossover study by Bairey Merz et al.,[14] the 2-week washout period was likely sufficient given the half-life of ranolazine (7 hours). However, the other crossover study (MERISA[13]) had no washout period between treatments and a short treatment period of 1 week, and there may be carry-over of effects between treatment periods. Four of the trials had a short treatment duration (1 to 14 weeks).[9,11,13,14] Reporting of methods and results were poor in 2 studies,[9,11] and reporting of harms was incomplete in all 5 trials. Although all studies included patients with chronic angina, the RIVER-PCI trial[10] is more reflective of an acute coronary syndrome population, and its relevance to the indication under review may be limited.

Indirect Evidence

No indirect treatment comparisons were submitted by the sponsor and no relevant published reports were identified in the literature search conducted by CADTH.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Study: ROLE

The Ranolazine Open Label Experience (ROLE) study[19] is a long-term extension that has been summarized to provide evidence regarding the safety and tolerability of ER ranolazine in patients with chronic angina.

The ROLE study[19] was an open-label long-term extension study that evaluated the safety and tolerability of ranolazine administered at a dose of 500 mg or 1,000 mg twice daily in patients with chronic angina who completed the CARISA or MARISA trials and were willing to participate in this extension program.[8,13] ROLE program subjects were enrolled at 123 outpatient sites in 12 countries.

All patients who completed the CARISA or MARISA trials were eligible if they were willing to participate in the ROLE program; this includes patients randomized to the placebo arm of the CARISA trial. A total of 746 patients were enrolled in the ROLE program: 603 from the CARISA trial and 143 from the MARISA trial. These patients represent 73% to 75% of the patients enrolled in the original trials. In terms of baseline demographics, 77.7% (580 of

746) were male, 52.0% (388 of 746) were younger than 65 years of age, and 96.8% (722 of 746) were White. As for the medical history, 63.8% (476 of 746) had hypertension, 57.5% (429 of 749) had previous myocardial infarction, 34.5% (257 of 746) had previous revascularization, 28.8% (215 of 746) had congestive heart failure, 23.1% (172 of 746) had unstable angina, and 22.8% (170 of 746) had diabetes. Strokes and cardiac arrest were previously reported in 4.7% (35 of 746) and 1.9% (14 of 746) of patients, respectively. As for history of ranolazine use, 26.4% (197 of 746) received the ranolazine for the first time while 73.6% (549 of 746) had previously received the drug.

Patients from the CARISA trial were initiated on 500 mg ER ranolazine twice daily and could be increased to 1,000 mg twice daily. Patients from the MARISA trial were initiated on 750 mg ER ranolazine twice daily and could be increased to 1,000 mg twice daily. Based on the clinical response of patients at up to 6 initial weekly visits, investigators could titrate to optimal ranolazine dosages between 500 and 1,000 mg twice daily as guided by clinical effects. In addition, background antianginal therapy was maintained during the ranolazine titration period, but the dosage could be increased, decreased, substituted, or discontinued at the discretion of the investigators. During the ROLE program, 58% of patients (432 of 746) were titrated to the maximum dose of 1,000 mg ranolazine twice daily, 28% (209 of 746) were titrated to a maximum dose of 750 mg twice daily, and 14% received a dose of 500 mg twice daily.

Results

At the time of analysis, 76.7% (571 of 746) of patients completed 2 years of open-label ranolazine treatment and 23.3% (173 of 746) discontinued therapy in the first 2 years of treatment, of which, 9.7% (72 of 746) was due to adverse events, 6.2% (46 of 746) was due to elective withdrawal, and 4.8% (36 of 746) was due to death. When including all follow-up time, the mean exposure time to ranolazine was 2.8 years (range: 6 days to 6.5 years), and 38.9% (290 of 746) of patients discontinued therapy, of which 12.6% (94 of 746) was due to adverse events, 12.7% (95 of 746) was due to elective withdrawal, and 7.5% (56 of 746) was due to death. The death of 8 additional patients after terminating participation in the ROLE program is noteworthy.

The adverse events are summarized in Figure 9. The adverse event profile of first-time ranolazine users did not differ from that of patients who had previously used ranolazine. The most common adverse events, aside from angina pectoris, which was reported in 14.9% (111 of 746) of patients, were dizziness (11.8%; 88 of 746), constipation (10.9%; 81 of 746), and peripheral edema (8.4%; 62 of 746). In terms of mortality, a total of 68 deaths were reported during the 2,372 patient-years of follow-up in the ROLE program, which corresponds to an annual mortality rate of 2.8 per patient-year. Among these deaths, 79.4% (54 of 68) were cardiovascular deaths and 20.6% (14 of 746) were non-cardiovascular deaths. The most common causes were myocardial infarction and tachyarrhythmia for cardiac deaths, and cancer and pulmonary embolism for non-cardiac deaths. The number of serious adverse events was not reported.

Figure 9: Summary of Adverse Events Reported During the ROLE Program With an Incidence of 4% or Greater

Preferred Term	Number of Patients (%) (n = 746)
Angina pectoris	111 (14.9)
Dizziness	88 (11.8)
Constipation	81 (10.9)
Peripheral edema	62 (8.3)
Angina, unstable	53 (7.1)
Fatigue	52 (7.0)
Hypertension	48 (6.4)
Cough	45 (6.0)
Chest pain	44 (5.9)
Nausea	42 (5.6)
Headache	41 (5.5)
Myocardial infarction	37 (5.0)
Diabetes mellitus	37 (5.0)
Back pain	36 (4.8)
Anemia	34 (4.6)
Arthralgia	33 (4.4)
Asthenia	33 (4.4)
Dyspnea	32 (4.3)
Vertigo	32 (4.3)
Influenza	31 (4.2)
Acute MI	28 (3.8)
Diarrhea	28 (3.8)

MI = myocardial infarction; ROLE = Ranolazine Open Label Experience.

