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## Drug Class Literature Scan: Antianginals

Date of Review: August 2026

Literature Search: 01/01/2021 – 05/12/2026

Date of Last Review: May 2017

### Current Status of PDL Class:

See **Appendix 1**.

### Plain Language Summary:

- New studies were searched to find new information for medicines used in the treatment of chest pain commonly known as angina.
- For people with continuing angina symptoms, treatment focuses on easing chest pain and lowering the risk of heart attack.
- There are many different medicines that can be used to treat angina:
  - Nitrates such as nitroglycerin help relax blood vessels and may be used for quick relief of chest pain episodes.
  - Longer-acting nitrates like isosorbide mononitrate or other medicines called calcium channel blockers can be added if chest pain symptoms continue.
  - Beta-blockers are medicines used to slow the heart and reduce its work.
  - Ranolazine is a medicine that is sometimes added when other medicines do not work well enough or if a person cannot tolerate other medicines.
- Current clinical practice guidelines do not strongly favor one type of drug (e.g. nitrates, calcium channel blockers, beta blockers, etc.) for all patients with chronic stable angina.
- Based on new studies found, no new changes to the Oregon Health Plan (OHP) preferred drug list are recommended.

### Conclusions:

- Clinical practice guidelines do not recommend one drug in the antianginal drug class over another due to insufficient comparative evidence. Guidelines for chronic coronary disease from the 2024 European Society of Cardiology (ESC) and AHA/ACC/ACCP/ASPC/NLA/PCNA recommend individualized agent selection based on comorbidity and tolerability.<sup>1,2</sup>
- Ranolazine (ASPRUZYO) is a new extended-release drug formulation supplied in oral granule sachets indicated for the treatment of adult patients with chronic stable angina pectoris.<sup>3</sup>
- Three new comparative RCTs were identified. One trial compared long acting cilostazol versus isosorbide mononitrate for patients with vasospastic angina;<sup>4</sup> the second trial compared ranolazine versus allopurinol for eligible symptomatic patients with a history of angioplasty;<sup>5</sup> and the third trial compared combination therapy with nicardipine and isosorbide dinitrate to prevent spasm in transradial percutaneous coronary intervention.<sup>6</sup>
- Two new FDA safety updates pertaining to antianginal agents were identified.<sup>7</sup>
- No new evidence was identified that would strengthen evidence of these drugs in populations based on demographic characteristics such as race, ethnicity, age or socioeconomic status.

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**Recommendations:**

- No changes to the preferred drug list (PDL) are recommended based on the evidence.
- Evaluate costs in executive session.

**Summary of Prior Reviews and Current Policy:**

Angina management includes a wide variety of classes depending upon the underlying cause. Current first-line treatments for angina include beta-blockers (e.g. , calcium channel blockers, or long-acting nitrates). If a patient is still symptomatic after treatment with one first-line agent, a second first-line agent from a different therapeutic class may be added. Ranolazine should be reserved for add-on therapy when a patient is symptomatic despite treatment with a beta blocker, CCB, or a long-acting nitrate. Short acting nitroglycerin should remain available for the immediate relief of angina in patients with stable ischemic heart disease.<sup>8</sup>

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Angina management includes a wide variety of testing, procedures, and drugs from different classes depending upon the underlying cause. This review will focus on antianginal drug therapy with nitrates. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

No new high-quality systematic reviews were identified. Three systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcomes studied (e.g., non-clinical).<sup>9-11</sup>

**New Guidelines:**

2024 European Society of Cardiology (ESC) Guidelines for the Management of Chronic Coronary Syndromes:<sup>1</sup>

Angina Management: Key ESC Guideline Recommendations and Evidence Summary:

