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Nitrates Review

Month/Year of Review: June 2012 **Date of Last Review:** NA
Classes Included: Nitrates

Reason for Review:
Nitrates including nitroglycerin, isosorbide dinitrate and isosorbide mononitrate have been used for many years, however they are currently not on Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Issues:
- Is there any reliable evidence showing nitrates' role in management of angina or other conditions?
- Is there evidence showing nitrates differ in benefits and harms within subgroups of patients?
- Is there any difference in effectiveness or harms among different formulations of nitrates?

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 dependant.

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.

Background:

Coronary artery disease (CAD) is the most common type of heart disease. In 2008, 405,309 people died from CAD.[1] Every year approximately 785,000 Americans have a first coronary attack, and another 470,000 Americans have recurrent attack.[2] In 2010, coronary heart disease alone was projected to cost the United States $108.9 billion, which includes the cost of health care services, medications, and lost productivity.[3] Angina is a symptom of CAD, commonly known as chest pain. It is discomfort that occurs when the heart muscle is not getting enough 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. This type of angina is a medical emergency.[4] UA and closely related conditions of non-ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of CAD. These conditions are characterized by an imbalance between myocardial oxygen supply and demand.

Nitrates are vasodilators that are used to prevent and relieve chest pain due to CAD. The most common types of nitrates are nitroglycerin (NTG), isosorbide dinitrate, and isosorbide mononitrate. NTG was the first introduced in 1879 for treatment of angina. NTG in its immediate release form remains as first line therapy for acute anginal symptoms. In patients with exertional stable angina, chronic nitrate therapy in oral or transdermal preparations, improves exercise tolerance, time to onset of angina, and ST-segment depression during exercise testing. In addition, isosorbide dinitrate in combination with hydralazine serves a role in the management of heart failure as an adjunct to standard treatment. Nitrates reduce myocardial demand while enhancing myocardial oxygen delivery. These effects are achieved at both cellular and cardiovascular level. At a cellular level, nitrates, upon interacting with reduced sulfhydryl groups (probably supplied by cysteine and a necessary co-factor) located within or near organic nitrate receptors located on smooth muscle cells of blood vessels, are converted to nitric oxide and, in turn, are able to activate guanylate cyclase, increase intracellular cyclic guanosine monophosphate (cGMP) concentrations, and, as a result, cause vasodilation of venous and arterial blood vessels. Depletion of sulfhydryl groups during this metabolic process may be a major factor in development of nitrate tolerance, along with compensatory physiologic mechanisms. Data also exists suggesting that organic nitrates increase intraplatelet cGMP concentrations thereby impeding platelet activity. These pharmacologic actions of nitrates appear to preferentially occur within portions of blood vessels containing damaged endothelium, thus making them extremely useful in the pharmacotherapy of acute ischemic events. In addition, the sulfhydryl group plays a role in the vasodilation effect of nitroglycerin. Addition of N-acetylcysteine (NAC), a sulfhydryl donor, to intracoronary administration of nitroglycerin increased the proximal and distal coronary artery diameters by additional 11% and 8%, respectively. The potentiative effects of NAC in patients with coronary artery disease were much smaller. At cardiovascular level, When administered to ischemic patients, nitrates cause both peripheral and coronary venous and arterial vasodilation resulting in decreased preload and afterload and increased coronary blood flow, thus increasing myocardial oxygen supply and decreasing myocardial oxygen demand. Clinical investigation has also suggested that organic nitrates interrupt platelet hyperactivity. These effects improve congestive symptoms in heart failure and improve the myocardial perfusion gradient in patients with CAD. Normal coronary artery cross-sectional area can be increased by 20% with either sublingual nitroglycerin or isosorbide. Both pre- and poststenotic vessels can be dilated by 30% to 40%, as well as eccentric lesions which retain some dynamic component. As a result of both lowered cardiac demand and increased regional flow from either direct venodilation of stenosis or improved collateral flow, nitrates can "homogenize" myocardial blood flow.[5]

Methods:
A MEDLINE Ovid search was conducted using all nitrates including: cardiovascular disease, angina, nitrates, NTG, isosorbide dinitrate and isosorbide mononitrate. The search was limited to meta-analysis, English language, and to studies conducted in humans from 2002 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Drugs Included in This Review

Drug	Dosage Form	Generic Availability
NTG	Sublingual tablet	Y
	Sublingual spray	N
	Transdermal patch	Y
	Transdermal ointment	N
Isosorbide mononitrate	Oral immediate or extended release tablets	Y
Isosorbide dinitrate	Oral immediate or extended release tablets	Y
	Oral extended release capsules	N

Guidelines
The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) updated treatment guidelines on UA and NSTEMI in (May 2011.)[6] The task force committee members reviewed and compiled published reports through a series of computerized literature searches of the English-language literature since 2002 and a final manual search of selected articles. The recommendations made were based primarily on these published data. The weight of the evidence was ranked highest (A) to lowest (C). The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with UA/NSTEMI summarize both clinical evidence and expert opinion. The key recommendations on role of nitrates therapy in UA/NSTEMI are as follow:

- Health care providers should instruct patients with suspected acute coronary syndrome (ACS) for whom nitroglycerin [NTG] has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely. *(Class I; Level of Evidence: C)*

- It is reasonable for health care providers and 9-1-1 dispatchers to advise patients who tolerate NTG to repeat NTG every 5 min for a maximum of 3 doses while awaiting ambulance arrival. *(Class IIa; Level of Evidence: C)*
- Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. *(Class I; Level of Evidence: C)*
- Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or ACE inhibitors. *(Class I; Level of Evidence: B)*
- Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 beats per minute), tachycardia (more than 100 beats per minute) in the absence of symptomatic HF, or right ventricular infarction. *(Class III; Level of Evidence: C)*
- Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. *(Class III; Level of Evidence: C)*
- All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. *(Class I; Level of Evidence: C)*
- Medical therapy with nitrates, beta blockers, and calcium channel blockers, alone or in combination, is recommended in patients with cardiovascular syndrome X. *(Class I; Level of Evidence: B)*

NICE Treatment Guideline on Stable Angina (July 2011):[7]

<u>Recommendations on preventing and Treating Episodes of Angina</u>

Offer a short-acting nitrate for preventing and treating episodes of angina. Advise people with stable angina:

- How to administer the short-acting nitrate
- To use it immediately before any planned exercise or exertion
- That side effects such as flushing, headache and lightheadedness may occur
- To sit down or find something to hold on to if feeling light-headed

When a short-acting nitrate is being used to treat episodes of angina, advise people:

- To repeat the dose after 5 minutes if the pain has not gone
- To call an emergency ambulance if the pain has not gone 5 minutes after taking a second dose

<u>Recommendations on Drugs for Treating Stable Angina</u>

- Offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina. Decide which drug to use based on comorbidities, contraindications and the person's preference.
- If the person cannot tolerate the beta blocker or a calcium channel blocker, consider switching to the other option (calcium channel blocker or beta blocker).
- If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker, consider either switching to the other option or using a combination of the two. When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine or felodipine.
- Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.
- If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:
  - A long-acting nitrate or
  - Ivabradine (not available in the US) or
  - Nicorandil (not available in the US) or
  - Ranolazine
- Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.
- For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:
  - A long-acting nitrate or
  - Ivabradine (not available in the US) or
  - Nicorandil (not available in the US) or
  - Ranolazine

Institute for Clinical Systems Improvement (ICSI) treatment guidelines on management of stable coronary artery disease:[8]

- In patients with mild, stable coronary artery disease, drug therapy may be limited to short-acting sublingual nitrates on an as-needed basis. Use of lower dose (e.g., 0.3 mg or one-half of a 0.4-mg tablet) may reduce the incidence of side effects such as headache or hypotension in susceptible patients;
- If beta-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy, low cost, and relatively few side effects. Tolerance to long-acting nitrates is an important clinical issue in some patients and can be avoided by appropriate daily nitrate-free intervals.

American College of Cardiology/American Heart Association: Guideline Update for the Diagnosis and Management of Chronic Heart Failure (2009)[9]:

For the treatment of heart failure, these guidelines recommend the combination of a fixed dose of isosorbide dinitrate and hydralizine to a standard medical regimen to improve outcomes for African Americans, with an NYHA functional class III or IV (Level of Evidence: A).[9]

New Systematic Reviews

There are very limited systematic reviews available that were published in the last decade. The only systematic review found within timeframe defined for this review was a meta-analysis of randomized clinical trials on nitrates use in stable angina by Wei J et al published in 2011.[10] The results based on 51 trials with 3,595 patients showed both intermittent and continuous regimens of nitrates lengthened exercise duration significantly by 31 seconds (95% CI 11.28 to 51.47, p=0.002) and 53 seconds (95%CI 15.86 to 89.27, p=0.005) respectively. The number of angina attacks was significantly reduced by 2.89 episodes weekly for continuous administration (95%CI 0.58 to 5.19, p=0.01) and 1.5 episodes (95%CI 0.92 to 2.08, p<0.00001) weekly for intermittent administration. With intermittent administration, increased dose provided with 21 seconds more length of exercise duration. With continuous administration, exercise duration was pronged more in low-dose group. Quality of life was not improved by continuous application of NTG patches and was similar between continuous and intermittent groups. In addition, 51.6% patients receiving nitrates complained of headache. The authors concluded long-term administration of nitrates was beneficial for angina prophylaxis and improved exercise performance but might be ineffective for improving quality of life. With continuous regimen, low-dose nitrates were more effective than high-dose ones for improving exercise performance. By contrast, with intermittent regimen, high-dose nitrates were more effective. In addition, intermittent administration could bring zero-hour effect. The heterogeneity test was performed to evaluate these trials, however the review did not conduct quality assessment due to lack of information on allocation concealment and randomization procedure in most trials.

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