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Experimental and early investigational drugs for angina pectoris

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Abstract

Introduction—Ischemic heart disease (IHD) is a major cause of death and disability among Western countries and angina pectoris is the most prevalent symptomatic manifestation. Strategies to improve management of chronic stable angina are a priority.

Areas covered—A comprehensive review was conducted using the Medline and Cochrane databases as well as the clinical trial databases in the United States and Europe. Traditional therapies for angina will be discussed. This review particularly emphasizes investigational therapies for angina (including pharmacological agents, cell and gene based therapies, and herbal medications).

Expert commentary—There has been renewed interest in older anti-angina agents (e.g., perhexiline, amiodarone, and phosphodiesterase-5 inhibitors). Other anti-inflammatory agents (e.g., allopurinol and febuxostat) are currently undergoing evaluation for angina therapy. Therapeutic angiogenesis continues to face some challenges. Future trials should evaluate the optimum patient population that would benefit from this form of therapy.

Keywords

angina; coronary artery disease; ischemic heart disease; pharmacology

1. Ischemic Heart Disease and Angina Pectoris

Ischemic heart disease (IHD) continues to be the major cause of death and disability among most Western countries, and angina pectoris is the most prevalent symptomatic manifestation. Thus, improving the management of angina is clearly a priority. Moreover, almost one third of the patients have suboptimal management with lifestyle modifications, and traditional therapies, therefore there is a need for novel pharmacological therapies [1,2]. A thorough understanding of the pathophysiology of IHD and angina is essential for optimal management and critical for the development of newer approaches to its therapy.

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Declaration of Interest

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2. Pathophysiology of Angina

Angina pectoris (or angina) represents the clinical symptom of myocardial ischemia. Myocardial ischemia results from an imbalance between myocardial oxygen demand and delivery [3]. This myocardial delivery-demand mismatch can occur as a result of increased oxygen demand, reduced supply or more frequent combinations of increased demand with limited supply.

Four main factors contribute to myocardial oxygen demand: systolic blood pressure, heart rate, myocardial wall tension, and myocardial contractility. The major determinants of oxygen supply include the myocardial (coronary) blood flow and oxygen carrying capacity of the blood (i.e., hemoglobin level). Increase in coronary blood flow usually compensates for an increase in myocardial oxygen demand during physiological conditions (e.g., exercise) among patients without flow-limiting obstruction [4]. Angina symptoms can be precipitated due to myocardial ischemia induced during exercise or emotional stress. Atherosclerotic coronary artery disease (CAD) with flow-limiting epicardial coronary artery obstruction remains the most prevalent etiology of myocardial ischemia [5]. A small proportion (about ~5%) will have coronary artery spasm, usually with some evidence for coronary atherosclerosis. Another subset of patients, dominated by women, have evidence for ischemia and experience angina symptoms, despite absence of flow-limiting epicardial coronary artery obstruction (e.g., angiographically “normal” or nonobstructive CAD). Many of these patients have evidence for coronary microvascular dysfunction (i.e., microvascular disease), usually a result of endothelial and/or vascular smooth muscle dysfunction involving the smaller coronary vessels.

Treatment of underlying CAD, by lifestyle modification, statins, and antianginal drugs, remains the mainstay for guideline-directed therapy for patients with angina [6]. Lifestyle modifications alone can be an effective treatment for angina, but this is beyond the scope of our review, and this area has been extensively discussed in guideline recommendations [6,7]. There has been particular emphasis on smoking cessation, healthy diet, regular exercise, and adequate blood pressure control, since these measures have been demonstrated to improve survival in patients with CAD [8,9]. Revascularization (either percutaneous coronary intervention or coronary artery bypass grafting) is recommended for subjects with persistent lifestyle-limiting angina despite appropriate pharmacological therapy. Revascularization effectively improves symptoms, however most populations do not receive a survival benefit [10,11]. Interestingly, despite appropriate revascularization, some patients continue to have evidence for ischemia and experience angina. Some others with angina cannot have complete revascularization due to anatomical limitations [12]. In this review, we will discuss the various pharmacological angina therapies with particular emphasis on investigational therapies for angina.