Category	Drug(s)	When to Use / Key Points	Class	Level
Core principle	All antianginal therapy	Tailor to HR, BP, comorbidities, tolerability, and angina mechanism	I	C
First line therapy	Beta blockers (metoprolol, atenolol, carvedilol)	Main initial therapy for symptom control	I	B
	Calcium channel blockers (amlodipine, diltiazem, verapamil)	Alternative or combined with BB depending on HR/BP	I	B
<b>Rapid symptom relief</b>	<b>Short acting nitrates (sublingual nitroglycerin)</b>	<b>Immediate relief of acute angina episodes</b>	<b>I</b>	<b>B</b>
Combination therapy	BB + DHP CCB (e.g., metoprolol + amlodipine)	If symptoms persist on single agent	IIa	B
<b>Second line / add on</b>	<b>Long-acting nitrates (isosorbide mono/dinitrate)</b>	<b>Add if symptoms persist on BB/CCB or use in selected patients</b>	<b>IIa</b>	<b>B</b>
	<b>Ranolazine</b>	<b>Add-on or alternative, especially if low HR/BP limits other drugs</b>	<b>IIa</b>	<b>B</b>
<b>Nitrate strategy</b>	<b>Long-acting nitrates</b>	<b>Use daily nitrate free interval to prevent tolerance</b>	<b>IIa</b>	<b>B</b>
Heart-rate-specific therapy	Ivabradine	For LVEF <40% with persistent symptoms despite therapy	IIa	B
Avoid misuse	Ivabradine	Not recommended if LVEF >40% without HF	III	B
Drug interaction caution	Ivabradine + verapamil/diltiazem	Avoid combination (↑ bradycardia risk)	III	B
<b>Contraindication</b>	<b>Nitrates + PDE 5 inhibitors (e.g., sildenafil)</b>	<b>Avoid due to severe hypotension risk</b>	<b>III</b>	<b>B</b>
	<b>Nitrates in hypertrophic cardiomyopathy</b>	<b>Avoid due to potential worsening obstruction</b>	<b>III</b>	<b>B</b>

Key: BB=beta blockers; BP=blood pressure; CCB=calcium channel blockers; DHP=dihydropyridine; LVEF=left ventricular ejection fraction; HF=heart failure

Class of recommendation (strength of recommendation)	Level of evidence (quality of evidence)
Class I: Strong evidence (beneficial)	Level A: High-quality evidence from multiple randomized trials or meta-analyses  Level B: Moderate evidence from a single RCT or large non-randomized studies
Class II: Weaker evidence or less agreement (reasonable)	
Class IIa: Weight of evidence favors benefit	
Class IIb: Benefit less well established	
Class III: Not useful or potentially harmful	

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Disease:<sup>2</sup>

*Pharmacologic Therapy for Angina: Evidence-Based Recommendations*

Pharmacologic management of chronic angina is directed toward relief of ischemic symptoms and improvement in functional status and quality of life. Recommendations are graded according to strength (Class of Recommendation) and quality (Level of Evidence). Therapy should be implemented in a stepwise, individualized manner, with escalation based on symptom burden and treatment tolerance.

<b>First-Line Antianginal Therapy</b>	<b>Second Line and Adjunctive Therapy</b>
<b>Beta-blockers, CCBs, or long-acting nitrates</b>	<b>Ranolazine:</b>
Strength: Class I; Quality: Level B-R	Strength: Class I; Quality: Level B-R
<ul style="list-style-type: none"> <li>Recommended as initial antianginal therapy to reduce symptom frequency and improve exercise tolerance.</li> <li>Selection should be individualized based on comorbid conditions (e.g., beta-blockers in prior myocardial infarction; CCBs in vasospastic angina).</li> </ul>	<ul style="list-style-type: none"> <li>Recommended for relief of angina symptoms, particularly in patients:                             <ul style="list-style-type: none"> <li>-With persistent symptoms despite first-line therapy; or</li> <li>-Who are unable to tolerate further titration of heart rate– or blood pressure–lowering agents.</li> </ul> </li> <li>Provides symptomatic benefit through metabolic modulation (late sodium current inhibition) without significant effects on heart rate or blood pressure.</li> </ul>
<b>Short-acting nitrates (e.g., sublingual nitroglycerin):</b>	
Strength: Class I; Quality: Level B-NR	
<ul style="list-style-type: none"> <li>Indicated for rapid relief of acute anginal episodes.</li> <li>Should be prescribed to all patients with angina for on-demand symptom control.</li> </ul>	

