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**Abbreviated New Drug Evaluation:** Ranolazine

**Month/Year of Review:** August 2012
**Generic Name:** Ranolazine

**End date of literature search:** May 2012
**Brand Name (Manufacturer):** Ranexa® (CV Therapeutics)
**Comparator Therapies:** Long acting Nitrates, beta blocker and Calcium channel blockers

**FDA Approved Indications:** Treatment of chronic angina in combination with amlodipine, β-blockers or nitrates in patients who have not achieved an adequate response with other antianginal drugs.[1]

**Research Questions:**

- Is ranolazine more effective than other antianginal agents?
- Is ranolazine safer than other antianginal agents?
- Are there subpopulations that will benefit from ranolazine in terms of effectiveness or harms compared to other antianginal agents?

**Conclusions:**

- There is low to moderate level of evidence that ranolazine shows improved exercise duration, time to onset of angina, and time to 1 mm ST-segment depression when used with other antianginal agents such as β blockers, calcium channel blockers (CCBs) and long-acting nitrates, compared to placebo.[2–4]
- There is no data to show ranolazine improves clinical outcomes, such as reduce mortality or cardiovascular events.
- A significant concern with ranolazine is its potential for QT prolongation.
- Currently there is limited data comparing ranolazine to other currently available antianginal agents.[5] One fair quality cross over study showed immediate release ranolazine is comparable to atenolol on time to onset of angina.[6]

**Recommendations**

- Make non-preferred due to the lack of comparative effectiveness data that ranolazine is more effective or safer than other antianginal agents for managing the risk of cardiovascular events or death.

**Background/Current landscape**

Angina is a symptom of coronary artery disease, commonly known as chest pain. It is discomfort that occurs when the heart muscle is not getting enough oxygen-rich blood. There are two forms of angina – stable or unstable. Stable angina happens during physical activity or under mental or emotional stress. Unstable angina (UA) is chest pain that occurs even at rest, without apparent reason. The currently available treatment options for chronic angina include long acting nitrates, β blockers and calcium channel blockers (CCBs). These agents either decrease oxygen demand and/or increase oxygen supply. Long acting nitrates reduce cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance and dilating coronary arteries. However, the use of nitrates as first-line agents has been limited because of tolerance that develops with chronic use.[7] β-blockers reduce heart rate and contractility by competitively blocking the response to β-adrenergic stimulation in the heart. β-blockers are recommended as first-line agents in patients with stable angina since they have been shown to reduce mortality following myocardial infarction.[8] CCBs increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. CCBs also decrease cardiac oxygen demand by reducing systemic vascular resistance and arterial pressure.[5] CCBs are often used because they are presumed to have similar efficacy and fewer side effects when compared to β-blockers. However, short-acting CCBs have been shown to increase the risk of cardiac events in patients with hypertension and nifedipine has been shown to increase mortality following acute ischemic syndromes.[8] Differences in long-term rates of survival or myocardial infarction between classes of antianginal agents have not been studied.

The exact mechanism of ranolazine is unknown. According to the manufacturer, it has a different mechanism of action than other agents and does not cause hemodynamic changes such as reduction in blood pressure and heart rate.[1] The American College of Cardiology/American Heart Association guideline on unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease.[8] NICE Treatment Guidelines on Stable Angina recommend for patients who cannot tolerate β-blockers and CCBs or both are contraindicated, consider ranolazine as one of the monotherapy treatment options and for patients who are on β-blocker or CCB monotherapy whose symptoms are not controlled and the other option (CCB or β-blocker) is contraindicated or not tolerated, ranolazine can be added as one of the treatment options.[9]

**Clinical Efficacy**

Ranolazine was developed in 1985 as an immediate-release and intravenous product. CV Therapeutics submitted CARISA[3] and MARISA[2], two pivotal efficacy trials evaluating ranolazine sustained release in patients with stable exertional angina. The primary endpoint for both studies was the change from baseline, compared to placebo, in treadmill exercise test duration.