3. Traditional Pharmacological Therapies for Angina

Pharmacological therapies for treatment of angina had primarily focused on limiting increases in myocardial oxygen demand through heart rate and systolic blood pressure reduction and/or enhancement of coronary blood flow by vascular smooth muscle relaxation

[13]. Not only does heart rate reduction improve angina symptoms, resting heart rate is an important predictor for increased risk of adverse events in patients with CAD [14]. The most frequently used anti-agents include beta-adrenergic blockers (BBs), calcium antagonists (CAs, both dihydropyridines and non-dihydropyridines), and nitrates [6,7]. Other pharmacological agents include ivabradine, ranolazine, and trimetazidine (Figure, Table 1). These agents are recommended by American and European guidelines as adjunctive therapy or for subjects who are intolerant to the traditional therapies (i.e., BBs, CAs, and nitrates) (Table 1) [6,7].

3.1 Heart rate modulation

BBs exert their effect mainly through limiting increases in heart rate. Besides improving angina symptoms; BBs have been shown to improve survival in subjects with depressed left ventricular ejection fraction and those with recent myocardial infarction [15,16]. However, the impact of BBs on survival in CAD patients in general has been questioned [17]. BBs, either selective or non-selective, are well tolerated in patients with chronic stable angina. Nebivolol, in particular, is a selective B1 antagonist, with vasodilator effect via nitric oxide production [18]. Nebivolol is approved by the Food and Drug administration for hypertension. Nebivolol has been shown to improve coronary flow reserve, supporting the suggestion of a beneficial effect on the coronary microcirculation [19,20]. An ongoing trial, nebivolol for the Relief of Microvascular Angina in Women (NIRVANA) [NCT01665508], is evaluating the effects of nebivolol for angina relief in women with microvascular disease.

In general, BBs are recommended as first-line therapy for management of angina [6,7]. A considerable proportion of patients with CAD are intolerant to BBs or encounter side effects from their use (e.g., fatigue), which further limit their use [16].

Ivabradine exerts its action through inhibition of a specific sinus node pacemaker current. Ivabradine reduces the resting heart rate without affecting the action potential duration [21]. In the ASSOCIATE trial, ivabradine added to therapy with atenolol improved exercise tolerance in subjects with stable angina [22]. In a meta-analysis of seven randomized trials, ivabradine improved exercise duration and time to onset of angina; however, this effect was noted only after 3 months of treatment [23]. In the Study Assessing the Morbidity–Mortality Benefits of the I(f) Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY), 19,102 patients with stable coronary artery disease without clinical heart failure were randomized to either ivabradine or placebo on a background of standard medical therapy. Ivabradine failed to reduce adverse cardiac events (i.e., cardiovascular death or myocardial infarction) [24]. The European Medicines Agency recommends that ivabradine be used only to alleviate symptoms of angina, and that considerations to stop treatment if there is no improvement in angina symptoms after 3 months, or if the improvement is only limited [25].

3.2. Late-sodium current inhibitor

Ranolazine is a late-sodium current inhibitor that reduces intracellular calcium overload during ischemia resulting in the distribution of myocardial blood flow towards the ischemic areas, thus reducing angina [26]. Several large randomized trials have demonstrated that

ranolazine, either as mono-therapy or as an adjunctive to other anti-anginal therapies (i.e., BBs, CAs, or nitrates), improves exercise tolerance and reduces angina symptoms in patients with chronic stable angina [27–29]. A recent large, multicenter, randomized trial found lack of benefit of ranolazine in reducing the risk of urgent revascularization or hospitalization with unstable angina in subjects with incomplete revascularization after percutaneous coronary intervention [30]. Some investigators had argued that incomplete revascularization does not necessarily imply ischemia, thus an ongoing trial (IMprovement of subjective WELL-being by ranolazine in patients with chronic angina and known myocardial ischemia [IMWELL]) is examining the effect on ranolazine in reducing angina symptoms in subjects who had incomplete revascularization after percutaneous coronary intervention but with proven ischemia [NCT02265796]. In contrast to BBs and CAs, both ivabradine and ranolazine do not exert any chronotropic or inotropic effect.

3.3. Vascular smooth muscle relaxation

3.3.1. Calcium antagonists—CAs improve angina primarily by reducing vascular smooth resistance and arteriolar dilation. CAs are classified into dihydropyridines (amlodipine and nifedipine) and non-dihydropyridines (verapamil and diltiazem). In addition, non-dihydropyridines reduce or limit the rise in heart rate related to stress. CAs improve symptoms with no impact on adverse cardiac events in patients with CAD [31]. The combination of non-dihydropyridines (i.e., verapamil and diltiazem) with BBs is not recommended in patients with CAD and left ventricular dysfunction [7].