**Escalation of Therapy for Persistent Symptoms:**

**Combination antianginal therapy (agents from different classes)**

Strength: Class I; Quality: Level B-R

- Recommended in patients with persistent angina despite monotherapy.
- Drug selection should consider hemodynamic effects and avoid contraindicated combinations (e.g., beta-blockers with non-dihydropyridine CCBs in patients with bradycardia or conduction disease).

**Therapies Not Recommended:**

- Ivabradine (in patients with normal left ventricular systolic function):  
Strength: Class III (Harm); Quality: Level B R
- Not recommended due to lack of benefit and increased risk of adverse outcomes.

*Interpretation of Recommendation Grading*

Strength of Recommendation (Class)	Quality of Evidence (Level)
Class I: Strong recommendation; benefit greatly outweighs risk; intervention should be performed	Level A: High-quality evidence from multiple randomized trials/meta-analyses
Class IIa: Moderate recommendation; benefit > risk; intervention is reasonable	Level B-R: Moderate-quality evidence from randomized trials
Class IIb: Weak recommendation; benefit ≥ risk; intervention may be considered	Level B-NR: Moderate-quality evidence from nonrandomized studies
Class III: No benefit or harm; intervention should not be performed	Level C: Limited evidence/expert opinion

**New Formulations:**

ASPRUZYO (ranolazine) is a new drug formulation indicated for the treatment of adult patients with chronic stable angina pectoris.<sup>3</sup> ASPRUZYO's unique attribute is its extended-release oral granule formulation, enabling controlled ranolazine delivery via aqueous dispersion, soft-food admixture, or enteral tube administration.<sup>3</sup> Ranolazine selectively inhibits the late inward sodium current (I<sub>NaL</sub>), reducing intracellular Na<sup>+</sup> and secondary Ca<sup>2+</sup> overload to improve diastolic relaxation and limit ischemia.<sup>3</sup> Key safety considerations include dose-dependent QT-interval prolongation and significant CYP3A-mediated drug-interaction potential, with avoidance recommended in moderate–severe hepatic impairment.<sup>3</sup>

**New FDA Safety Alerts:****Table 1. Description of New FDA Safety Alerts.<sup>7</sup>**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
isosorbide dinitrate/hydralazine	BIDIL	3/2019	Contraindications	-Do not use BiDil™ in patients who are taking PDE-5 inhibitors, such as avanafil, sildenafil, tadalafil, or vardenafil. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia. -Do not use BiDil™ in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension.
nitroglycerin	NITROMIST	6/2022	Contraindications  Warnings	NitroMist™ is contraindicated in patients with acute circulatory failure or shock.  Patients who may be volume-depleted or who are already hypotensive are at increased risk of symptomatic hypotension.

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## Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
isosorbide dinitrate	ISOSORBIDE DINITRATE	TABLET	Y
isosorbide mononitrate	ISOSORBIDE MONONITRATE	TABLET	Y
nitroglycerin	NITRO-DUR	PATCH TD24	Y
nitroglycerin	NITROGLYCERIN PATCH	PATCH TD24	Y
nitroglycerin	NITROGLYCERIN	TAB SUBL	Y
nitroglycerin	NITROSTAT	TAB SUBL	Y
isosorbide dinit/hydralazine	BIDIL	TABLET	N
isosorbide dinit/hydralazine	ISOSORBIDE DINIT-HYDRALAZINE	TABLET	N
isosorbide dinitrate	ISOSORBIDE DINITRATE	TAB SUBL	N
isosorbide mononitrate	ISOSORBIDE MONONITRATE	TAB ER 24H	N
isosorbide mononitrate	ISOSORBIDE MONONITRATE ER	TAB ER 24H	N
nitroglycerin	NITRO-BID	OINT. (G)	N
nitroglycerin	NITROGLYCERIN	OINT. (G)	N
nitroglycerin	NITROGLYCERIN	SPRAY	N
nitroglycerin	NITROLINGUAL	SPRAY	N
ranolazine	RANOLAZINE ER	TAB ER 12H	N