Source: Permission obtained from the publisher to use Table 3 from Long-Term Safety of a Novel Antianginal Agent in Patients With Severe Chronic Stable Angina: The Ranolazine Open Label Experience (ROLE) by Koren MJ, Crager MR, Sweeney M. (2007).[19]

Summary and Critical Appraisal

Evidence from the ROLE study[19] suggests good safety and tolerability of ER ranolazine at dosages of 500 mg and 1,000 mg twice daily. The discontinuation of ranolazine due to adverse events was more common in older patients, with dizziness and constipation the most reported adverse events. Some limitations relating to the internal validity of the ROLE study include potential selection bias, lack of blinding, lack of comparator group, and lack of systematic follow-up after discontinuation of the ROLE program, which may have significantly affected the validity of the safety and efficacy results. Because completion of the CARISA or MARISA trial was an eligibility criterion for the ROLE program, patients who discontinued those trials due to adverse events or death were excluded. This could have produced a population of patients more tolerant of ranolazine and with a survival bias, resulting in fewer adverse events being reported. Additionally, the lack of blinding could have introduced bias in the reporting of subjective adverse events in favour of ranolazine if patients believed the drug was beneficial. The lack of a comparator group makes it difficult to interpret mortality results and the lack of systematic follow-up after discontinuation of ranolazine in the ROLE program could have missed important information regarding the long-term effects of ranolazine. In terms of external validity, results from the ROLE study may be generalizable to the Canadian population as the study included Canadian patients with stable angina pectoris and the dosages of 500 mg and 1,000 mg twice daily align with Health Canada's dosing for this population. As well, drug titration was guided by clinical effects as it would in clinical practice.

Discussion

Summary of Available Evidence

A total of 8 studies were identified from the literature for inclusion in the systematic review, including 2 pivotal trials (ERICA,[7] CARISA[8]), 1 additional key study (TERISA[12]), and 5 other studies.[9-11,13,14] One open-label extension study (ROLE) was also summarized.[19]

The 3 key studies (ERICA, CARISA, and TERISA) were 6- to 12-week multi-centre, randomized, double-blind, placebo-controlled, parallel design trials.[7,8,12] These studies examined the efficacy and safety of ranolazine 750 mg or 1,000 mg ER twice daily versus placebo, as add-on therapy to 1 or 2 antianginal drugs, in adults with coronary artery disease and stable angina (N = 565 to 949) who were experiencing angina symptoms or had limited exercise capacity despite standard antianginal treatments. The primary outcomes were angina frequency or exercise duration. For these 3 studies, the mean age of patients enrolled ranged from 61.3 years to 64.2 years, and most patients were male (61% to 80%) and White (≥ 98%), with a history of myocardial infarction (56% to 82%), heart failure (28% to 52%), unstable angina (20% to 36%), and diabetes (19% to 100%).

Five other studies were described briefly in this report due to limitations related to study design, population, sample size, outcomes measures, or other sources of bias that limited the utility or robustness of the findings.[9-11,13,14] The 5 studies included 1 open-label[11] and 4 double-blind randomized trials.[9,10,13,14] Three trials used a parallel design[9-11] and 2 were randomized crossover studies.[13,14] The studies enrolled 29 to 2,651 patients with stable angina who received ranolazine 500 mg to 1,500 mg twice daily compared with placebo or usual care (add-on to background antianginal drugs in 4 trials,[9-11,14] monotherapy in 1 trial[13]). The treatment duration ranged from 1 week[13] to 1.8 years.[10] Outcomes of interest included angina symptoms, exercise duration, health-related quality of life, and major cardiovascular events.

The ROLE study[19] was an open-label long-term extension study that evaluated the safety and tolerability of ranolazine administered at a dose of 500 mg or 1,000 mg twice daily in patients with chronic angina who completed the CARISA or MARISA trials. A total of 746 patients were enrolled and these patients had a mean treatment duration of 2.8 years.

Interpretation of Results

Efficacy

All 3 key trials (ERICA, TERISA, and CARISA) reported reductions in angina frequency and nitroglycerin consumption relative to baseline in the ranolazine 1,000 mg twice daily and placebo groups. Patients who received ranolazine had fewer angina episodes per week than patients who received placebo, with differences that were statistically significant in the ERICA study (trimmed mean episodes per week: 2.9 versus 3.3) and TERISA study (LS mean episodes per week: 3.8 versus 4.3). Similarly, the differences in nitroglycerin use were statistically significant, favouring ranolazine versus placebo in the ERICA (trimmed mean doses per week: 2.0 versus 2.7) and TERISA studies (LS mean doses per week: 1.7 versus 2.1). Some issues were noted with the statistical analysis of the ERICA study. The decision to analyze angina and nitroglycerin use data using trimmed means was made post hoc, after the data were found to be skewed and to include extreme outliers (i.e., up to 160 angina episodes per week). Moreover, there were imbalances between groups in

nitroglycerin use at baseline, and the primary analysis was not adjusted for baseline rates, potentially biasing the results in favour of the active drug. The authors conducted a secondary analysis that adjusted for baseline nitroglycerin use and stated that differences remained statistically significant; however, no further information was provided. In addition, no information was provided on the extent of missing diary data in the CARISA or ERICA studies, or how missing data were handled in the analysis. Although the CARISA study reported data for angina frequency and nitroglycerin use, there was no control of the type I error and thus these outcomes should be interpreted as supportive evidence only.

The CARISA study observed improvements in exercise duration for all groups, with statistically significant differences that favoured ranolazine 1,000 mg versus placebo (LS mean difference = 24 seconds) at trough drug levels. Similar differences favouring ranolazine versus placebo at peak drug levels were also observed (LS mean difference = 26 seconds), but the type I error was not controlled for this outcome, or for other secondary outcome measures (time to angina onset or time to ECG ischemia) that showed results that favoured ranolazine; these should be viewed as supportive evidence only.

