

Month/Year of Review: November 2014
PDL Classes: Anti-anginals, Cardiovascular

Date of Last Review: June 2012
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Table 1. Current Status of PDL Class.¹

Current Preferred Agents	Current Non-Preferred Agents
Nitrates	
Isosorbide dinitrate capsule (<i>Dilatrate-SR</i> ®) Isosorbide dinitrate tablet (<i>generic</i> , <i>Isordil Titradose</i> ®) Isosorbide mononitrate tablet (<i>generic</i>) Nitroglycerin capsule, extended release (<i>generic</i> , <i>Nitro-Time</i> ®) Nitroglycerin patch, 24-hour transdermal (<i>generic</i> , <i>Minitran</i> ®, <i>Nitro-Dur</i> ®) Nitroglycerin tablet, sublingual (<i>Nitrostat</i> ®)	Amyl nitrate solution, nasal inhalation (<i>generic</i>) Isosorbide dinitrate capsule, extended release (<i>Dilatrate-SR</i> ®) Isosorbide dinitrate tablet, extended release (<i>generic</i> , <i>IsoDitrate</i> ®) Isosorbide mononitrate tablet, extended release (<i>generic</i> , <i>Imdur</i> ®) Nitroglycerin solution, translingual (<i>generic</i> , <i>Nitrolingual</i> ®, <i>NitroMist</i> ®) Nitroglycerin ointment, transdermal (<i>Nitro-Bid</i> ®)
Cardiovascular Agent, Miscellaneous	
	Ranolazine ER tablet (<i>Ranexa</i> ®)

Previous Conclusions:

- Most studies of short-acting nitrate treatment in unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI) have been small and uncontrolled. The rationale for NTG in UA/NSTEMI is extrapolated from pathophysiological principles and extensive, although uncontrolled, clinical observations. Recommendations from American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in this setting have Class I recommendation as first line treatment, yet they only have evidence level C grading.
- The role for long acting nitrates is for patients with stable angina who cannot tolerate or are contraindicated to a beta-blocker or calcium channel blocker.
- The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.
- Available formulations differ in both onset and duration of action. There is insufficient evidence demonstrating differences in formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of long term use and is dose and duration-dependent.

Previous Recommendations:

- Add nitrates to PDL
- Include a short acting nitrate for angina prevention and treatment. There is no clinical advantage of nitroglycerin spray over NTG sublingual.
- Include a long-acting nitrate for angina prophylaxis and treatment of angina and include isosorbide dinitrate ER for the management of heart failure.

- Further evaluate costs of various formulations for preference.

Conclusions and Recommendations:

- There is high quality evidence sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with stable ischemic heart disease.³
- There is high quality evidence long-acting nitrates are recommended for relief of symptoms when first-line therapy (i.e., beta-blockers or calcium channel blockers) is contraindicated or causes unacceptable side effects. Long-acting nitrates may also be used in combination with beta-blockers for symptom relief when initial treatment with beta-blockers is unsuccessful.^{3,4}
- There is low quality evidence that ranolazine reduces weekly angina frequency compared to placebo (mean difference -0.687 episodes per week; 95% CI, -0.973 to -0.402).²
- There is insufficient evidence comparing ranolazine to nitrates at reducing angina frequency.²
- Available formulations for nitrate products differ in both onset and duration of action. There is insufficient evidence demonstrating clinical differences between formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of continuous, around-the-clock use.
- No new evidence requires changes to the PDL at this time. Evaluate comparative costs in executive session.
- No further review or research needed.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from 2012 through September 2014 assessing clinically meaningful outcomes (e.g., symptom relief, morbidity and mortality) of anti-anginal or nitrate therapy to active controls was performed. Placebo-controlled RCTs were excluded because anti-anginal or nitrate therapy are well established in medical literature and clinical practice. The search was limited to evaluation of patients with angina or heart failure and was conducted with limits to randomized controlled trials and for English. Studies evaluating intravenous nitrate therapy were excluded. Search terms included: angina; angina pectoris; stable angina; unstable angina; heart failure; nitroglycerin; nitrate; isosorbide dinitrate; isosorbide mononitrate; ranolazine. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs Drug Class Reviews, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review and meta-analysis was conducted to assess the effects of ranolazine on symptoms, electrocardiographic signs of ischemia and hemodynamic changes in patients with stable coronary artery disease.² Only trials randomly allocating patients prospectively to ranolazine or a control (placebo or active) were included in the analysis. However, only data evaluating symptom management is reviewed here. The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two independent reviewers screened articles for eligibility. Methodological quality of trials was assessed by Detsky method, scoring for method of randomization, blindness, adequate description of outcome and outcome assessment, inclusion/exclusion criteria, number of patients excluded and reasons, description of therapy in treatment and control groups and appropriateness of statistical analysis. The assumption of statistical homogeneity was tested by Q statistic and further quantified by I^2 statistics. Six trials enrolling 9223 patients with a median follow-up of 9 weeks were eligible for inclusion.

All 6 trials were placebo-controlled and only 3 trials assessed weekly nitroglycerin consumption and weekly angina frequency.