3.3.2. Nitrates—Nitrates primarily exert their effect by relaxation of vascular smooth muscle. This effect is mediated by triggering nitric oxide and cyclic guanylate cyclase. Nitrates have been shown to improve angina symptoms, however, this class is ineffective in improving quality of life and the risk of adverse events [32]. Short-acting nitrate preparations (such as sublingual) are considered the drugs of choice during acute angina pectoris, while longer-acting preparations are used for prophylaxis of angina [7].

3.3.3. Nicorandil—Nicorandil is a nitrate derivative of nicotinamide, which stimulates the potassium channel, thus resulting in the dilation of the coronary arteries. In a large, multicenter, randomized trial enrolling 5126 patients with stable angina on standard anti-angina therapy, nicorandil reduced the composite of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain at a median of 1.6 years compared with placebo; however, the risks of coronary heart disease death or non-fatal myocardial infarction was not reduced [33]. In a propensity score matched analysis of 5116 Japanese patients with CAD, nicorandil was associated with a reduction in the risk of all-cause mortality, compared with controls [34]. Nicorandil was further evaluated in patients with coronary slow flow or microvascular disease. In a single-center, randomized trial of 54 patients with slow flow, nicorandil reduced the angina attacks compared with sustained release nitroglycerine [35]. A currently ongoing multicenter, randomized trial in China, Nicorandil Treatment of Patients Diagnosed as Coronary Heart Disease with Stable Angina (SIGMART), is further testing nicorandil on the background of standard therapy in patients with stable angina [NCT01396395]. Nicorandil has been approved for the treatment of angina in some countries like Japan, France, and the United Kingdom for many years.

3.3.4. Molsidomine—Molsidomine is a direct nitric oxide donating vasodilator. In 172 patients with stable angina, molsidomine was associated with a reduction in the pro-inflammatory marker (soluble ICAM-1) after 4 weeks and 12 months of treatment. This medication was associated with a reduction in angina attacks and nitrate use [36]. Both higher (i.e., 16 mg daily) and lower doses (i.e., 8 mg daily) were demonstrated to improve angina, however, hypotension was a noticeable side effect from the higher dose [37]. Although these initial results appeared promising, this medication was challenged in the MEDCOR trial. This trial was a double-blind, placebo-controlled randomized trial that evaluated the effect of molsidomine 16 mg daily in subjects with CAD undergoing percutaneous coronary intervention. At 12 months, molsidomine did not improve endothelial dysfunction compared with placebo [38]. Molsidomine is approved as a second-line anti-angina therapy in some countries in Europe.

3.4. Metabolic modulation

Trimetazidine is a “metabolic modulator” which exerts its action by inhibiting fatty acid oxidation and improving myocardial glucose utilization (glucose becomes the primary source for adenosine triphosphate production in the myocardial cells during hypoxia). In a meta-analysis of 23 randomized trials with 1378 patients, trimetazidine improved angina symptoms compared with placebo or other anti-angina therapies [39]. To date, there has been no large randomized trial evaluating the safety of trimetazidine or its impact on objective outcomes.

4. Investigational/Ongoing Investigational Pharmacological Therapies for Angina

4.1. Heart rate reduction

4.1.1. Eleclazine—Eleclazine, or GS-6615, is a more potent and longer-acting modification of ranolazine that is currently undergoing evaluation in subjects with long QT syndrome [NCT01849003], while another trial is testing the exercise capacity in subjects with symptomatic hypertrophic cardiomyopathy (LIBERTY-HCM) [40]. However, there is no report of development identified for phase I trials in patients with CAD.

4.1.2. Amiodarone/Dronedarone—Amiodarone was initially developed as an anti-angina therapy. In a small double-blind, randomized trial, amiodarone improved exercise capacity and reduced angina symptoms, compared with placebo, in patients with symptomatic CAD who continued to be symptomatic despite triple angina therapy [41]. However, owing to potential for serious side effects concerns from long-term use, amiodarone has not been widely utilized as anti-angina, and is mainly used as anti-arrhythmic. We have occasionally used low-dose amiodarone (i.e., 200 mg daily or less) as added therapy in very elderly patients who continue to have limiting angina with no other therapeutic options. An ongoing trial, Safety of Amiodarone and Ranolazine Together in Patients with Angina (SARA) [NCT01558830], is investigating the safety and efficacy of amiodarone and ranolazine in subjects with stable CAD. Amiodarone is an approved medication for arrhythmias, however, it is undergoing continued investigation for angina. Its less toxic derivative, dronedarone, reduced unstable angina hospitalizations in the ATHENA

trial among patients with atrial fibrillation and may be worthy of further investigation for angina [42].

