The Role of Nitrates in the Management of Stable Ischemic Heart Disease: A Review of the Current Evidence and Guidelines

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Coronary artery disease is the leading cause of mortality in the United States and can result in significant morbidity. In particular, stable ischemic heart disease (SIHD) is a condition that affects nearly 9 million individuals in the United States alone, with substantial annual health care costs related to recurrent medical visits and chronic disease management. Nitrates form a cornerstone of SIHD management by reducing myocardial oxygen consumption and increasing exercise capacity by several mechanisms, including increasing epicardial blood flow through vasodilation and decreased vascular resistance, blunting coronary steal, and reducing preload. Yet the role of nitrates may be underappreciated in clinical practice and their utilization may be limited due to concerns of tolerance to treatment, a lack of randomized data validating their ability to prevent adverse cardiovascular events, and the pervasive use of percutaneous interventions without robust attempts at implementing optimal medical therapy. In this review, we discuss both the recent ACC/AHA/ACP/AATS/PCNA/SCAI/STS and European Society of Cardiology guidelines, with a particular focus on indications, contraindications, and future directions of nitrate therapy in SIHD.

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KEY WORDS:

Angina • Coronary artery disease • Stable ischemic heart disease • Nitrates

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, accounting for approximately one in seven deaths in the United States alone.[1] Approximately 16 million individuals in the United States have a diagnosis of CAD, manifesting as stable angina or stable ischemic heart disease (SIHD) in 9 million individuals.[1] Importantly, SIHD can be the initial presentation of CAD.

Angina is a consequence of a regional imbalance between myocardial oxygen supply and demand. Stable angina, or SIHD, is typically characterized as symptoms brought on by physical exertion or stress, lasting for known duration, and relieved by rest or anti-anginal medications.[2-4] In this review, we specifically evaluate the role of nitrates as part of optimal medical therapy (OMT) in SIHD management, which includes lifestyle interventions and aggressive pharmacologic therapies for secondary prevention. Many clinicians prescribe short-acting nitroglycerin for acute relief of angina, but its role as a prophylactic agent against known angina-provoking activities remains underappreciated and limits the ability to comprehensively reduce the burden of symptoms and improve the quality of life in SIHD patients with OMT.

Nitrates Overview

Nitrates have been in clinical use since 1878[5,6] and are the leading class of agents to treat and alleviate anginal symptoms. Nitrates form the basis of SIHD management by reducing myocardial oxygen consumption and increasing exercise capacity through several mechanisms (Figure 1).[5,7,8]

These medications have a complex mechanism of action, affecting multiple pathways as follows: (a) blocking calcium entry in smooth muscle cells, leading to relaxation through the production of 4 cyclic guanosine monophosphate (cGMP); (b) vasodilation of venous capacitance vessels, leading to reduced preload resulting in decreased myocardial oxygen consumption; (c) at higher doses, causing arterial dilation including the epicardial arteries; and (d) promoting redistribution of coronary blood flow from healthy to ischemic areas.[5,8]

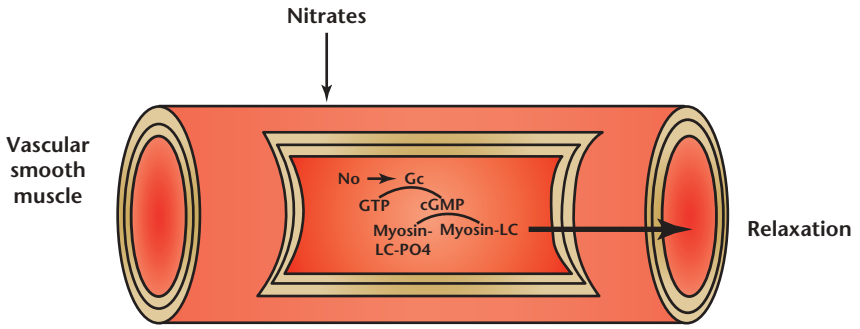

Figure 1. Mechanisms of action of nitrates on vascular smooth muscle. cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; Myosin-LC-PO4; myosin light chain phosphatase; NO, nitric oxide.