The between-group differences of approximately 0.4 to 0.5 angina events per week (ERICA and TERISA) and 24 seconds on an exercise test (CARISA), were considered clinically relevant by some but not all clinical experts consulted for this review. Both the FDA and National Institute for Health and Care Excellence concluded that the observed improvements in angina frequency and exercise duration were modest, and of unclear clinical significance.[15,16] Because CADTH did not receive any input from patient groups, this submission is lacking information on treatment goals and unmet needs from patients' perspectives. The clinical experts stated that the goals of therapy vary from patient to patient and are highly dependent on each person's health status, and ability to perform everyday activities. For those with more severe symptoms, a treatment that allows them to complete activities of daily living without angina symptoms would be deemed a success, whereas a much higher threshold would be desired for younger or more active patients. All the experts consulted stated that, in practice, treatment response is evaluated subjectively based on patients' perceived changes in symptom frequency or functional abilities.

Data on the impact of ranolazine on health-related quality of life were limited. No differences were found between ranolazine and placebo on the disease perception/quality-of-life domain of the SAQ in the ERICA study, and although statistical differences were detected in the angina frequency domain, the LS mean differences of 4.1 points did not exceed the 10-point MID reported in the literature. Moreover, Stone et al.[7] stated that the SAQ was not validated in the Eastern European population where the trial was conducted. No differences between groups on the change from baseline in the SF-36 PCS and MCS in the TERISA study were found to be statistically significant, although this instrument may be less sensitive to change than the SAQ in patients with angina, and the duration of the trial may have been insufficient to demonstrate a change in health-related quality of life.

None of the key trials were designed to assess the impact of ranolazine on major cardiovascular events or mortality, although this drug was not expected to affect these outcomes. With regards to ranolazine dosing, the target dose in the 3 key trials was 1,000 mg twice daily, and efficacy data are lacking for the 500 mg twice daily dose, which is the starting dose listed in the product monograph.

This review's protocol identified gender as a subgroup of interest due to statements in the draft Canadian product monograph and US label that suggest ranolazine may be less

effective in women based on data from the ERICA and CARISA studies. The US label states the following:

> Effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In CARISA, the improvement in Exercise Tolerance Test (ETT) in females was about 33% of that in males at the 1,000 mg twice-daily dose level. In ERICA, where the primary end point was angina attack frequency, the mean reduction in weekly angina attacks was 0.3 for females and 1.3 for males. (p. 15)[23]

The trends suggested in the US label were not observed in the TERISA study, in which women showed stronger treatment effects than men. But more importantly, none of the trials were designed or powered to detect differences between gender subgroups. The treatment by gender interaction term did not provide evidence of a difference in the ERICA and TERISA studies (no data for CARISA). Moreover, the female subgroups were small in the ERICA and CARISA studies, and the apparent differences in effect size may have occurred by chance. Imbalances between groups at baseline were possible as none of the trials stratified randomization by gender. Given the limitations of the subgroup data, no conclusions can be drawn about gender effects of ranolazine.

In addition to the issues related to internal validity, several factors that may limit the external validity of the key studies were identified. The pivotal trials were conducted between 1999 and 2005, and most patients in the ERICA and TERISA studies were from Eastern Europe, thus the management of patients with stable angina may not have been optimized according to current clinical standards. Moreover, most patients were White and male, and may not be reflective of racial and gender distribution in Canada. The TERISA study enrolled an enriched population that was adherent to the study drug and outcome reporting. Background therapies were limited to 1 or 2 drugs, and in the TERISA study, patients who were taking more than 2 antianginal drugs at baseline were required to stop additional therapies. Consequently, these trials may have included patients whose symptoms could have been controlled with standard therapies.

Although 5 other trials met the inclusion criteria, due to concerns regarding their internal or external validity, these trials contributed little additional evidence to support the use of ranolazine. As the open-label study by Saha et al.[11] trial was rated as low in methodological quality, minimal conclusions can be drawn from its findings. The studies by Willis et al.,[9] and Bairey Merz et al.[14] failed to detect statistically significant differences between ranolazine and placebo for the outcomes of interest to this review. The MERISA study reported that monotherapy with ranolazine 500 mg twice daily increased exercise duration by 24 seconds, and ranolazine 1,000 mg twice daily increased exercise duration by 34 seconds, relative to placebo, in patients with coronary artery disease and stable angina who were previously responding to standard antianginal drugs.[13] However, given the short treatment duration (1 week), potential carry-over effects between treatment periods in this crossover study, and the use of ranolazine as monotherapy in patients previously controlled with antianginal drugs, the relevance of this study's findings to this review is limited. The RIVER-PCI study[10,17] found no statistically significant difference between ranolazine 1,000 mg twice daily and placebo in the time to first occurrence of ischemia-driven revascularization or hospitalization, or time to sudden cardiac death, cardiovascular death, and myocardial infarction, or in SAQ domains. This study enrolled patients with chronic angina who had incomplete revascularization after percutaneous coronary intervention completed within the previous 14 days and is more reflective of an acute coronary syndrome population. As a result, its generalizability to the indication under review may be limited.

Harms

Overall, the reporting of harms data in the published reports was poor, as the authors provided limited data that contained important gaps. The 3 key trials were of short duration (6 to 12 weeks), and comparative longer-term safety data in patients with stable angina were limited. Although safety data were reported for the RIVER-PCI trial (median follow-up of 1.8 years), this study included an acute coronary syndrome population, which may have different risks of experiencing adverse events than patients with stable angina. The ROLE extension study had a mean treatment duration of 2.8 years but was open-label, uncontrolled, and enrolled a select population that showed initial tolerance to ranolazine. Ranolazine has been marketed in the US and Europe for several years, thus additional post-marketing safety surveillance data are available for this drug.