4.2. Vascular smooth muscle relaxation

4.2.1. Rho kinase inhibitors—Rho kinase inhibitors exhibit antihypertensive activity through alternations in the Rho/ROCK pathway [43]. The Rho-related GTP binding proteins regulate the sensitivity of vascular smooth muscle in relation to calcium resulting in a reduction in vascular smooth muscle hyper contractility. This vasodilation is expected to reduce myocardial oxygen demand (by decreasing systolic BP and hence LV afterload) and improve myocardial perfusion by dilating smaller vessels and relieving coronary macro and microvascular spasm. The latter should help to redistribute myocardial blood flow toward ischemic regions. Fasudil has been the most widely investigated among this class. In a multicenter randomized trial, fasudil improved the time to ST depression on exercise test compared with placebo, with no difference in the class or frequency of angina [44]. In another study, intra-coronary administration of fasudil increased oxygen saturation in coronary sinus vein from subjects with angiographically proven CAD, but not in those with angiographically normal epicardial coronary arteries [45]. A novel Rho kinase inhibitor, DW1865, was tested in experimental studies and was shown to be ten times more potent than fasudil in inhibiting Rho kinase. DW1865 resulted in a significant dose-related reduction in blood pressure. In addition, DW1865 blocked angiotensin II-induced stress fiber formation and cellular hypertrophy [46]. To date, there has been no reported study that investigated the benefits of DW1865 in angina patients. Nevertheless, this is a promising approach, particularly for patients with coronary microvascular dysfunction.

4.2.2. Endothelin receptor blockers—Endogenous endothelin release promotes vasoconstriction in subjects with CAD [47]. Theoretically, endothelin receptor antagonists would be beneficial in improving myocardial ischemia. There has been no randomized clinical trial to date that evaluated this hypothesis. In fact, intra-coronary injection of a selective endothelin receptor antagonist, BQ-123, prevented the normal reduction of myocardial ischemia on repeated balloon inflations in subjects undergoing percutaneous coronary intervention compared with intra-coronary saline injections [48].

4.2.3. Phosphodiesterase-5 inhibitors—Similar to amiodarone, phosphodiesterase-5 inhibitors were initially developed as an anti-angina therapy, however, earlier phase I trials were not promising. This effect is mediated by endogenous release of nitric oxide (through cyclic guanyl monophosphate inhibition). These drugs are mainly utilized for erectile dysfunction and pulmonary hypertension. An ongoing trial, Effects of Sildenafil on Signs and SYmptoms of Ischemia, Myocardial Blood Flow, and Markers of ANgiogenesis in Patients with Refractory CoronarY Artery Disease [EUCTR2010-023375-26], is investigating whether sildenafil improves myocardial perfusion by angiogenesis in patients with angina refractory to medical treatment.

4.3. Metabolic modulation

4.3.1. Mildronate—Mildronate is a fatty acid oxidation inhibitor. In experimental studies, mildronate reduced the infarct size during acute myocardial ischemia [49]. In a double-

blind, randomized controlled trial enrolling 317 patients with chronic CAD, mildronate was superior to placebo in improving exercise tolerance at 12-months [50]. A dose-dependent improvement in exercise tolerance has been observed with mildronate [51]. This medication has been investigated only in Eastern Europe.

4.3.2. Perhexiline—Perhexiline is another agent which functions by inhibiting fatty acid oxidation. Perhexiline was studied in the past [52,53], however, there had been concerns regarding liver toxicity and peripheral neuropathy [54,55], therefore this medication was not further investigated for decades. These side effects are believed to occur mainly in those with slow metabolism of perhexiline, and could be reduced if the plasma concentration of the drug is maintained between 150–600 ng/ml [56]. More recently, a retrospective analysis of two tertiary centers in the United Kingdom including 151 patients with chronic heart failure and angina revealed that perhexiline therapy provided relief of angina symptoms in ~60% of the patients and was well tolerated [57].

4.4. Miscellaneous agents

4.4.1. Allopurinol—Allopurinol is a xanthine oxidase inhibitor, which has been widely used for prevention of gout flare recurrence. In a double blinded, multicenter randomized trial, high-dose allopurinol (i.e., 600 mg daily) improved the time to ST-segment depression during exercise testing and increased the exercise time in subjects with angiographically-proven CAD compared with placebo [58]. This effect is believed to be secondary to reduction in vascular oxidative stress and improvement in endothelial function in subjects with stable CAD [59]. To date, no further large studies have been performed to further evaluate the efficacy and safety of allopurinol in subjects with CAD.