In addition to varied mechanisms of action, there are many different formulations of nitrates available to the clinician (Table 1). Short-acting formulations include a sublingual tablet, spray, ointment, and transdermal patch. These are often used to relieve acute anginal pain and may be used to prevent exercise-induced ischemia.[9] Sublingual nitroglycerin has been shown to be more effective due to its quick absorption time (1–3 min) and duration of approximately 30 minutes. The ability of sublingual nitroglycerin to relieve acute anginal attacks and prophylactically increase exercise capacity has been well established, with relief of symptoms within 5 minutes of taking one to two sublingual dose(s) (0.3-0.6 mg each) of nitroglycerin.[7,9,10] Guideline recommendations advise that if additional doses are necessary, they should be administered at 5-minute intervals for a maximum dose of 1.2 mg within 15 minutes,[3,4] and that patients should seek immediate medical attention if relief is not achieved within this timeframe. Sublingual nitrates may also be used prophylactically prior to any angina-producing activity.[7] Long-acting nitrates reduce the frequency of angina symptoms in patients with SIHD and may potentiate the duration of action of short-acting preparations.[5] Long-acting nitrate formulations include an ointment, patches, and oral formulations including isosorbide dinitrate or isosorbide mononitrate. Despite the key role of nitrates in preventing angina, tolerance can develop rapidly, especially with long-acting formulations. It

TABLE 1

Commonly Used Nitrates in Clinical Practice

Nitrate	Begins Acting	Duration of Action
Oral nitrates		
Isosorbide nitrates	15-30 min	3-6 h
Isosorbide-5-mononitrate	within 30 min	6-8 h
Transdermal nitroglycerin	within 30 min	8-14 h

has been observed that tolerance develops within 12 to 24 hours and therefore patients require a nitrate-free period of at least 8 hours per day.[11] Nitrate tachyphylaxis is a complex, yet poorly understood process with several proposed mechanisms, including: (a) inactivation of nitric oxide (NO) due to overproduction of superoxide radicals, leading to vasodilation and increased response to vasoconstrictors[12]; (b) limited sulfhydryl groups, leading to impaired bioactivation of nitroglycerin[13]; (c) inhibition of biotransformation of nitrates to NO[14,15]; (d) additional release of vasoconstrictors such as catecholamine and angiotensin II substances[7]; and (e) decrease in vascular smooth muscle relaxation due to decreased activation of large-conductance calcium-dependent potassium channels.[16,17]

Tolerance is conceptually divided into the early pseudo-tolerance phase and the late vascular tolerance phase, which includes morphological changes to the vasculature. Pseudo-tolerance is primarily driven by reciprocal vasoconstriction and intravascular volume expansion, whereas vascular tolerance refers to the long-term intrinsic vascular changes that underlie the loss of responsiveness to nitrates. Regardless of the mechanism of action, preventing tolerance to the effects of nitrate treatment requires discontinuation of nitrate therapy for approximately 8 to 10 hours per day, as mentioned above.[4] Predictably, interruptions in nitrate therapy lead to increased frequency of angina and decreased exercise capacity during nitrate-free periods,[11,18] although oral long-acting nitrates are reported to be associated with lower rates of nocturnal angina.[5] Recently, differences between nitrates have been recognized, and pentaerythrityl tetranitrate (PETN) appears to be devoid of tolerance, endothelial dysfunction, and oxidative stress while maintaining the protective properties. Nonetheless, concern regarding tolerance to nitrate treatment preventing a sustained therapeutic benefit may contribute to underutilization of long-acting nitrates by physicians and patients.[5]

Before angina-provoking physical activity, short-acting nitrates, in either tablet or spray form, can be used to prevent symptoms. However, instead of utilizing short-acting nitrates to prophylactically prevent angina symptoms, some patients may avoid exertional physical activity altogether, thereby adversely affecting their long-term prognosis.[19] The most common adverse drug effects of short-acting nitrates include rebound headaches, dizziness, postural hypotension, paradoxical bradycardia, and syncope.[20] Nitrate rebound or withdrawal may be seen with abrupt discontinuation of long-acting nitrates and may manifest as new onset of symptoms. In one analysis, the incidence of treatment-related headache was dose dependent, increasing from no adverse events with placebo to three (6%), five (10%), six (12%), and eight (16%) events with 0.2, 0.4, 0.8, and 1.6 mg nitroglycerin spray, respectively.[21] Though generally well tolerated, some patients with SIHD rarely experience intense sensitivity to nitroglycerin and suffer from debilitating headaches, with NO-donor nitroglycerin postulated to contribute to the pathophysiology of migraine or cluster-like headaches.[22] Concomitant use with phosphodiesterase inhibitors, such as sildenafil, vadenafil, and tadalafil, is contraindicated due to the possibility of excessive vasodilation leading to severe hypotension along with paradoxical bradycardia, resulting in adverse systemic effects due to hypoperfusion.[23]