In the key short-term studies, the frequency of adverse events was approximately 5% to 6% higher in the ranolazine groups than in placebo groups. Nausea, dizziness, and constipation were consistently reported more frequently among those who received ranolazine compared with placebo. The frequency of withdrawals due to adverse events ranged from 1% to 14% and from 1% to 11% in the ranolazine and placebo groups, respectively. Not all published reports provided data on serious adverse events, but an integrated safety review of phase II and III trials conducted by the FDA reported serious adverse events in 5.4% of patients who received ranolazine compared with 3.0% who received placebo.[15] Limited data were reported on arrythmias or cardiovascular events. During the 3 key trials there were a total of 5 deaths among patients who received ranolazine 1,000 mg and 6 deaths among those who received placebo during the 3 trials (≤ 1.1% per group) and in the RIVER-PCI study 3% of patients died per group. No new safety signals were detected in the open extension study.

Ranolazine has clinically relevant drug interactions with other medications, including metformin, simvastatin, lovastatin, diltiazem, verapamil, and digoxin, that are often prescribed in patients with cardiac disease. The product monograph states that dose reductions of ranolazine or other drugs may be required to avoid toxicity.[5] Concurrent use with inducers or strong inhibitors of CYP3A4 and class IA or class III antiarrhythmics is contraindicated, and the product monograph includes precautions for use with moderate CYP3A4 inhibitors, P-glycoprotein inhibitors, and drugs metabolized by CYP2D6. Due to the QT prolongation associated with ranolazine, the product monograph contains warnings regarding concurrent use with other drugs or conditions that may increase the risk of clinically significant arrhythmias.

Conclusions

In patients with coronary artery disease and stable angina pectoris, ranolazine 1,000 mg ER twice daily as an add-on to 1 or 2 standard antianginal drugs reduced angina frequency and nitroglycerin consumption in the short-term, relative to placebo plus standard treatments. Short-term treatment with ranolazine as add-on therapy also improved exercise duration on a modified Bruce protocol exercise test compared with placebo plus standard treatments. The between-group differences in angina frequency and exercise duration were modest and may not be clinically important to patients.

The impact of ranolazine on health-related quality of life is uncertain. None of the key trials was designed to evaluate the effect of ranolazine on cardiovascular events or mortality in patients with stable angina. Data are lacking on the efficacy of the 500 mg dose of ranolazine and for ranolazine compared with other antianginal treatments.

Ranolazine was associated with increased frequency of nausea, constipation, and dizziness relative to placebo. Safety data were limited by the quality of the reporting in the published trials and the short duration of the key randomized controlled trials.

The findings of the key trials may not be representative of the broader Canadian population with stable angina. Given the time frame and the countries where the trials were conducted, the management of coronary artery disease may have been suboptimal, according to current Canadian practice standards. In addition, 1 study enrolled an enriched population that was adherent to treatment and outcome reporting.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 15, 2020
Alerts:	Weekly search updates until project completion
Study Types:	A CCT/RCT filter was applied
Limits:	Publication date limit: No date limits used Humans Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for 1 character
?	Truncation symbol for 1 or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CDSR and DARE)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
1	Ranolazine/
2	(Corzyna* or Ranexa* or ranolazine* or 62anolazine* or Ran-4 or Ran4 or Ran-D or RS-43285 or RS43285 or RS-43285193 or RS-43285-193 or 43285-RS or Caroza* or Cartinex* or ranev* or razine* or Latixa* or Ralozine* or Ranasafe* or Ranola* or Ranolin* or Ranosin* or CVT-303 or CVT303 or A6IEZ5M406).ti,ab,rn,nm,kf,ot.
3	1 or 2
4	3 use 62anol
5	*ranolazine/
6	(Corzyna* or Ranexa* or ranolazine* or 62anolazine* or Ran-4 or Ran4 or Ran-D or RS-43285 or RS43285 or RS-43285193 or RS-43285-193 or 43285-RS or Caroza* or Cartinex* or ranev* or razine* or Latixa* or Ralozine* or Ranasafe* or Ranola* or Ranolin* or Ranosin* or CVT-303 or CVT303).ti,ab,kw,dq.
7	5 or 6
8	7 use oemezd
9	conference abstract.pt.
10	conference review.pt.
11	9 or 10
12	8 not 11
13	4 or 12
14	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
15	Randomized Controlled Trial/
16	exp Randomized Controlled Trials as Topic/
17	“Randomized Controlled Trial (topic)”/
18	Controlled Clinical Trial/
19	exp Controlled Clinical Trials as Topic/
20	“Controlled Clinical Trial (topic)”/
21	Randomization/
22	Random Allocation/
23	Double-Blind Method/
24	Double Blind Procedure/
25	Double-Blind Studies/
26	Single-Blind Method/
27	Single Blind Procedure/
28	Single-Blind Studies/
29	Placebos/
30	Placebo/
31	Control Groups/
32	Control Group/
33	(random* or sham or placebo*).ti,ab,hw,kf,kw.
34	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
35	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.

MULTI-DATABASE STRATEGY	
36	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
37	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
38	allocated.ti,ab,hw.
39	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
40	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
41	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
42	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
43	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
44	(phase adj3 (III or “3”) adj3 (study or studies or trial*)).ti,hw,kf,kw.
45	or/14-44
46	13 and 45
47	exp animals/
48	exp animal experimentation/ or exp animal experiment/
49	exp models animal/
50	nonhuman/
51	exp vertebrate/ or exp vertebrates/
52	or/47-51
53	exp humans/
54	exp human experimentation/ or exp human experiment/
55	or/53-54
56	52 not 55
57	46 not 56
58	remove duplicates from 57

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Search date:	September 4, 2020
Keywords:	Ranolazine and angina
Limits:	Publication years: No date limits used
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Table 12: Excluded Studies

