Ranolazine as an additional antianginal therapy in patients with stable symptomatic coronary artery disease

Benjamín Sanfuentes[a,b], Juan Francisco Bulnes[b,c]

[a] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[b] Proyecto Epistemonikos, Santiago, Chile
[c] Unidad Coronaria, Hospital Dr. Sótero del Río, Santiago, Chile

***Corresponding author** jfbulnes@gmail.com

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Abstract

Introduction

There are several effective therapeutic alternatives for stable coronary artery, in terms of prevention of cardiovascular morbidity and mortality. However, the best way to achieve symptomatic control is a matter of debate, particularly in those who do not respond to first-line therapy. This summary aims to evaluate the role of ranolazine as an additional therapy to standard antianginal treatment in patients with persistent symptoms.

Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified four systematic reviews including 16 studies overall, all of which were randomized trials. We concluded additional treatment with ranolazine might decrease the frequency of anginal episodes but increase adverse effects. It probably has no effect on the risk of death or acute myocardial infarction.

Problem

Coronary artery disease includes a wide range of clinical manifestations, from acute presentations, such as myocardial infarction, to chronic conditions, such as stable coronary artery disease. The latter has a significant impact on both mortality and quality of life. There are several pharmacological alternatives with proven effect on reducing mortality - both cardiovascular and total - and improving the quality of life through symptomatic relief. However, there is a subgroup of patients that does not respond adequately to such therapy.

Ranolazine is a drug that inhibits late sodium currents that are abnormally active in the ischemic myocardiocyte. Its effect prevents intracellular calcium overload (as it is exchanged for sodium) with the consequent diastolic dysfunction that underlies the angina.

This is why it has been proposed as an effective therapeutic option in stable coronary disease with suboptimal response to conventional treatment.

Key messages

- Ranolazine might decrease the frequency of anginal episodes in stable symptomatic coronary artery disease, but the certainty of the evidence is low.
- Ranolazine probably leads to an increase in the incidence of adverse effects.
- Ranolazine probably results in little or no difference in mortality, incidence of acute myocardial infarction or quality of life in stable symptomatic coronary artery disease.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews[1-4] that included 16 primary studies reported in 19 references[5-23], all corresponding to randomized trials. However, five trials were conducted in patients without stable coronary disease (microvascular angina or acute coronary syndrome)[7,9,10,11,22]; five used ranolazine as monotherapy[12,13,14,17,23]; and two measured clinically irrelevant outcomes (time to ST segment depression and mild adverse effects)[6,16]. This table and the summary in general are based on four randomized trials that used ranolazine as an additional therapy in patients with stable coronary artery disease and reported outcomes critical for decision-making[5,8,18,20].
What types of patients were included*	All trials included symptomatic adults with coronary artery disease confirmed by angiography. One trial[20] included patients with ejection fraction less than 40%, while the remaining three excluded patients with severe heart failure (defined as NYHA functional class III or IV)[5,18,21]. All trials excluded patients with decompensated cardiac comorbidities (hypertension, pericarditis, among others) or systemic diseases (such as liver damage, chronic renal failure, diabetes). Likewise, three of the trials[5,18,21] excluded patients with a history of arrhythmia or comedication with proarrhythmic drugs. The average age of the participants ranged from 61 to 72 years in the different trials.
What types of interventions were included*	All trials used ranolazine 1 g every 12 hours. Additionally, one trial[20] used standard medical therapy with ranolazine 500 mg every 12 hours; while another trial[21] also used standard medical

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	therapy associated with ranolazine 750 mg every 12 hours. All trials compared against placebo associated with standard treatment.
What types of outcomes were measured	The outcomes were grouped by the systematic reviews as follows: • All cause mortality • Acute myocardial infarction • Quality of life (measured with different scales: Seattle Angina Questionnaire (SAQ), Rose Dyspnea Scale (RDS), Medical Outcomes Short Form-36 (SF-36) and Patient's Global Impression of Change (PGIC)). • Frequency of anginal episodes. The average follow-up of the trials was 5.75 months with a range from 9 weeks to 14 months.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information on the effects of ranolazine on symptomatic stable coronary artery disease is based on four randomized trials involving 2364 patients.

Three trials measured all cause mortality (2053 patients)[5,8,18], three measured quality of life (1533 patients) [8,18,20], two reported acute myocardial infarction (1509 patients)[5,18] and three reported the frequency of anginal episodes (2004 patients)[5,8,18].

The summary of findings is as follows:

- Ranolazine might lead to little or no difference in mortality in stable symptomatic coronary artery disease, but the certainty of the evidence is low.
- Ranolazine probably results in little or no difference in the incidence of acute myocardial infarction in stable symptomatic coronary artery disease. The certainty of the evidence is moderate.
- Ranolazine probably results in little or no difference in quality of life. The certainty of the evidence is moderate.
- Ranolazine might decrease the frequency of anginal episodes in patients with stable symptomatic coronary artery disease, but the certainty of the evidence is low.
- Ranolazine probably leads to an increase in the incidence of adverse effects. The certainty of the evidence is moderate.