Hypertrophic obstructive cardiomyopathy is considered another contraindication to nitrate use as they can hasten a rapid decline in preload and stroke volume, precipitating worsening angina and an increase in the outflow tract gradient. Similarly, in patients with severe aortic stenosis, a decrease in systemic vascular resistance in the setting of decreased aortic valve surface area may lead to

arterial hypotension and/or syncope.[24,25] Judicious use of nitrates is essential after a myocardial infarction (MI) and in patients with congestive heart failure, with careful monitoring of hemodynamic stability warranted to guide pharmacotherapy.[5]

Role of Nitrates in the Guidelines for SIHD Treatment

With regard to angina relief, the current guidelines from the 2012 ACC/AHA/ACP/AATS/PCNA/SCAL/STS and the European Society of Cardiology recommend short-acting nitrates as the standard initial therapy for acute effort angina, sublingual nitroglycerin (0.3-0.6 mg) administered every 5 minutes (maximum 1.2 mg) or isosorbide dinitrate (5 mg sublingually) (Class Ib).[3,4] However, the guidelines recommend first-line treatment for angina prophylaxis with a beta blocker (Class IA). When beta blockers are contraindicated or cause intolerable side-effects, calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms. Likewise, if beta blockers alone fail to alleviate symptoms, the addition of either calcium channel blockers or long-acting nitrates is recommended; however, there has been insufficient evidence to suggest a mortality benefit of monotherapy versus combination therapy.[26] The choice of pharmacologic agent should be based on the patient's preference and underlying comorbidities.[3,4,26]

Ultimately, both the US and European guidelines recommend short-acting nitroglycerin for immediate relief of symptoms and a beta blocker and/or calcium channel blocker as first-line measures in angina prophylaxis. However, deriving a clinical benefit from beta blocker therapy alone requires significant pharmacological beta blockade, rarely achieved in routine clinical practice.[27] Moreover, a recent meta-analysis of 21,860 stable CAD or SIHD patients determined no benefit in reducing the incidence of cardiovascular death, non-fatal MI, non-fatal stroke, or myocardial revascularization with routine use of beta blockers.[28] Thus, pharmacologic secondary prevention in patients with SIHD may not be served with beta blockers alone.

As part of a robust OMT regimen, short-acting nitrates are a critical component to reduce angina symptoms and subsequent angina-related readmissions and should be employed in the majority of SIHD patients when appropriate.[5] Despite disparate results between clinical trials and retrospective observational studies, the guidelines make it clear that preventing death and MI does not solely define effective management, as successful treatment also requires robust attempts to curb stable angina symptoms, thereby improving quality of life. In fact, treatment options in SIHD include medical therapy alone or with myocardial revascularization via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Regardless of the choice of therapy, intensive lifestyle modifications should be the starting point for both SIHD management strategies.[29]

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Nitrates: Trials and Implications

Few randomized controlled trials have addressed the effect of nitrate therapy on clinical outcomes in patients with SIHD, and the few that have focused on the spray formulation predated the evolution of contemporary disease-modifying therapies for OMT.[5] In 1986, Parker and colleagues showed that nitroglycerin spray administered before an exercise test increased both time to the onset of angina and time to development of moderate angina during exercise.[30] Ten years later, the benefit of nitrate spray in patients with exercise-induced angina was further supported, showing a significant delay in time to onset of moderate angina in all active treatment groups compared with placebo.[21] In 2011, Wei and associates published a systematic review and meta-analysis to assess all available formulations of nitrate therapy in SIHD trials.[31] They demonstrated beneficial effects of nitrate administration in terms of exercise performance and the extent of ST segment depressions with treadmill testing. Thus, an abundance of clinical data supports the use of short-acting nitrates before exercise in delaying the time to onset of angina, with objective correlation of increased time to ST segment depression on an electrocardiogram (ECG).[21,30,31] However, nearly a decade has passed since further clinical studies have been conducted to further define the role of nitrates in SIHD management, and most of the current information on nitrates comes from animal models. Although observations made in animal models are of potential clinical importance, they may not necessarily apply or translate in a clinical setting. Organic nitrates remain the only class of anti-anginal agents that have never been tested in long-term, large-scale clinical outcome studies or