4.4.2. Febuxostat—Febuxostat is an emerging xanthine oxidase inhibitor which is more potent than allopurinol. Careful monitoring of liver function tests is important since there have been reports of serious liver toxicity. An ongoing trial, the influence of febuxostat on coronary artery endothelial dysfunction in participants with chronic stable angina [NCT01763996], is a placebo-controlled trial aiming to test the efficacy of febuxostat in improving coronary artery flow after 12 weeks of treatment in subjects with CAD.

4.4.3. Testosterone—Testosterone is thought to improve endothelial function and relax the vascular smooth muscle. In addition, testosterone was demonstrated to reduce inflammatory cytokines and total cholesterol level in patients with established CAD [60]. This observation is important since in men with angina, those who had lower testosterone levels tend to have worse CAD than those with normal levels of testosterone [61]. In 14 men with CAD, intravenous testosterone resulted in an increased time to ST-segment depression on exercise test [62]. Subsequently, low-dose transdermal testosterone therapy was formally tested in a double-blind, placebo controlled trial. In 46 men with chronic stable angina, low-dose transdermal testosterone therapy reduced exercise-induced myocardial ischemia [63]. Long-term testosterone therapy was further evaluated in one trial [64]. In 15 men with stable angina, low dose testosterone reduced time to ischemia over the course of 12 months compared with placebo. However, there has been increasing concern regarding the risk of all-cause mortality, myocardial infarction, and stroke with low dose testosterone in men with

CAD [65]. However, the level of testosterone at the end of the follow-up was not measured in this study, therefore, the efficacy and safety of low-dose testosterone in subjects with CAD remains unanswered.

5. Therapeutic Angiogenesis

Patients with severe CAD often develop collateral vessels to the ischemic myocardial areas, however, this physiological mechanism is often insufficient to relieve the angina symptoms of myocardial ischemia. Therapeutic angiogenesis aims at stimulating new vessels which could, in part, improve blood supply to areas with inadequate blood flow. Vascular endothelial growth factor (VEGF) is among the earlier growth factors expressed during ischemia. Fibroblast growth factor has been shown to promote angiogenesis and potentiate the effect of VEGF. Therefore, there has been interest in these protein factors as targets for therapeutic angiogenesis [66]. Clinical trials investigating these therapies have been challenging due to the heterogeneous patient population, suboptimal patient selection, and the different end points. In the AGENT-3 and AGENT-4 trials, we found benefit in the women with refractory angina and no other treatment options [67].

In three phase I/IIa trials, intramyocardial bone marrow stem cells for subjects with refractory angina had provided some promising results [68–70]. In a phase IIb, double-blind, placebo-controlled, randomized trial (ACT34–CMI) with 167 patients with refractory angina, intramyocardial injections of autologous CD34+ cells resulted in improvement in angina frequency and exercise tolerance [71]. The ongoing RENEW study, a phase III, randomized trial with planned enrollment of 444 patients with refractory angina, will provide insight regarding the efficacy of cell therapy in subjects with refractory angina [72].

6. Herbal Medications

Herbal medications are widely used in China for treatment of various medical conditions. *Salviae miltiorrhiza* is a famous Chinese medication that has been used as an adjunctive therapy in patients with CAD. Several Chinese injections contain salvia, for example, Danshen, Danhong, and Guaxin Shutong injections. Some suggest that these injections are effective in improving angina symptoms [73,74]. Trials are ongoing [NCT01681316 and NCT02280850] to further test the efficacy of these therapies. Overall, the efficacy and safety of these therapies remain unanswered knowledge gaps.

7. Expert Opinion

Angina remains a major concern, and a remarkable proportion of patients remain symptomatic despite traditional pharmacological therapies. Lifestyle changes remain an important aspect for therapy. Among the various traditional therapies, BBs remain the most extensively studied and used, and therefore are considered as first-line agents. Some patient subsets receive a survival benefit, including those with depressed ejection fraction and recent myocardial infarction. CAs and nitrates, on the other hand, provide symptomatic relief, with no benefit on hard outcomes. Other second-line agent traditional therapies (i.e., ranolazine and ivabradine) have been studied extensively. Ranolazine has evidence from multiple

randomized trials showing improvement in angina and exercise tolerance. However there is only limited evidence to support the conclusion that ivabradine improves angina in patients without heart failure. Triamterezine has been available in some countries, and the evidence with this medication is uncertain. Nicorandil has been approved as a second-line agent in some countries