CARISA[3] was a good quality study that included 823 chronic stable angina patients, and was a randomized placebo-controlled parallel-group trial including 12 weeks of active treatment and a rebound assessment. Patients were stratified according to sub-maximal doses of background therapy with amlodipine, atenolol, or diltiazem. The primary endpoint of exercise duration at trough showed a significant improvement in ranolazine 750mg twice daily ($p = 0.03$) and 1000 mg twice daily ($p = 0.03$) compared to placebo beginning after 2 weeks, However, the effect was modest (23.7 and 24 seconds compared to 750mg and 1000mg, respectively) and was not consistently significantly different when analyzed by subgroups. The improvement in exercise tolerance test for women was about 33% of that in men. Ranolazine reduced the mean (SE) angina attacks per week from 3.3 (0.3) for placebo to 2.5 (0.2) for ranolazine 750mg ($p=0.006$) to 2.1 (0.2) for ranolazine 1000mg ($p<0.001$).

MARISA[2] was a 4-period placebo-controlled poor quality, crossover study of 191 patients with chronic stable exertional angina responding to antianginal therapy. 175 patients were included in the near/all completer population and 185 patients in the intention to treat (ITT) population. Pooling data from all

periods, the trial reported improvements for exercise duration (p<0.001), time to angina (p<0.001), and time to onset of 1mm ST depression (p<0.001), with all doses of ranolazine compared to placebo. The trial has poor quality rating due to major study flaws such as lack of interim washout between treatment periods, lack of baseline measurements for each period, presence of treatment-by-period interaction and possible carryover effect. In addition, the analysis population only included the patients who completed at least 3 of their 4 double blinded study periods, hence the analysis was not true ITT as it was reported.

ERICA[4] was a fair quality clinical trial studying the efficacy of the SR formulation of ranolazine. It was a placebo control, randomized in patients with persisting symptoms despite maximum recommended dose of amlodipine. A total of 565 patients were randomized: 281 patients to ranolazine and 284 patients to placebo. The average weekly rate of angina attacks in ranolazine – versus placebo-treated patients was significantly lower (trimmed mean2.88 ± 0.19 on ranolazine vs. 3.31 ± 0.22 on placebo; p = 0.028) and weekly nitroglycerin consumption was also significant less in ranolazine group (2.03 ± 0.20 on ranolazine vs. 2.68 ± 0.22; p = 0.014). The treatment effect appeared consistent across subgroups.

RAN 80[6] was a double-blind crossover of 158 patients with chronic stable angina responding to therapy. Patients were randomized to ranolazine IR 400mg three times a day, atenolol 100mg once daily, and placebo three times a day. There was no washout between treatment periods. Significant improvements in peak exercise duration by treadmill or bicycle testing was seen with ranolazine (51.0 sec; 95% CI 34.2 – 67.8, p< 0.001) and atenolol (39.5 sec; 95% CI 22.7 -56.3, P < 0.001) compared to placebo, but not between the active-treatments (11.4 sec; 95% CI -5.4 to 28.2;p= NS). The study used immediate release formulation of ranolazineand the duration was short term at 4 weeks.