randomized trials.[12] An appropriate clinical trial to investigate the treatment effects and safety of different nitrate formulations in SIHD patients is greatly needed. Nonetheless, aggregating and assimilating the data from observational studies and the landmark SIHD strategy trials conducted over the past decade, short- and long-acting nitrates have an underappreciated role in preventing angina attacks from exertional activities.

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The Role of OMT and Nitrates in SIHD Management Strategy Trials

With the increasing global prevalence of CAD, many physicians have assumed an association between the presence of stable coronary stenosis or SIHD and adverse cardiovascular events. Thus, clinicians have historically recommended that patients with SIHD undergo elective myocardial revascularization in order to improve quality of life as well as to potentially mitigate rates of mortality.[32] Yet the results of randomized trials comparing the outcomes of initial myocardial revascularization versus conservative management with OMT, especially those carried out in the contemporary era over the past decade, have demonstrated no significant differences between the two initial strategies with regard to hard clinical endpoints, such as mortality and recurrent MI.[33-35]

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (N = 2287) compared PCI combined with OMT versus OMT alone and found no significant difference in the primary endpoint of all-cause mortality and non-fatal MI rate (19% vs 18.5% of patients; HR, 1.05; 95% CI, 0.87–1.27; $P = .62$) during a median follow-up period of 4.6 years.[33] Of note, 60% to 65% of patients at the beginning of the trial received combinations of short- and long-acting nitrates; however, this number significantly dropped to 40% at 5-year follow-up (in both PCI and OMT groups). In a subsequent analysis evaluating quality of life, 53% of patients in the revascularization arm were angina-free at 3 months versus 42% in the OMT arm ($P < .001$), but this advantage dissipated by 3 years.[36] The early benefits derived from PCI may be dampened by restenosis in target vessels, incomplete revascularization, or progression of nonculprit lesions originally deemed to be insignificant obstructions.[37-39]

The BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial randomized 2368 diabetic SIHD patients to OMT combined with revascularization, with either PCI (n = 798) or CABG (n = 378), or to OMT alone (n = 1192).[34] The 5-year survival rates were similar between the revascularization and OMT arms of the study (88.3% vs 87.8%, with an absolute difference of 0.5%; 95% CI, –2.0-3.1; $P = .97$). However, a secondary analysis did demonstrate that the composite of death, MI, and stroke was lower with CABG than with OMT alone (22.4% vs 30.5%; $P = .01$), with the reduction in the number of nonfatal MIs driving the difference in the secondary endpoint. Similarly to the results of the COURAGE trial, PCI provided improved angina control over OMT in the first year of follow-up, but, thereafter, similar angina symptoms were reported between the PCI and OMT arms.[40] Meanwhile, complete revascularization with CABG had a sustained quality-of-life benefit over OMT through the 5-year follow-up.

In the FAME–2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) trial, SIHD patients were randomized to fractional flow reserve (FFR)–guided PCI combined with OMT or OMT alone.[35] After only randomizing 888 individuals and a median follow-up of 7 months, recruitment was terminated due to a significant difference in the primary endpoint between the FFR-guided PCI and OMT arms (4.3% vs 12.7%; $P < .001$), driven by the lower rates of urgent revascularization in the FFR-guided PCI group (1.6% vs 11.1% at 7 months, $P < .001$)[35] at the expense of 351 more revascularizations in the PCI group. Still, 10% of patients in the PCI group had angina at the 6-month follow-up despite optimal revascularization, with 80% in the OMT group free of angina.[41] However, the hard clinical endpoints of mortality (0.2% vs 0.7% at 7 months, $P = .31$) and nonfatal MI (3.4% vs 3.2% at 7 months, $P = .89$) were similar between initial revascularization and medical therapy strategies.