Ranolazine as additional therapy in stable symptomatic coronary artery disease

Patients Patients with symptomatic coronary artery disease.
Intervention Standard medical therapy + ranolazine
Comparison Standard medical therapy + placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT ranolazine	**WITH ranolazine**		
	Difference: patients per 1000			
Mortality	6 per 1000	5 per 1000	RR 0.87 (0.25 to 3.04)	⊕⊕◯◯ Low[1,3]
	Difference: 1 patient less (Margin of error: 4 less to 12 more)			
Acute myocardial infarction	8 per 1000	6 per 1000	RR 0.7 (0.19 to 2.58)	⊕⊕⊕◯ Moderate[3]
	Difference: 2 patients less (Margin of error: 6 less to 13 more)			
Quality of life**	SMD: 0.13 worse (Margin of error: 0.05 better to 0.32 worse)		--	⊕⊕⊕◯ Moderate[2]
Frequency of anginal episodes	4.3	3.52	--	⊕⊕◯◯ Low[1,3]
	MD: 0.78 better (Margin of error: 0.27 to 1.28 better)			
Adverse effects	249 per 1000	302 per 1000	RR 1.21 (1.06 a 1.39)	⊕⊕⊕◯ Moderate[1]
	Difference: 53 patients more (Margin of error: 15 to 97 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
SMD: Standard mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT ranolazine** is based on the risk in the control group of the trials. The risk **WITH ranolazine** (and its margin of error) is calculated from relative effect (and its margin of error).
** The standardized mean difference is used when the outcome has been measured in different scales and is difficult to clinically interpret it. As a general rule, values less than 0.2 are of little clinical relevance, values of 0.5 of moderate relevance and 0.8 of important clinical relevance.

[1] The certainty of the evidence was downgraded in one level because two trials presented moderate risk of bias [8],[18].
[2] The certainty of evidence was downgraded in one level due to inconsistency, since it presents an I^2 of 58%.
[3] The certainty of the evidence was downgraded in one level due to imprecision because, when taking into account the confidence interval, it could be decided whether to use the drug or not.

Follow the link to access the interactive version of this table (Interactive Summary of Findings - iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary applies to patients with stable coronary artery disease, generally older than 60 years, who despite being in standard antianginal treatment, remain symptomatic. Standard antianginal therapy refers to the use of beta-blockers or, alternatively, non-dihydropyridine calcium channel blockers associated with a long-acting nitrate as needed.

About the outcomes included in this summary

The outcomes selected in the summary of findings table are those considered critical for decision making by the authors of the summary. They coincide with the outcomes most frequently reported by systematic reviews identified.

The quality of life outcome was measured at different scales, so the size of the effect of the intervention was calculated using the standardized mean difference.

Balance between benefits and risks, and certainty of the evidence

As reported in the summary of findings table, the use of ranolazine increases the incidence of adverse effects. In addition, the fact that the certainty of the evidence associated to the anginal episodes frequency is low, the balance between benefits and risks is unfavorable.

Resource considerations

Currently, there is no certainty that ranolazine could have a benefit on patients with stable coronary disease, since the quality of the evidence is not sufficient for the outcomes studied. Therefore, it is not possible to make an adequate cost/ benefit balance.

What would patients and their doctors think about this intervention

Considering the existing evidence, most patients and physicians should lean against the use of ranolazine in patients with stable coronary artery disease.

However, in symptomatic patients despite standard antianginal treatment, they could opt for its use. In these cases it is important to inform about the limitations of the existing evidence.

Differences between this summary and other sources

The conclusions of this summary are in agreement with those of the only review that included the four randomized trials used in our analysis[3].

Our summary is in concordance with a guideline that considers the use of ranolazine in patients who remain symptomatic with standard antianginal treatment[24]. Another guideline considers its use in patients with contraindications to other antianginal agents, although this analysis was not the goal of our summary[25].

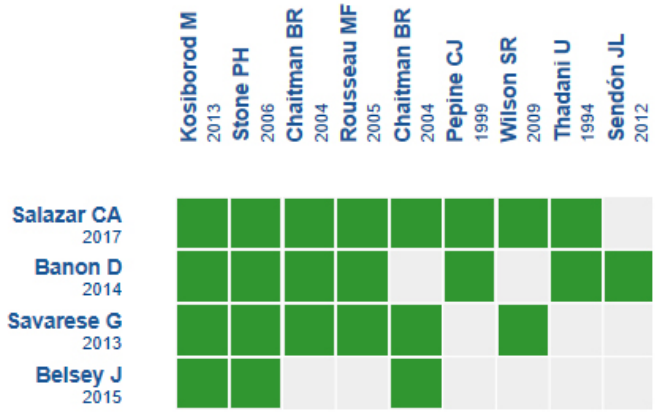
Could this evidence change in the future?

The probability that the conclusions of this summary change in the future varies depending on the outcome. For mortality and frequency of angina episodes, the probability is moderate according to the certainty of the current evidence. In turn, for the outcomes acute myocardial infarction and quality of life, the probability is low.

There are both systematic reviews[26] and ongoing randomized trials[27,28] evaluating this question, that could provide relevant additional information or greater certainty of evidence for decision-making.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Ranolazine for ischemic heart disease.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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Correspondence to
Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile