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Drug Class Literature Scan: Antianginals

Date of Review: May 2017

Date of Last Review: November 2014
Literature Search: 01/01/2014 – 04/2017

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- This class scan identified 2 systematic reviews from the Cochrane Collaboration[1,2], 1 new randomized controlled trial[3] and 1 new formulation.[4]
- There is no pivotal new evidence since the last review that does not support current first line treatment of angina with beta blockers or calcium channel blockers. Ranolazine and long-acting nitrates should be reserved for add-on therapy when a combination of 2 first line drugs cannot be used or as monotherapy when neither of the first-line drugs can be used. Short acting nitroglycerin should remain available for the immediate relief of angina in patients with stable ischemic heart disease.
- There is insufficient to very low quality evidence that perioperative prophylactic administration of nitrates does not significantly decrease the incidence of perioperative cardiac events or reduce all-cause mortality up to 30 days post operation. However, data remains limited and were not able to be combined for meta-analysis.
- There is low quality evidence that ranolazine as monotherapy compared to placebo does not reduce cardiovascular mortality (21/1317 vs. 20/1287; RR 1.03; 95% CI 0.56 to 1.88).
- There is moderate quality evidence from 3 trials, that add-on ranolazine reduced the frequency of angina episodes from 4.1 episodes per week to 0.66 lower per week (MD -0.66; 95% CI -0.97 to -0.35) compared to placebo, but also moderate quality evidence of an increase in the risk of non-serious adverse events (29% vs. 24%; RR 1.22; 95% CI 1.06 to 1.40; NNH 20).
- There is insufficient evidence that the sublingual powder formulation of nitroglycerin provides any clinical benefit over other formulations currently available.

Recommendations:
- Make sublingual powder nitroglycerin (GONITRO™) non-preferred on the PDL.
- No other review or research needed.
  After evaluation of comparative costs in executive session, no PDL changes were recommended.

Previous Conclusions:
- There is high quality evidence sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with stable ischemic heart disease.

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- 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.
- 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).
- There is insufficient evidence comparing ranolazine to nitrates at reducing angina frequency.
- 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.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Nitrates:

A Cochrane Systematic review was published in 2016 that assessed the effects of nitrates compared with other interventions or placebo in reducing cardiac risk in patients undergoing non-cardiac surgery.[5] A literature search through January 2016 identified 27 RCTs (n=8244) that were included in the analysis. The primary outcome was all-cause mortality up to 30 days post operation and secondary outcomes included perioperative incidence of cardiac morbidity (acute myocardial infarction, heart failure, arrhythmia, etc.) There were 12 different comparisons of 3 different nitrates, including nitroglycerin, isosorbide dinitrate and nicorandil. Nicorandil is not available in the U.S. and will not be discussed further. Studies included surgical procedures mostly that were low to moderate risk for perioperative cardiac complications and almost all of the participants were in the hospital for elective non-cardiac surgery with a wide range of baseline cardiovascular risk. [5] Due to a variety of morbidity outcomes and differences in reporting, there were limited results available for meta-analysis. The overall methodological quality of the studies was fair to low.

Only one study (n=60) evaluated differences in all-cause mortality up to 30 days post operation and found very low quality evidence of no difference between nitroglycerin and no treatment (0 vs. 1; RR 0.33; 95% CI 0.01 to 7.87). [5] There was also very low quality evidence of no difference between nitroglycerin in

placebo in all-cause mortality (1 vs. 0; RR 2.81; 95% CI 0.12 to 63.83; 2 studies; n=89). [5] There were no comparisons that resulted in a significant difference in secondary outcomes, including angina, acute myocardial infarction, acute heart failure, cardiac arrhythmia or cardia arrest. Overall, data did not suggest that nitroglycerin or isosorbide dinitrate is associated with improvements in mortality or cardiac complications in patients undergoing non-cardiac surgery. However, data is insufficient to draw strong conclusions or see differences between nitrates and placebo.[5]

Ranolazine

A second Cochrane Systematic Review evaluated ranolazine for stable angina pectoris.[2] RCTs comparing ranolazine monotherapy or ranolazine add-on therapy versus placebo or other anti-anginals in people with stable angina were included from a literature search through February 2016. Seventeen RCTs (n=9975) were included. Most studies were either fully or partly funded by drug companies and most were performed in North America, Europe and Australia. Two studies provided data for 62% of participants and were from 2007 and 2016. [2] Seven studies evaluated ranolazine as add-on therapy to either beta blockers, calcium channel blockers or both. Overall, risk of bias was assessed as unclear and there were limited data to inform most planned comparisons on outcomes of interest. There were insufficient evidence to compare ranolazine to other anti-anginals. [2]

There were no studies evaluating add-on ranolazine compared to placebo on cardiovascular or non-cardiovascular mortality (the primary outcomes). There was only one study that reported data on cardiovascular mortality for ranolazine as monotherapy compared to placebo. The authors concluded an uncertain effect from low quality evidence (21/1317 vs. 20/1287; RR 1.03; 95% CI 0.56 to 1.88). [2] There was moderate quality evidence from 3 trials, that add-on ranolazine 1000 mg twice daily reduced the frequency of angina episodes from 4.1 episodes per week to 0.66 lower per week (MD -0.66; 95% CI -0.97 to -0.35) compared to placebo, but also moderate quality evidence of an increase in the risk of non-serious adverse events (29% vs. 24%; RR 1.22; 95% CI 1.06 to 1.40). [2] There was low quality evidence of no difference in all-cause mortality (RR 0.83; 95% CI 0.26 to 2.71), moderate quality evidence of no difference in quality of life and low quality evidence of similar risk of non-fatal acute myocardial infarction (RR 0.40; 95% CI 0.08 to 2.07) [2]. Quality of evidence was downgraded due to insufficient number of events. For comparisons of ranolazine as monotherapy versus placebo, there was an very low to low quality evidence of no difference in cardiovascular mortality (16 per 1000 in both groups), all-cause mortality (49 per 1000 in both groups), quality of life (mean quality of life in ranolazine group was 0.28 points higher on a scale from 0-100), non-fatal acute myocardial infarction (7.5% vs. 85%; RR 0.88; 95% CI 0.69 to 1.12), and frequency of angina episodes (mean angina episode frequency of 0.08 higher per week in ranolazine group from baseline of 2.08 episodes per week). There was very low quality evidence from 3 studies of an increased risk for non-serious adverse events (RR 1.50; 95% CI 1.12 to 2.00). [2] There was insufficient data on serious adverse events. The authors concluded that there was evidence of clinical benefit from the use of ranolazine as add-on therapy only by reducing the frequency of angina episodes; however, there was also evidence of clinical harm for the use of ranolazine as either monotherapy or add-on therapy by increasing the risk of non-serious adverse events. Additionally, studies varied in the dosage and type of formulation used, the presence of comorbidities, and duration of follow-up (1 week to more than 2 years). [2]

New Guidelines:

A 2014 focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease was published from the American College of Cardiology and American Heart Association (ACC/AHA).[6] The intent of the focused update is to include pivotal new evidence that may effect changes in current recommendation. However, new recommendations based on this new evidence were made only for diagnostic testing, chelation therapy, and revascularization. Since no new data or recommendations were considered for treatment with anti-anginals, this updated guideline will not be presented further.

New Formulations:
In June, 2016 the FDA approved a sublingual powder formulation of nitroglycerin (GONITRO™) for prevention or acute relief of an attack of angina pectoris.[4] It is the first powder formulation available in the US. Currently, sublingual and spray formulations are available. Approval was based on a comparative bioavailability study comparing nitroglycerin powder to the nitrolingual pump spray product.[7] The recommended dosage is one or two 400 mcg packets at the onset of an attack to be placed under the tongue. [4]

In one unpublished, randomized, double-blind, crossover trial in 51 patients with exertional angina pectoris, doses of nitroglycerin powder from 200-1600 mcg were shown to cause a dose-related increase in exercise tolerance, time to onset of angina, and time to ST-segment depression, compared to placebo. [4] Information could only be found from the package insert. There are no clinical studies available comparing this product to other available formulations and no evidence it improves clinical outcomes. Adverse reactions that occurred at a frequency greater than 2% or more than placebo included headache, dizziness and paresthesia. [4]

New FDA Safety Alerts:
None

Fourth Quarter 2016 Utilization:
Utilization of antianginals in the Oregon Medicaid fee for service (FFS) population from 10/1/16 through 12/31/16 consisted primarily for preferred products (98%) with only 31 paid claims for a non-preferred agent. There was only 1 paid claim for ranolazine in this quarter. Most of the unpaid claims were for patients enrolled in a CCO. Of the non-preferred medications, most of the claims were for isosorbide mononitrate ER.