A greater amount of equipoise should exist in the initial approach to SIHD management, with OMT being the most evidence-based approach to date in the majority of SIHD patients. OMT comprises disease-modifying pharmacotherapies including aspirin, statins, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, as well as anti-anginal agents, such as nitrates, beta blockers, calcium channel blockers, and ranolazine.

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approach to SIHD management, with OMT being the most evidence-based approach to date in the majority of SIHD patients.[33-35] OMT comprises disease-modifying pharmacotherapies including aspirin, statins, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, as well as anti-anginal agents, such as nitrates, beta blockers, calcium channel blockers, and ranolazine.[3-5,42] Anti-anginal therapies decrease myocardial oxygen consumption by lowering heart rate and blood pressure, reducing contractility, and increasing oxygen supply via increased coronary blood flow, resulting in the relief of symptoms and prolonged exercise duration.[27] Short- and rapid-acting nitrates are critical components of OMT and should complement secondary prevention measures in patients with angina, including those individuals with refractory and recurrent angina in those who have already undergone either a percutaneous or surgical myocardial revascularization.

Summary

Management of SIHD is a primary concern of clinicians and policymakers alike, as SIHD levies a substantial economic and health toll, with direct and indirect expenditures totaling billions of dollars.[1,5] Moreover, prevalence of SIHD increases as a function of age, with half of all patients with stable angina aged $>$ 65 years, and there are no signs of the trend reversing as the US population ages, with increasing rates of comorbidities such as diabetes and obesity.[43]

A thorough evaluation of an SIHD patient requires assessment of comorbid conditions (ie, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, and chronic kidney disease) and traditional cardiovascular risk factors (ie, age, gender, tobacco use, and family history).[5] Further diagnostic and prognostic evaluations include noninvasive testing and cardiac catheterization to determine anatomic and ischemic burdens of disease, respectively, although the value of ischemic burden in prognosticating future adverse cardiovascular events in SIHD has recently been questioned.[44-46] With the persistent health and economic burden of SIHD, determining the optimal management strategy and employing it evenly across diverse patient populations is paramount. Since elective PCI has become a ubiquitous treatment option for SIHD in clinical practice, the role of OMT overall and nitrates in particular in controlling angina symptoms and improving clinical outcomes may be underappreciated among clinicians and patients alike.

Conclusions

Thorough attempts by clinicians to administer short- and long-acting nitrates to patients could fill a gap in secondary prevention in SIHD management, improve patient quality of life, and prevent adverse cardiovascular events. Education is necessary to emphasize that nitrates form part of the foundation of

MAIN POINTS

- Stable ischemic heart disease (SIHD) levies a substantial economic and health toll, with direct and indirect expenditures totaling billions of dollars.
- The prevalence of SIHD increases as a function of age, with half of all patients with stable angina aged $>$ 65 years, and there are no signs of the trend reversing as the US population ages, with increase in comorbidities such as diabetes and obesity.
- A thorough evaluation of an SIHD patient requires assessment of comorbid conditions (ie, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, and chronic kidney disease) and traditional cardiovascular risk factors (ie, age, gender, tobacco use, and family history).
- Further diagnostic and prognostic evaluations include noninvasive testing and cardiac catheterization to determine anatomic and ischemic burdens of disease, respectively, although the value of ischemic burden in prognosticating future adverse cardiovascular events in SIHD has recently been questioned.
- With the persistent health and economic burden of SIHD, determining the optimal management strategy and employing it evenly across diverse patient populations is paramount. Since elective percutaneous coronary intervention has become a ubiquitous treatment option for SIHD in clinical practice, the role of optimal medical therapy overall and nitrates in particular in controlling angina symptoms and improving clinical outcomes may be underappreciated among clinicians and patients alike.

SIHD management, regardless of whether conservative or invasive strategies are undertaken. Despite their pivotal role in the management of SIHD, organic nitrates are one of the only classes of anti-anginal agents that have not been tested in a long-term, large-scale randomized trial to determine the efficacy of various nitrate formulations for improving clinical outcomes, including adverse cardiovascular events and quality of life. ■

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