Reference	Reason for exclusion
1. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol. 2009;53(17):1510-1516. 2. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. Eur Heart J. 2006;27(1):42-48. 3. Sendon JL, Lee S, Cheng ML, Ben-Yehuda O, investigators Cs. Effects of ranolazine on exercise tolerance and angina frequency in patients with severe chronic angina receiving maximally-tolerated background therapy: analysis from the Combination Assessment of Ranolazine In Stable Angina (CARISA) randomized trial. European Journal of Preventive Cardiology. 2012;19(5):952-959. 4. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA. 2007;297(16):1775-1783. 5. Mega JL, Hochman JS, Scirica BM, et al. Clinical features and outcomes of women with unstable ischemic heart disease: observations from metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36). Circulation. 2010;121(16):1809-1817. 6. Gutierrez JA, Karwatowska-Prokopczuk E, Murphy SA, et al. Effects of Ranolazine in Patients With Chronic Angina in Patients With and Without Percutaneous Coronary Intervention for Acute Coronary Syndrome: Observations From the MERLIN-TIMI 36 Trial. Clin Cardiol. 2015;38(8):469-475. 7. Fanaroff AC, James SK, Weisz G, et al. Ranolazine After Incomplete Percutaneous Coronary Revascularization in Patients With Versus Without Diabetes Mellitus: RIVER-PCI Trial. J Am Coll Cardiol. 2017;69(18):2304-2313. 8. Arnold SV, Morrow DA, Wang K, et al. Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: results from the MERLIN-TIMI 36 randomized trial. Circulation Cardiovascular Quality & Outcomes. 2008;1(2):107-115. 9. Arnold SV, McGuire DK, Spertus JA, et al. Effectiveness of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina according to baseline hemoglobin A1c. Am Heart J. 2014;168(4):457-465.e452. 10. Caminiti G, Fossati C, Battaglia D, Massaro R, Rosano G, Volterrani M. Ranolazine improves insulin resistance in non-diabetic patients with coronary heart disease. A pilot study. Int J Cardiol. 2016;219:127-129.	Population
11. Villano A, Di Franco A, Nerla R, et al. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol. 2013;112(1):8-13. 12. Tagliamonte E, Rigo F, Cirillo T, et al. Effects of ranolazine on noninvasive coronary flow reserve in patients with myocardial ischemia but without obstructive coronary artery disease. Echocardiography. 2015;32(3):516-521. 13. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. Am J Cardiol. 2005;95(3):311-316. 14. Golino M, Spera FR, Manfredonia L, et al. Microvascular ischemia in patients with successful percutaneous coronary intervention: effects of ranolazine and isosorbide-5-mononitrate. Eur Rev Med Pharmacol Sci. 2018;22(19):6545-6550.	Intervention
15. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Evaluation of a novel anti-ischemic agent in acute coronary syndromes: design and rationale for the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes (MERLIN)-TIMI 36 trial. Am Heart J. 2006;151(6):1186.e1181-1189.	Study design

Reference	Reason for exclusion
16. Mehta PK, Goykhman P, Thomson LE, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging. 2011;4(5):514-522. 17. Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). J Am Coll Cardiol. 2007;49(10):1027-1034. 18. Kohn CG, Parker MW, Limone BL, Coleman CI. Impact of angina frequency on health utility values of patients with chronic stable angina. Health & Quality of Life Outcomes. 2014;12:39. 19. Khot AM, Anuradha HV, Prakash VS, Shivamurathy MC. Antianginal Efficacy and Tolerability of Ranolazine as an Add-on Drug to Concomitant Medications Primarily Metoprolol in Chronic Stable Angina Patients: A Prospective, Open-Label Study. J Pharmacol Pharmacother. 2017;8(1):21-27. 20. Bavry AA, Park KE, Choi CY, Mahmoud AN, Wen X, Elgendy IY. Improvement of Subjective Well-Being by Ranolazine in Patients with Chronic Angina and Known Myocardial Ischemia (IMWELL Study). Cardiology & Therapy. 2017;6(1):81-88. 21. Babalis D, Tritakis V, Floros G, et al. Effects of ranolazine on left ventricular diastolic and systolic function in patients with chronic coronary disease and stable angina. Hjc Hellenic Journal of Cardiology. 2015;56(3):237-241. 22. Weisz G, Farzaneh-Far R, Ben-Yehuda O, et al. Use of ranolazine in patients with incomplete revascularization after percutaneous coronary intervention: design and rationale of the Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial. Am Heart J. 2013;166(6):953-959.e953.	
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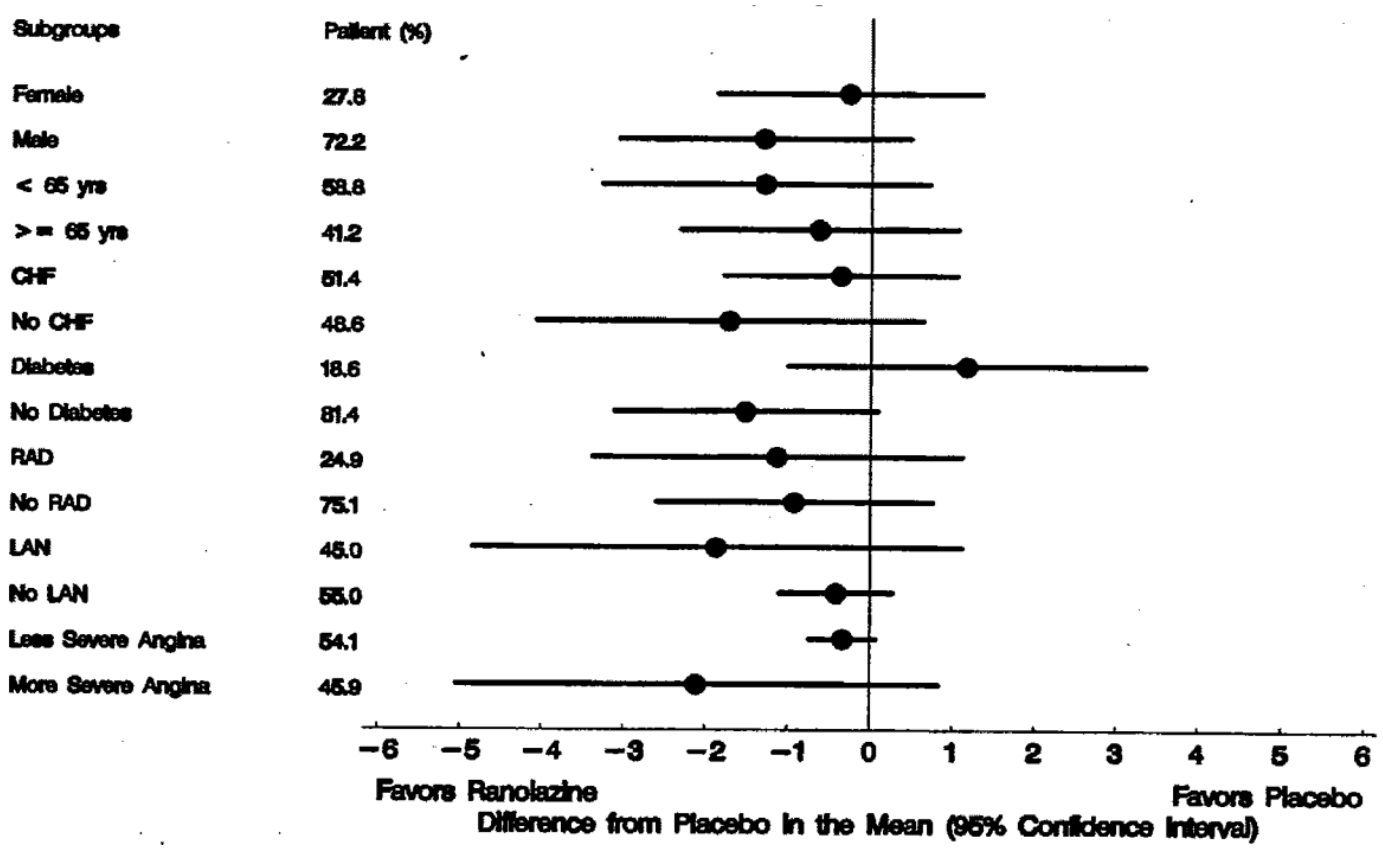
30. Gratsianskii NA. [Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. Results of CARISA]. Kardiologiia. 2004;44(3):78. 31. Arnold SV, Kosiborod M, McGuire DK, et al. Effects of ranolazine on quality of life among patientswith diabetes mellitus and stable angina. JAMA Internal Medicine. 2014;174(8):1403-1405.	Report type (letter, not English language)