Among the investigational pharmacological therapies, there has been renewed interest in older agents (e.g., perhexiline, amiodarone, and phosphodiesterase-5 inhibitors). Other anti-inflammatory agents (e.g., allopurinol and febuxostat) and metabolic modulatory agents (e.g., mildronate) are currently undergoing evaluation for angina therapy. To date, data regarding the effectiveness of these investigational pharmacological therapies suggest that these agents exhibit only mild effect on symptoms in patients with refractory angina. Data have not been sufficient to withdraw conclusions regarding the impact of these investigational on adverse events (Table 2). Therapeutic angiogenesis continues to face some challenges when added to drugs for angina; however, the results of trials with ACT34-CMI have been encouraging. Future trials should define the optimum patient population (phenotype) likely to derive benefit from this novel form of therapy when added to drugs for angina, as well as the best vector cell. Herbal medications have been widely available in some countries; however, evidence for their use in angina remains a knowledge gap. We believe that there are many knowledge gaps, and further innovative therapies are needed for the treatment of patients with refractory angina.

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Camm AJ, Manolis A, Ambrosio G, et al. Unresolved issues in the management of chronic stable angina. *Int J Cardiol.* 2015; 201:200–207. [PubMed: 26298381]
2. Ambrosio G, Komajda M, Mugelli A, et al. Management of stable angina: A commentary on the European Society of Cardiology guidelines. *Eur J Prev Cardiol.* 2016; 23:1401–1412. [PubMed: 27222385]
3. Winchester DE, Pepine CJ. Angina treatments and prevention of cardiac events: an appraisal of the evidence. *Eur Heart J Suppl.* 2015; 17:G10–G18. [PubMed: 26740801]
4. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev.* 2008; 88:1009–1086. [PubMed: 18626066]

5. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation*. 2016; 133:e38–e60. [PubMed: 26673558]
6. Fihn SD, Gardin JM, 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: a report of 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:e354–e471. [PubMed: 23166211] Guidelines for stable angina
7. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34:2949–3003. [PubMed: 23996286] Guidelines for stable angina
8. Elgendy IY, Bavry AA, Gong Y, et al. Long-term mortality in hypertensive patients with coronary artery disease: Results from the US cohort of the International Verapamil (SR)/Trandolapril Study. *Hypertension*. 2016 Sep 12. pii: HYPERTENSIONAHA.116.07854.
9. Abrams J. Clinical practice. Chronic stable angina. *N Engl J Med*. 2005; 352:2524–2533. [PubMed: 15958808]
10. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008; 359:677–687. [PubMed: 18703470]
11. Elgendy IY, Conti CR, Bavry AA. Fractional flow reserve: an updated review. *Clin Cardiol*. 2014; 37:371–380. [PubMed: 24652785]
12. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circulation*. 2012; 125:2613–2620. [PubMed: 22550156]
13. Gupta AK, Winchester D, Pepine CJ. Antagonist molecules in the treatment of angina. *Expert Opin Pharmacother*. 2013; 14:2323–2342. [PubMed: 24047238]
14. Kolloch R, Legler UF, Champion A, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VERapamil-SR/trandolapril STudy (INVEST). *Eur Heart J*. 2008; 29:1327–1334. [PubMed: 18375982]
15. Winchester DE, Pepine CJ. Usefulness of beta blockade in contemporary management of patients with stable coronary heart disease. *Am J Cardiol*. 2014; 114:1607–1612. [PubMed: 25260949]
16. Elgendy IY, Mahmoud A, Conti CR. Beta-blockers in the management of coronary artery disease: are we on the verge of a new paradigm shift? *Recent Pat Cardiovasc Drug Discov*. 2014; 9:11–21. [PubMed: 25174339] Review article discussing beta-blocker therapy for patients with coronary artery disease
17. Bangalore S, Steg G, Deedwania P, et al. β -Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012; 308:1340–1349. [PubMed: 23032550]
18. Kobusiak-Prokopowicz M, Jolda-Mydlowska B, Zubkiewicz A, et al. Impact of nebivolol on levels of serum nitric oxide, plasma von Willebrand factor and exercise stress testing parameters in hypertensive and ischemic heart disease patients. *Cardiol J*. 2008; 15:162–168. [PubMed: 18651401]
19. Togni M, Vigorito F, Windecker S, et al. Does the beta-blocker nebivolol increase coronary flow reserve? *Cardiovasc Drugs Ther*. 2007; 21:99–108. [PubMed: 17235472]
20. Tagliamonte E, Cirillo T, Rigo F, et al. Ivabradine and bisoprolol on doppler-derived coronary flow velocity reserve in patients with stable coronary artery disease: Beyond the heart rate. *Adv Ther*. 2015; 32:757–767. [PubMed: 26293212]
21. Savelieva I, Camm AJ. If inhibition with ivabradine: electrophysiological effects and safety. *Drug Saf*. 2008; 31:95–107. [PubMed: 18217787]
22. Tardif JC, Ponikowski P, Kahan T. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J*. 2009; 30:540–548. [PubMed: 19136486]