Ranolazine reduced weekly angina frequency compared to placebo by a mean difference of -0.687 episodes per week (95% CI, -0.973 to -0.402; heterogeneity $p=0.337$; $I^2=11.2\%$). In addition, ranolazine reduced weekly nitroglycerin consumption by a mean difference of -0.534 doses per week (95% CI, -0.789 to -0.280; heterogeneity $p=0.186$; $I^2=37.7\%$). No important heterogeneity was identified between the 3 trials evaluating these outcomes.²

New Treatment Guidelines:

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: Executive Summary: A Report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2012)³

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. Class of Recommendation (COR) is an estimate of the size of the treatment effect, with consideration given to risks versus benefits. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effects. Level A evidence is from data derived from multiple randomized, controlled trials or meta-analyses; Level B evidence is from data derived from a single randomized trial or nonrandomized studies; Level C evidence consists of consensus opinion, case studies or standard of care.

Beta-blockers are the initial anti-ischemic medications recommended for relief of angina symptoms in patients with stable ischemic heart disease (SIHD). Long-acting nitrates are indicated for relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects. In addition, long-acting nitrates are indicated in combination with beta-blockers for symptom relief when the initial treatment with beta-blockers is unsuccessful (*Class I Recommendation, Level of Evidence B*).

Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with SIHD (*Class I Recommendation, Level of Evidence B*).

Ranolazine should only be considered as a substitute for beta-blockers for relief of symptoms in patients with SIHD if initial treatment with beta-blockers is contraindicated (*Class IIa Recommendation, Level of Evidence B*). Ranolazine in combination with beta-blockers should only be considered for relief of symptoms when initial treatment with beta-blockers is not successful (*Class IIa Recommendation Level of Evidence A*).

National Institute for Health and Care Excellence (NICE) Clinical Guideline for Management of Stable Angina (2012)⁴

NICE clinical guidelines are systematically-developed recommendations on how healthcare and other professionals should care for people with specific conditions in the national health system of England and Wales. Guidelines are developed by the National Clinical Guideline Center for Acute and Chronic Conditions and represent best available evidence. The recommendations in this guideline relate only to people with a diagnosis of stable angina.

Either a beta-blocker or a calcium channel blocker is recommended as first-line therapy of stable angina. Decision of which drug class to use is based on patient comorbidities, contraindications and patient preference. If the patient cannot tolerate agents from one drug class, it is recommended to switch to the other drug class. In addition, if patient symptoms persist, consider switching to the other drug class or using a combination of the two. It is not recommended

to offer other anti-anginal drugs other than from these two drug classes as first-line therapy in patients with stable angina.

If a patient cannot tolerate beta-blockers and calcium channel blockers, or both are contraindicated, monotherapy with either a long-acting nitrate or ranolazine is recommended. Alternatively, if patient symptoms persist on beta-blocker or calcium channel blocker monotherapy and the other option (calcium channel blocker or beta-blocker) is contraindicated or not tolerated, monotherapy with either a long-acting nitrate or ranolazine is recommended. Clinical decisions on which drug to use are based on patient comorbidities, contraindications and patient preference.

A third anti-anginal drug should only be considered in patients with persistent angina symptoms despite two anti-anginal drugs and the person is waiting for revascularization, or revascularization is not considered appropriate or acceptable.

Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines for the Management of Patients with Refractory Angina (2012)⁵

Refractory angina is a persistent, painful condition characterized by the presence of angina caused by coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery. This guideline included only systematic reviews, randomized controlled trials and quasi-experimental and pre-posed studies. Observational, retrospective and case studies did not meet inclusion criteria and are not considered in this guideline. Specific outcomes included chest pain, nitrate use, morbidity, quality-of-life, exercise tolerance and mortality.

Specific nitrates were not assessed in the guideline since one outcome evaluated in the guideline was the decreased use of nitrates. Ranolazine was evaluated, though it is not approved for refractory angina specifically. Robust RCTs focused on refractory angina are needed before ranolazine can be recommended as an anti-anginal agent in this population. Ranolazine may have benefit at reducing angina symptoms, particularly in patients who cannot tolerate standard anti-anginal agents that may suppress heart rate and blood pressure (*Weak Recommendation, Moderate-Quality Evidence*).

Allopurinol, another medication studied for angina, requires more robust RCTs focused on refractory angina (*Strong Recommendation, Low-Quality Evidence*).

New drugs:

None.

New Formulations/Indications:

None.

New FDA safety alerts:

None.

New Trials:

A total of 54 citations resulted from the initial Medline search. All citations were excluded because of either inappropriate study design or because clinically meaningful outcomes were not assessed as described previously in the methodology.

References:

1. The OHP Preferred Drug List (PDL). The Oregon Health Plan website. Available at <http://www.oregon.gov/OHS/healthplan/pages/pdl.aspx>. Accessed 6 October 2014.
2. Savarese G, Rosano G, D'Amore C, et al. Effects of ranolazine in symptomatic patients with stable coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol.* 2013;169:262-270.
3. Fihn S, Gardin J, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: Executive Summary: A Report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2012;126:3097-3137.
4. NICE Clinical Guideline 126. Management of stable angina. Last modified December 2012. Available at www.nice.org.uk/guidance/CG126. Accessed 6 October 2014.
5. McGillion M, Arthur H, Cook A, et al. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines. *Can J Cardiol.* 2012;28 Suppl 1:S20-S41.