**Comparative Clinical Efficacy**

**Relevant Endpoints: 1) All cause Mortality**

**2) MI**

**3) Tolerability**

**Study Endpoints: 1) Exercise duration**

**2) Time to onset of angina**

**3) Time to 1mm ST depression**

**4) Number of angina attacks per week**

**5) Number of NTG consumption**

## Evidence Table

| Ref./ Study Design[1] | Drug Regimens | Patient Population | N | Duration | Efficacy Results[2] (CI, p-values) | ARR / NNT[3] | Safety Results^ (CI, p-values) | ARR / NNH | Quality Rating[4]; Comments |
|---|---|---|---|---|---|---|---|---|---|
| **CARISA[3] (Combination Assessment of Ranolazine in Stable Angina)** | | | | | | | | | |
| Chaitman et al<br><br>DB, PC, RCT; PG | R1: 750mg ranolazine BID<br>R2: 1,000mg ranolazine BID<br>P: placebo | Mean age (P/R1/R2): 63.7/64.3/63.9<br><br>Male (P/R1/R2): 75.1%/77.8%/79.6<br><br>Background antiangina Drug (P/R1/R2):<br>Atenolol – 43.9%/42.7%/42.6%<br>Amlodipine – 30.1%/30.8%/32.4%<br>Diltiazem – 26%/26.5%/25.1%<br><br>Angina frequency (attacks/wk; P/R1/R2): 4.6/4.3/4.7<br><br>NTG use (tablet/wk; P/R1/R2): 4.0/4.0/3.7 | N= 823<br>P: 269<br>R1: 279<br>R2: 275 | 12 weeks followed b long term open-label study up to 39 months | <u>Exercise duration at trough ranolazine level on treadmill - 1° end point (P/R1/R2 in seconds):</u><br>Change from baseline – 91.7/115.4/140.3<br>Difference from placebo:<br>R1: 23.7 (p = 0.03)<br>R2: 24.0 (p = 0.03)<br><br><u>Time to onset of angina at trough ranolazine level - 2° end point (P/R1/R2 in seconds):</u><br>Change from baseline – 114.3/144.0/140.3<br>Difference from placebo:<br>R1: 29.7 (P = 0.01)<br>R2: 26.0 (p = 0.03)<br><br><u>Time to ECG ischemia at trough ranolazine level - 2° end point (P/R1/R2 in seconds):</u><br>Change from baseline – 125.1/145.1/146.2<br>Difference from placebo:<br>R1: 19.9 (p = 0.10)<br>R2: 21.1 (p = 0.09)<br><br><u>Angina attack frequency (2° end point):</u><br>Difference from placebo:<br>R1: 0.8 attacks/wk (p = 0.006)<br>R2: 1.2 attacks/wk (p < 0.001) | NA | Any events (P/R1/R2): 26.4%/31.2%/32.7% (CI , p not reported)<br><br>The most common dose-related ADEs: dizziness, constipation, nausea and asthenia.<br><br>QT prolongation:<br>P: 421.5 mSec.<br>R1: 427.6 mSec.<br>R2: 430.7 mSec. (p<0.001)<br><br>Mortality:<br>P: 1.1% (3/269)<br>R1: 0.7% (2/279)<br>R2: 0.4% (1/275) | **NA** | Good<br>Internal Validity Review of Bias:<br><u>Selection:</u> Low bias; the randomizatio and allocation concealment was clear.<br><u>Performance:</u> Low bias; blinding of patients and study monitors<br><u>Attrition:</u> Relatively low attrition at 10.4% from all study groups. The reasons for drop out were not explained. ITT analysis.<br><br>External Validity Review of Bias:<br><u>Patient characteristics:</u> There were smaller number of patients in placebo group who had CABG, but not statistically significant.<br><u>Setting:</u> The method of recording angina attacks was not reported.<br><u>Outcomes:</u> The study was not designed to show the clinical outcomes such as MI, mortality as primary endpoint. |