23. Ye L, Ke D, Chen Q, et al. Effectiveness of ivabradine in treating stable angina pectoris. *Medicine* (Baltimore). 2016; 95:e3245. [PubMed: 27057864]
24. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014; 371:1091–1099. [PubMed: 25176136] Pivotal randomized trial that demonstrated lack of benefit from ivabradine in patients with coronary artery disease without clinical heart failure
25. Corlentor and Procoralan [Internet]. London: European Medicines Agency; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Corlentor_and_Procoralan/human_referral_prac_000044.jsp&mid=WC0b01ac05805c516f [cited 2016 Sep 22]
26. Saad M, Mahmoud A, Elgendy IY, et al. Ranolazine in cardiac arrhythmia. *Clin Cardiol*. 2016; 39:170–178. [PubMed: 26459200]
27. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004; 291:309–316. [PubMed: 14734593]
28. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004; 43:1375–1382. [PubMed: 15093870]
29. Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol*. 2006; 48:566–575. [PubMed: 16875985]
30. Weisz G, Gnreux P, Inguez A, et al. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016; 387:136–145. [PubMed: 26474810] Pivotal randomized trial which showed no benefit for ranolazine in subjects with incomplete revascularization after percutaneous coronary intervention
31. Kawanishi DT, Reid CL, Morrison EC, et al. Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination. *J Am Coll Cardiol*. 1992; 19:409–417. [PubMed: 1732370]
32. Wei J, Wu T, Yang Q, et al. Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol*. 2011; 146:4–12. [PubMed: 20557963]
33. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002; 359:1269–1275. [PubMed: 11965271] Multicenter randomized placebo-controlled trial demonstrating the benefit of nicorandil in patients with stable angina
34. Horinaka S, Yabe A, Yagi H, et al. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese Coronary Artery Disease (JCAD) study. *Circ J*. 2010; 74:503–509. [PubMed: 20081320]
35. Sani HD, Eshraghi A, Nezafati MH, et al. Nicorandil versus nitroglycerin for symptomatic relief of angina in patients with slow coronary flow phenomenon: A randomized clinical trial. *J Cardiovasc Pharmacol Ther*. 2015; 20:401–416. [PubMed: 25701829]
36. Van Hove C, Carreer-Bruhwyler F, Gczy J, et al. Long-term treatment with the NO-donor molsidomine reduces circulating ICAM-1 levels in patients with stable angina. *Atherosclerosis*. 2005; 180:399–405. [PubMed: 15910868]
37. Messin R, Opolski G, Fenyvesi T, et al. Efficacy and safety of molsidomine once-a-day in patients with stable angina pectoris. *Int J Cardiol*. 2005; 98:79–89. [PubMed: 15676171]
38. Barbato E, Herman A, Benit E, et al. Long-term effect of molsidomine, a direct nitric oxide donor, as an add-on treatment, on endothelial dysfunction in patients with stable angina pectoris undergoing percutaneous coronary intervention: Results of the MEDCOR trial. *Atherosclerosis*. 2015; 240:351–354. [PubMed: 25875387]
39. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. *Cochrane Database Syst Rev*. 2005; 4:CD003614.