Appendix 3: Detailed Outcome Data

Figure 10: Effect of Ranolazine on Weekly Angina Frequency by Subgroup From the ERICA Study — Full Analysis Set

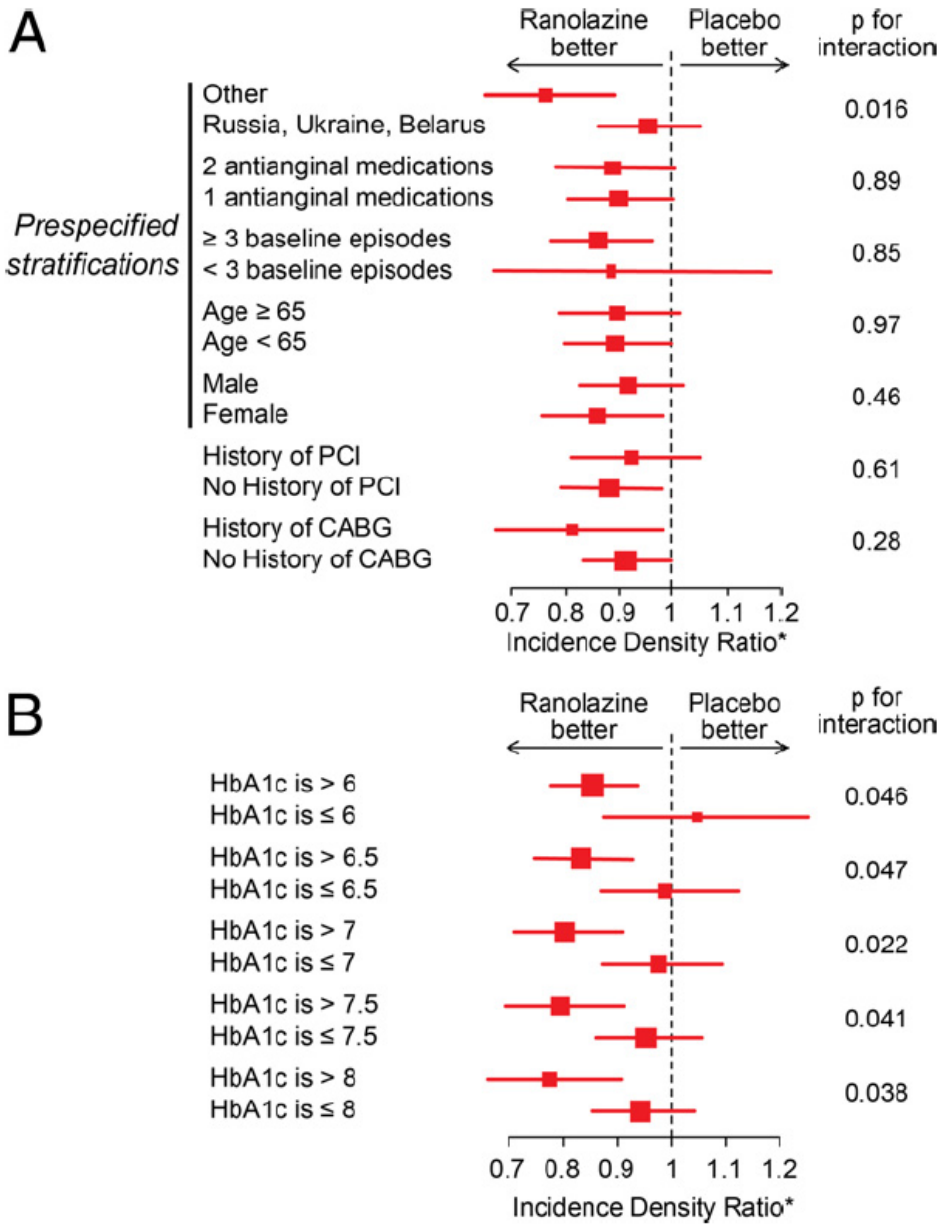


CHF = congestive heart failure; LAN = long-acting nitrate; RAD = right axis deviation; yrs = years.