| **ERICA[4] (Efficacy of Ranolazine In Chronic Angina trial)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Stone et al<br><br>DB, PC, PG; RCT | R: 1,000mg ranolazine with amlodipine 10mg daily<br>P: Placebo with amlodipine 10mg daily | Stable patients with CAD and ≥ 3 anginal attacks/wk despite of max. dose of amlodipine at 10mg/day.<br><br>Mean age: (P/R): 62.0/61.3<br><br>Gender Male% (P/R): 73%/72%<br><br>Baseline weekly angina attacks (P/R): 5.68/5.59<br><br>Previous CABG (P/R): 12%/10%<br><br>Previous PCI (P/R): 9%/12% | N = 565<br>R: 281<br>P: 284 | 6 weeks | <u># of Angina attacks per week trimmed mean ± SE (1° end point):</u><br>R: 2.88 ± 0.19<br>Placebo: 3.31 ± 0.22<br>P = 0.028<br><br><u>Weekly NTG consumption trimmed mean ± SE (2° end point) :</u><br>R: 2.03 ± 0.20<br>Placebo: 2.68 ± 0.22<br>P = 0.01<br><br><u>Seattle Angina Questionnaire (SAQ) scores on in 5 dimensions: angina frequency, physical limitations, angina stability, disease perception, and treatment satisfaction (2° end point) :</u><br>Out of 5 dimensions, only scores in angina frequency dimension is statically significant:<br>R: 18.5 ±18.8<br>Placebo: 22.5 ± 19.0<br>P = 0.008 | <u>NA</u><br><br>NA | Any ADEs: (CI and p value not reported<br>R: 39.9%<br>P: 35.3%<br><br>Other common ADEs ( R/P):<br>Constipation: 8.9%/ 1.8%<br>Peripheral edema: 5.7%/2.8%<br>Dizziness: 3.9%/2.5%<br>Nausea: 2.8%/0.7%<br>Headache: 2.8%/2.5%<br><br>Discontinuation due to ADEs<br>R: #3 pts<br>Placebo: #4 pts | NA | Fair<br>Internal Validity Review of Bias:<br><u>Selection:</u> Low bias; the randomizatio and allocation concealment was clear<br><u>Performance:</u> Low bias; blinding of patients and study monitors.<br><u>Attrition:</u> Low attrition at 2% from all study groups. It appears to be ITT analysis.<br>• Subgroup analysis performed for baseline characteristics and treatment results.<br>•<br>External Validity Review of Bias:<br><u>Setting:</u><br>• Study design is multi-national. SAQ was not culturally and linguistically validated in the locations where th trial took place.<br>• Level of activities were not controlled or tested, the weekly angina attacks could be due to activity levels vs. drug effect.<br><u>Outcomes:</u><br>• The use of patient anginal diaries rather than ambulatory Holter monitors to detect episodes of ischemia added a subjective component to the design.<br>• Short term study for a chronic disease. Ranolazine long term benefit remains unclear. |

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|---|---|---|---|---|---|---|---|---|---|
| Rousseau et al[6]<br><br>DB, MC, PC, XO | R: 400mg ranolazine IR 3 times a day<br>AT: atenolol 100mg daily<br>Placebo | Patients with well documented CAD and chronic angina who were on standard doses of atenolol<br><br>Mean age: 59 ± 8<br><br>Male: 89% | N = 158 | 21 – 30 days | Time increase to onset of angina (1° end point):<br>R vs. Placebo: 51.0 sec. (34.2 – 67.8) p< 0.001<br>AT vs. placebo: 39.5 sec. (22.7 -56.3) P < 0.001<br>R vs. AT: 11.4 (-5.4 to 28.2); NS<br><br>Time increase to 1 mm ST-segment depression (2° end point):<br>R vs. Placebo: 52.6 sec. (34.8 – 70.5) p < 0.001<br>AT vs. placebo: 51.0 sec. (33.1 – 68.9) p < 0.001<br>R vs. AT: 1.6 sec. (-16.3 to 19.6) NS<br><br>Increase in exercise duration (2° end point):<br>R vs. Placebo: 37.1sec. (22.2 – 52.0) P< 0.001<br>AT vs. Placebo: 16.0 sec. ( 1.1 – 30.9) p < 0.04<br>R vs. AT: 21.1 sec. (6.2 – 36.0), p = 0.006 | NA | Any ADEs (R/AT/Placebo): 29%/25%/17% (CI and p value not reported)<br><br>Common ADEs (R/AT/Placebo):<br>Asthenia: 12.3/16.9%/2.6%<br>Dizziness: 1.3%/5.8/2.6%<br>Nausea: 3.9%/0/3.2%<br>Constipation: 3.2%/0/0.6%<br><br>Discontinuation due to ADEs<br>R: #2 patients<br>AT: None<br>Placebo: #2 patients | NA | Fair<br>Internal Validity Review of Bias:<br>Selection: potential bias; the randomization and allocation concealment were not reported among 6 possible treatment sequences.<br>Performance: potential bias; despite of the reported blinding of patients and study monitors, ranolazine, atenolol and placebo were dosed at different frequency.<br>Attrition: Low attrition<br><br>External Validity Review of Bias:<br>Setting:<br>• Study used immediate release form of ranolazine with 3 times daily dose vs. atenolol and placebo once daily dose.<br>• Two exercise protocols were used among study centers.<br>• There was no washout between treatment periods.<br>Outcomes:<br>• Short term study for a chronic disease. Ranolazine long term benefit remains unclear. |

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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**Appendix A: Specific Drug Information**

**CLINICAL PHARMACOLOGY** [1]

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current (INa). However, the relationship of this inhibition to angina symptoms is uncertain.