## Appendix 2: New Comparative Clinical Trials

A total of 58 citations were manually reviewed from the initial literature search. After further review, 56 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). Abstracts of the remaining trials are summarized below.

### Long-acting cilostazol versus isosorbide mononitrate for patients with vasospastic angina: a randomized controlled trial.<sup>4</sup>

**Background:** Cilostazol has a vasodilatory function that may be beneficial for patients with vasospastic angina (VSA). We conducted a randomized, open-label, controlled trial to compare the efficacy and safety of long-acting cilostazol and isosorbide mononitrate (ISMN) for VSA.

**Methods:** The study included patients with confirmed VSA between September 2019 and May 2021. Participants were randomly assigned to receive long-acting cilostazol (test group, 200 mg once daily) or conventional ISMN therapy (control group, 20 mg twice daily) for 4 weeks. The clinical efficacy and safety were evaluated using weekly questionnaires.

**Results:** Forty patients were enrolled in the study (long-acting cilostazol, n = 20; ISMN, n = 20). Baseline characteristics were balanced between the two groups. Long acting cilostazol showed better angina symptom control within the first week compared to ISMN [reduction of pain intensity score, 6.0 (4.0-8.0) vs. 4.0 (1.0-5.0), P = 0.005; frequency of angina symptom, 0 (0-2.0) vs. 2.0 (0-3.0), P = 0.027, respectively]. The rate of neurological adverse reactions was lower in the cilostazol group than in the ISMN group (headache or dizziness, 40 vs. 85%, P = 0.009; headache, 30 vs. 70%, P = 0.027).

**Conclusion:** Long-acting cilostazol provided comparable control of angina and fewer adverse neurologic reactions within 4 weeks compared to ISMN. Long-acting cilostazol provides more intensive control of angina within 1 week, suggesting that it may be an initial choice for the treatment of VSA.

### **Ranolazine Versus Allopurinol for Eligible Symptomatic Patients With a History of Angioplasty: Comparative Efficacy Study<sup>5</sup>**

**Background:** Recurrent angina, which is defined as a return of chest pain or chest discomfort, occurs in many patients undergoing coronary interventions.

**Objective:** This study aims to compare the antianginal efficacy of ranolazine versus allopurinol for eligible symptomatic patients with a history of angioplasty.

**Methods:** A total of 62 eligible symptomatic patients with a history of angioplasty were randomly allocated into two groups. For group A, 300 mg of allopurinol was administered twice daily, while for group B, 1000 mg of ranolazine daily was prescribed for a duration of 4 weeks. An initial screening visit was done for all participants where patients' medical history was recorded and a physical examination was given; electrocardiography, blood pressure, and heart rate measurements were done as well. The patients were also given a blood and exercise test. At the end of the medication period, participants were revisited, and the tests were done again. All the required data were collected via a researcher-made form, and data analysis was conducted using SPSS. The study was approved by a formal ethics committee.