Note: More severe angina refers to patients with average baseline weekly angina frequency above the study median.

Source: Reproduced from the FDA Medical Review.[15]

Figure 11: Effect of Ranolazine on Weekly Angina Frequency by Subgroup From the TERISA Study — Full Analysis Set



CABG = coronary artery bypass graft surgery; HbA1c = glycated hemoglobin; PCI = percutaneous coronary intervention.

* Incidence density ratio (or the relative difference in the incidence rates) of weekly angina frequency, according to the generalized linear model with negative binomial distribution, within pre-specified stratifications and categorical subgroups (A). B shows the exploratory analysis of subgroups of HbA1c by various thresholds.

Source: Permission obtained from the publisher to use Figure 3 from Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) by Kosiborod M, Arnold SV, Spertus JA, et al. (2013).[12]

Figure 12: Change From Baseline in Exercise Test Duration (Seconds) at Peak and Trough by Gender for the CARISA Study — Full Analysis Set LOCF

	Ran SR 750 (N=272)		Ran SR 1000 (N=261)	
peak	*Female (N=59)*	*Male (N=211)*	*Female (N=47)*	*Male (N=208)*
LS Mean Difference (SE) vs. placebo	-1.9 (22)	44.3 (12.2)	-12.7 (23.5)	35.3 (12.2)
95% CI	-45.1, 41.3	20.4, 68.2	-58.7, 33.4	11.3, 59.3
p-value	NS	<0.001	NS	0.004
trough				
	Female (N=59)	*Male (N=213)*	*Female (N=51)*	*Male (N=210)*
LS Mean Difference (SE) vs. placebo	1.3 (22.5)	28.9 (12.4)	8.6 (23.4)	26.1 (12.5)
95% CI	(-42.9, 45.5)	(4.5, 53.2)	(-37.4, 54.6)	(1.6, 50.6)
p-value	NS	0.02	NS	0.037

CI = confidence interval; LOCF = last observation carried forward; LS = least squares; NS = not statistically significant; RAN = ranolazine; SE = standard error; SR = sustained release.

Note: The mean exercise duration at baseline was not reported for these subgroups.

Source: Reproduced from the FDA Medical Review.[15]

Figure 13: Change From Baseline SAQ Domains for the ERICA Study — Full Analysis Set

SAQ score dimension	Placebo (N=281)	Ranolazine (N=277)	p-value
Angina frequency			
N	279	277	
LSM (SEM)	18.6 (1.27)	22.7 (1.25)	
LSM Difference (SEM)		4.1 (1.55)	0.008 (ANCOVA)
Physical Limitation			
N	270	269	
LSM (SEM)	6.6 (0.94)	6.9 (0.93)	
LSM Difference (SEM)		0.3 (1.15)	NS
Anginal Stability			
N	279	277	
LSM (SEM)	18.2 (1.57)	19.7 (1.57)	
LSM Difference (SEM)		1.5 (1.94)	NS
Disease Perception			
N	279	277	
LSM (SEM)	10.9 (1.14)	12.4 (1.13)	
LSM Difference (SEM)		1.5 (1.39)	NS
Treatment Satisfaction			
N	279	277	
LSM(SEM)	8.2 (0.81)	7.9 (0.80)	
LSM Difference (SEM)		-0.2 (0.99)	NS

Results confirmed by the statistical reviewer.
LSM (SEM) and LSM Difference are Least Square mean estimates from ANCOVA model. The p-values were calculated from ANCOVA testing the difference of change in SAQ scores between ranolazine and placebo treatment groups, using the baseline score and pooled center as covariates.

ANCOVA = analysis of covariance; LSM = least squares mean; NS = not statistically significant; SAQ = Seattle Angina Questionnaire; SEM = standard error of the mean.

Note: The mean exercise duration at baseline was not reported for these subgroups.

Source: Reproduced from the FDA Statistical Review.[18]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID) in the SAQ and SF-36.

Table 13: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
SAQ	Disease-specific measure of HRQoL in patients with CAD, consisting of 5 scales: "physical limitation," "anginal stability," "angina frequency," "treatment satisfaction," and "disease perception." There are 19 items in total, each scored on an ordinal scale (range: 1 to 5 or 6) from worst to best status. Scores ranging from 0 to 100 are calculated for each scale with higher scores indicating better health status.	Validity was determined to be acceptable in patients with CAD. Test-retest reliability was determined to be acceptable in patients with CAD. The SAQ was sensitive to detect change over time in patients with CAD.	The MID was identified to be a change of 10 points in patients with CAD.
SF-36	Generic, preference-based measure of HRQoL consisting of 36 items grouped into 8 domains: "physical functioning," "mental health," "social functioning," "vitality," "role physical," "role emotional," "general health," and "bodily pain." Scores ranging from 0 to 100 are calculated for each scale with higher scores indicating better health status.	The SF-36 is a validated instrument that has demonstrated acceptable test-retest reliability in populations with angina. Compared to the SAQ, the SF-36 appeared to be less sensitive to changes in HRQoL for populations with angina.	The MID was identified to be between 2.5 points and 5 points for either the PCS or MCS. No MID was identified in populations with stable angina.