**DRUG SAFETY**[1]

*Serious (REMS, Black Box Warnings, Contraindications)*: No listed BBW. Ranolazine is contraindicated in patients 1) taking strong inhibitors of cytochrome P450 3A (CYP3a); 2) taking inducers of CYP3A; and 3) with liver cirrhosis. Ranolazine has been shown to prolong the QT interval in a dose-dependent manner. However, clinical experience in patients with acute coronary syndrome did not show an increased risk of proarrhythmia or sudden death. In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on ranolazine than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. Ranolazine has precautions on QT prolongation.

*Tolerability:* At recommended doses, about 6% of patients discontinued treatment with Ranexa because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on ranolazine than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

*Pregnancy/Lactation rating:* C. There are no adequate well-controlled studies in pregnant women. Ranolazine should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

*Look-alike / Sound-alike (LA/SA) Error Risk Potential*

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

| NME Drug Name | Lexi-Comp | USP Online | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|---|
| LA/SA for ranolazine [generic] | None | None | None | None | Ranitidine, ranibizumab |
| LA/SA for Ranexa®[brand] | None | None | None | None | Pradexa®, Krystexxa® |

**ADVERSE REACTIONS (incidence > 0.5%)**[1]

| Adverse Events | Incidence % |
|---|---|
| **Cardiaovascular** | |
| Bradycardia | 0.5 – 2.0 |
| Hypotension/orthrostatic hypotension | 0.5 – 2.0 |
| Palpitations | 0.5 – 2.0 |
| QT prolongation | NR |
| **Central Nervous System** | |
| Dizziness | 6.2 |
| Headache | 5.5 |
| Vertigo | 0.5 – 2.0 |
| **Gastrointestinal Disorders** | |
| Abdominal pain | 0.5 – 2.0 |
| Constipation | 4.5 |
| Dry mouth | 0.5 – 2.0 |
| Nausea | 4.4 |
| Vomiting | 0.5 – 2.0 |
| **Respiratory** | |
| Dyspnea | 0.5 – 2.0 |
| **Other** | |
| Peripheral edema | 0.5 – 2.0 |
| Tinitus | 0.5 – 2.0 |

**DOSE & AVAILABILITY:**[1]

| STRENGTH | FORM | ROUTE | FREQUENCY | RENAL ADJ | HEPATIC ADJ | Pediatric Dose | Elderly Dose | OTHER DOSING CONSIDERATIONS |
|---|---|---|---|---|---|---|---|---|
| 500mg, 1,000mg | Tablet, Extended release | Oral | Twice daily | Not defined. | Contraindicated in patients with liver cirrhosis | Not been established. | Same as adult dose, start at the low end of the dosing range. | • The tablet should not cut/crushed/chew. |

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**PHARMACOKINETICS:**[1]

| Parameter | Result |
|---|---|
| Oral Bioavailability | 76% |
| Tmax | 2-5 hours |
| Protein Binding | Approximately 62% |
| Elimination | Approximately 75% of dose is excreted in urine and 25% in feces |
| Half-Life | Ranging from 6 to 22 hours |
| Metabolism | Metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites has not been well characterized. |

**ALLERGIES/INTERACTIONS:**[1]

*Drug-Drug*: Ranolazine is almost completely metabolized by the cytochrome P450 (CYP) isoenzyme system. Therefore the potential for numerous drug interactions does exist. As such, other strong CYP3A inhibitors should not be coadministered.

*Food-Drug*: Grapefruit juice or grapefruit containing products.

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