References:

1. Zhao N, Xu J, Singh B, Yu X, Wu T, Huang Y. Nitrates for the prevention of cardiac morbidity and mortality in patients undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2016(8).
2. Salazar CA, Basilio Flores JE, Veramendi Espinoza LE, Mejia Dolores JW, Rey Rodriguez DE, Loza Munarriz C. Ranolazine for stable angina pectoris. *Cochrane Database Syst Rev.* 2017;2:Cd011747.
3. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2015;373(24):2314-2324.
4. GONITRO (nitroglycerin) sublingual powder Prescribing Information. 06/2016. Espero pharmaceuticals.
5. Zhao N, Xu J, Singh B, Yu X, Wu T, Huang Y. Nitrates for the prevention of cardiac morbidity and mortality in patients undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2016(8):CD010726.
6. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology.* 2014;64(18):1929-1949.
7. Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, et al. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. *J Clin Gastroenterol.* 2016;50(2):147-151.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE ER	DILATRATE-SR	ISOSORBIDE DINITRATE	Y
ORAL	CAPSULE ER	NITROGLYCERIN	NITROGLYCERIN	Y
ORAL	TABLET	ISORDIL	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISORDIL TITRADOSE	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	Y
ORAL	TABLET	ISOSORBIDE MONONITRATE	ISOSORBIDE MONONITRATE	Y
SUBLINGUAL	TAB SUBL	NITROSTAT	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	MINITRAN	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	NITRO-DUR	NITROGLYCERIN	Y
TRANSDERM	PATCH TD24	NITROGLYCERIN PATCH	NITROGLYCERIN	Y
ORAL	TAB ER 12H	RANEXA	RANOLAZINE	N
ORAL	TAB ER 24H	ISOSORBIDE MONONITRATE ER	ISOSORBIDE MONONITRATE	N
ORAL	TABLET	BIDIL	ISOSORB DINIT/HYDRALAZINE HCL	N
ORAL	TABLET ER	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	N
SUBLINGUAL	TAB SUBL	ISOSORBIDE DINITRATE	ISOSORBIDE DINITRATE	N
TRANSDERM	OINT. (G)	NITRO-BID	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROGLYCERIN	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROLINGUAL	NITROGLYCERIN	N
TRANSLING	SPRAY	NITROMIST	NITROGLYCERIN	N

Appendix 2: New Comparative Clinical Trials

A total of 65 citations were manually reviewed from the initial literature search. After further review, 64 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Redfield, et al.[3] RCT, DB, PC	Isosorbide Mononitrate 120 mg vs. placebo	Heart Failure with Preserved Ejection Fraction (n=110)	Daily activity level measured by the average daily accelerometer units	<u>Daily activity level:</u> Isosorbide: 8922 units Placebo: 9303 units Treatment difference -381 (-780 to 17); p=0.06 There was also no significant difference in the six-minute walk test or quality of life.

Abbreviations: DB = double-blind; PC = placebo-controlled; RCT = randomized clinical trial

Appendix 3: Abstracts of Clinical Trials

1. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2015 Dec 10;373(24):2314-24. doi: 10.1056/NEJMoa1510774. Epub 2015 Nov 8.

BACKGROUND:

Nitrates are commonly prescribed to enhance activity tolerance in patients with heart failure and a preserved ejection fraction. We compared the effect of isosorbide mononitrate or placebo on daily activity in such patients.

METHODS:

In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase, daily accelerometer units during all three dose regimens, quality-of-life scores, 6-minute walk distance, and levels of N-terminal pro-brain natriuretic peptide (NT-proBNP).

RESULTS:

In the group receiving the 120-mg dose of isosorbide mononitrate, as compared with the placebo group, there was a nonsignificant trend toward lower daily activity (-381 accelerometer units; 95% confidence interval [CI], -780 to 17; P=0.06) and a significant decrease in hours of activity per day (-0.30 hours; 95% CI, -0.55 to -0.05; P=0.02). During all dose regimens, activity in the isosorbide mononitrate group was lower than that in the placebo group (-439 accelerometer units; 95% CI, -792 to -86; P=0.02). Activity levels decreased progressively and significantly with increased doses of isosorbide mononitrate (but not placebo). There were no significant between-group differences in the 6-minute walk distance, quality-of-life scores, or NT-proBNP levels.

CONCLUSIONS:

Patients with heart failure and a preserved ejection fraction who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than did patients who received placebo. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT02053493.).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 1 2017
1 exp isosorbide dinitrate.mp. or Isosorbide Dinitrate/ 1532
2 nitroglycerin.mp. or Nitroglycerin/ 5983
3 isosorbide mononitrate.mp. 230
4 ranolazine.mp. or Ranolazine/ 681
5 1 or 2 or 3 or 4 7990
6 limit 5 to (English language and humans and yr="2015-Current" and 9clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or systematic reviews)) 65