CAD = coronary artery disease; MID = minimal important difference; HRQoL = health-related quality of life; MCS = mental component score; PCS = physical component score; SAQ = Seattle Angina Questionnaire; SF-36 = Short Form (36) Health Survey.

Seattle Angina Questionnaire

The SAQ is a disease-specific questionnaire used to measure health-related quality of life in patients with coronary artery disease.[28] The questionnaire is self-reported and takes less than 5 minutes to complete. The 5 scales of the SAQ measure "physical limitation" (9 items), "anginal stability" (1 item), "angina frequency" (2 items), "treatment satisfaction" (4 items), and "disease perception" (3 items). The SAQ has a total of 19 items assessed on an ordinal scale (range: 1 to 5 or 6) with lower numbers indicating a lower level of functioning. Scores are summed across items within each of the 5 scales and transformed to a score between 0 and 100 by subtracting the lowest possible score for each respective scale, dividing this value by the range of the scale, and multiplying by 100. Higher scores indicate better health status. There is no summary score for the SAQ as each scale measures a unique dimension of coronary artery disease.

During the development of the SAQ, the validity, test-retest reliability, and responsiveness were determined to be acceptable in a sample of predominantly elderly, male patients with coronary artery disease.[28]

The validity of each of the 5 scales was evaluated using the Pearson correlation coefficient (r) against external measures for each scale.[28] The "physical limitation" scale was correlated with the total exercise duration in patients undergoing the exercise treadmill test and with the Duke Activity Status Index (r = 0.43 to 0.84). The "anginal stability" scale was assessed in patients with or without unstable angina at the time of coronary angioplasty, with results showing that scores were lower in patients with unstable angina compared with those with stable angina (2-tailed t-test, P = 0.03). Among 134 patients with stable angina, anginal stability scores correlated with patients' global assessment of change after 3 months (r = 0.70). The angina frequency scale was assessed in the aforementioned patients with stable angina and scores in this scale correlated with 1-year nitroglycerin refills (r = 0.31). The treatment satisfaction scale was assessed against the American Board of Internal Medicine's Patient Satisfaction Questionnaire and showed high correlation (r = 0.67). Finally, the disease perception scale was highly correlated with the general perceptions scale of the SF-36 (r = 0.60). Overall, the validity of the SAQ was determined to be moderate to strong.

Test-retest reliability was evaluated in patients with initially stable coronary artery disease using paired t-tests and the intraclass correlation coefficient (ICC) to analyze 3-month changes in scores.[28] No statistically significant differences were noted in the 3-month period, and the ICCs were high for all scales (ICC > 0.70), except for the angina stability scale (ICC = 0.24).

The responsiveness to large clinical changes was evaluated using 2-tailed paired t-tests of baseline and 3-month follow-up scores among 45 patients (mean age = 60.2 years; proportion male = 0.87) with coronary artery disease who underwent successful angioplasty.[28] In these patients, all scales of the SAQ, except for the treatment satisfaction scale, showed dramatic improvements in the scores (P < 0.0001).

Kimble et al. investigated the reliability and validity of the SAQ in a sample of 175 women with chronic stable angina.[35] Using Cronbach alphas to determine internal consistency, the 4 scales that had more than 1 item demonstrating acceptable reliability in this population, with alpha values of 0.67, 0.69, 0.72, and 0.91 for disease perception, angina frequency, treatment satisfaction, and physical limitation, respectively. An alpha value could not be calculated for angina stability as it only had 1 item. For assessing validity, factor analysis showed that the SAQ was a valid instrument in women and that 5 factors accounted for 70.2% of its variance.

In a study by Spertus et al.,[28] patients with initially stable angina were classified into 3 groups (16 patients who improved, 117 who remained stable, and 28 who deteriorated) and paired t-tests were used to assess the 3-month mean change from baseline to estimate the MID.[28] The MID was estimated to be a change of 10 points in the SAQ score in patients with stable angina.

SF-36

The SF-36 is a 36-item, general health status questionnaire that has been used in clinical trials in many disease areas to assess the impact of disease on health-related quality of life.[29] It is a patient self-reported questionnaire consisting of 8 health domains: "physical functioning," "mental health," "social functioning," "vitality," "role physical," "role emotional,"

"general health," and "bodily pain."[30] A subscale score is calculated for each of the 8 categories. The SF-36 also provides 2 component summaries, the PCS and MCS, which are derived from aggregating the 8 domains according to a scoring algorithm. The PCS and MCS range from 0 to 100, with higher scores indicating better health status. Summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both PCS and MCS scales are transformed to have a mean of 50 and an SD of 10; all scores above or below 50 are therefore considered above or below the average of the reference population.

While assessing health-related quality of life in patients with heart disease, Dempster and Donnelly found that, although the SF-36 appeared to have good psychometric properties, it was uncertain if the instrument was sensitive to changes in this population.[36] The authors cautioned that, for patients with ischemic heart disease, the mental health and general health scales were less responsive to changes and the role emotional and role physical scales were subject to ceiling effects.

The SF-36 has previously been reported as both valid and reliable in many disease populations. In a survey of 107 patients with angina pectoris, Dougherty et al. found that, in general, the SF-36 test-retest reliability was acceptable when patients were assessed at baseline and again after 2 weeks.[37] The body pain subscale showed the lowest reliability of the 8, with an ICC of 0.35 (other subscale ICCs ranged from 0.54 to 0.84). The authors also found the SF-36 to be less responsive to changes in general health-related quality of life compared with other instruments, such as the SAQ and Quality of Life Index-Cardiac Version III, which are a disease-specific and a more global quality-of-life measure, respectively. Dougherty et al. also noted that the SF-36 was not able to discriminate among different classes of angina, nor was it sensitive to changes during the anti-anginal trial.

The MID for either the PCS or MCS has been reported to be between 2.5 points and 5 points.[31-33] No MID was identified in populations with stable angina.

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