**Results:** The mean age of participants in the two groups (A and B) was 57.36 (SD 8.36) and 60.27 (SD 9.17) years, respectively. Among the 62 patients, 34 (59%) were men, while 28 (41%) were women. Creatinine, fasting blood sugar, C-reactive protein, N-terminal prohormone of brain natriuretic protein, uric acid, white blood cell, and hemoglobin levels of participants were not significantly different between groups ( $P > .05$ ). Both allopurinol and ranolazine increased the total exercise time and decreased the ST depression of the patients. Additionally, they both improved the chest pain severity and Duke Treadmill Score of patients. At the same time, ranolazine had a statistically greater effect on ST depression reduction (mean 2.64, SD 0.74 vs mean 1.57, SD 0.49), while allopurinol showed better efficacy in reducing chest pain severity (mean 1.86, SD 0.37 vs mean 0.59, SD 0.21) and the Duke Treadmill Score (mean -14.77, SD 3.65 vs mean -6.88, SD 1.93).

**Conclusions:** Based on the results, the antianginal efficacy of allopurinol and ranolazine was approved but with different effects on ST depression, chest pain severity, and the Duke Treadmill Score. Therefore, the precise differences in their effects need to be explored further.

### **Combination Therapy With Nicardipine and Isosorbide Dinitrate to Prevent Spasm in Transradial Percutaneous Coronary Intervention (from the NISTRA Multicenter Double-Blind Randomized Controlled Trial)<sup>6</sup>**

**Background:** Verapamil and nitroglycerin are widely used to prevent radial artery spasm (RAS) during percutaneous cardiovascular procedures. However, these agents are not typically available in most African countries and consequently, isosorbide dinitrate is often the only spasmolytic treatment.

**Objective:** Our aim was to compare the efficacy of isosorbide dinitrate alone versus isosorbide dinitrate used together with nicardipine to prevent RAS during transradial coronary procedures.

**Methods:** This was a randomized controlled double-blind multicenter trial. Patients ( $n = 1,523$ ) were randomized to receive either a sole therapy of isosorbide dinitrate ( $n = 760$ ) or the combination of isosorbide dinitrate and nicardipine ( $n = 763$ ). Our primary end point was the occurrence of RAS; defined as considerable perceived hindrance of catheter advancement. Our secondary end points were severe RAS; defined as (1) severe arm pain, (2) the need for either morphine or midazolam treatment, and (3) necessity for crossover to the contralateral radial or femoral artery.

**Results:** RAS incidence was reduced with the combination therapy versus isosorbide dinitrate alone (15% vs 25%,  $p < 0.001$ ), with a number needed to treat of 10 patients. There was also a significant reduction in the incidence of the secondary end points with combination therapy (3.6% vs 8.2%,  $p < 0.001$ ), with a number needed to treat of 22 patients. This result was driven by reductions in both femoral crossover (0.5% vs 2.4%,  $p = 0.003$ ) and the use of morphine or midazolam injections (1.6% vs 3.5%,  $p = 0.02$ ) with combination therapy.

**Conclusion:** In conclusion, we demonstrated the superiority of the combination therapy of isosorbide dinitrate and nicardipine over isosorbide dinitrate alone in reducing the incidence of RAS.

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## Appendix 1: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to May 12, 2026

- 1 exp Isosorbide Dinitrate/3598
- 2 isosorbide mononitrate.mp./458
- 3 exp Nitroglycerin/12892
- 4 isosorbide dinitrate hydralazine.mp./39
- 5 exp Ranolazine/827
- 6 antianginals.mp./52
- 7 exp Angina Pectoris/ or angina.mp./78807
- 8 1 or 2 or 3 or 4 or 5 or 6/16845
- 9 7 and 8 /3695
- 10 limit 9 to (english language and humans and yr="2021 -Current")/58

## Appendix 2: Key Inclusion Criteria

<b>Population</b>	People with angina
<b>Intervention</b>	Drugs from antianginal PDL class (nitrates, ranolazine)
<b>Comparator</b>	Placebo or active treatment
<b>Outcomes</b>	Mortality, cardiovascular morbidity (angina pectoris, acute myocardial infarction, etc.), adverse events from treatment
<b>Timing</b>	Not applicable
<b>Setting</b>	Outpatient