40. Olivotto I, Hellowell JL, Farzaneh-Far R, et al. Novel approach targeting the complex pathophysiology of hypertrophic cardiomyopathy: the Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) Trial. *Circ Heart Fail*. 2016; 9:e002764. [PubMed: 26915375]
41. Meyer BJ, Amann FW. Additional antianginal efficacy of amiodarone in patients with limiting angina pectoris. *Am Heart J*. 1993; 125:996–1001. [PubMed: 8465772]
42. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009; 360:668–678. [PubMed: 19213680]
43. Feng Y, LoGrasso PV, Defert O, et al. Rho kinase (ROCK) inhibitors and their therapeutic potential. *J Med Chem*. 2016; 59:2269–2300. [PubMed: 26486225]
44. Vicari RM, Chaitman B, Keefe D, et al. Efficacy and safety of fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol*. 2005; 46:1803–1811. [PubMed: 16286163] Randomized trial testing the efficacy of fasudil
45. Fukumoto Y, Mohri M, Inokuchi K, et al. Anti-ischemic effects of fasudil, a specific Rho-kinase inhibitor, in patients with stable effort angina. *J Cardiovasc Pharmacol*. 2007; 49:117–121. [PubMed: 17414222]
46. Oh KS, Oh BK, Park CH, et al. Cardiovascular effects of a novel selective Rho kinase inhibitor, 2-(1H-indazole-5-yl)amino-4-methoxy-6-piperazino triazine (DW1865). *Eur J Pharmacol*. 2013; 702:218–226. [PubMed: 23376156]
47. Kinlay S, Behrendt D, Wainstein M, et al. Role of endothelin-1 in the active constriction of human atherosclerotic coronary arteries. *Circulation*. 2001; 104:1114–1118. [PubMed: 11535565]
48. Kyriakides ZS, Kremastinos DT, Kolettis TM, et al. Acute endothelin-A receptor antagonism prevents normal reduction of myocardial ischemia on repeated balloon inflations during angioplasty. *Circulation*. 2000; 102:1937–1943. [PubMed: 11034942]
49. Sesti C, Simkhovich BZ, Kalvinsh I, et al. Mildronate, a novel fatty acid oxidation inhibitor and antianginal agent, reduces myocardial infarct size without affecting hemodynamics. *J Cardiovasc Pharmacol*. 2006; 47:493–499. [PubMed: 16633095]
50. Dzerve V, Matisone D, Pozdnyakov Y, et al. Mildronate improves the exercise tolerance in patients with stable angina: results of a long term clinical trial. *Sem Cardiovasc Med*. 2010; 16:1–8.
51. Dzerve V. MILSS I Study Group. A dose-dependent improvement in exercise tolerance in patients with stable angina treated with mildronate: a clinical trial "MILSS I". *Medicina (Kaunas)*. 2011; 47:544–551. [PubMed: 22186118]
52. Pepine CJ, Schang SJ, Bemiller CR. Effects of perhexiline on coronary hemodynamic and myocardial metabolic responses to tachycardia. *Circulation*. 1974; 49:887–893. [PubMed: 4828610]
53. Pepine CJ, Schang SJ, Bemiller CR. Effects of perhexiline on symptomatic and hemodynamic responses to exercise in patients with angina pectoris. *Am J Cardiol*. 1974; 33:806–812. [PubMed: 4207576]
54. Roberts RK, Cohn D, Petroff V, et al. Liver disease induced by perhexiline maleate. *Med J Aust*. 1981; 2:553–554. [PubMed: 7321956]
55. Bouche P, Bousser MG, Peytour MA, et al. Perhexiline maleate and peripheral neuropathy. *Neurology*. 1979; 29:739–743. [PubMed: 220563]
56. Cole PL, Beamer AD, McGowan N, et al. Efficacy and safety of perhexiline maleate in refractory angina. A double-blind placebo-controlled clinical trial of a novel antianginal agent. *Circulation*. 1990; 81:1260–1270. [PubMed: 2180591]
57. Phan TT, Shivu GN, Choudhury A, et al. Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. *Eur J Heart Fail*. 2009; 11:881–886. [PubMed: 19656806]
58. Noman A, Ang DS, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet*. 2010; 375:2161–2167. [PubMed: 20542554] Randomized trial evaluating the efficacy of allopurinol in patients with coronary artery disease
59. Rajendra NS, Ireland S, George J, et al. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. *J Am Coll Cardiol*. 2011; 58:820–828. [PubMed: 21835317]

60. Malkin CJ, Pugh PJ, Jones RD, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab.* 2004; 89:3313–3318. [PubMed: 15240608]
61. Rosano GM, Sheiban I, Massaro R, et al. Low testosterone levels are associated with coronary artery disease in male patients with angina. *Int J Impot Res.* 2007; 19:176–182. [PubMed: 16943795]
62. Rosano GM, Leonardo F, Pagnotta P, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation.* 1999; 99:1666–1670. [PubMed: 10190874]
63. English KM, Steeds RP, Jones TH, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation.* 2000; 102:1906–1911. [PubMed: 11034937]
64. Mathur A, Malkin C, Saeed B, et al. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol.* 2009; 161:443–449. [PubMed: 19542238]
65. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 2013; 310:1829–1836. [PubMed: 24193080] Large cohort study which demonstrated potential harm with low dose testosterone
66. Attanasio S, Schaer G. Therapeutic angiogenesis for the management of refractory angina: current concepts. *Cardiovasc Ther.* 2011; 29:e1–e11. Review article discussing therapeutic angiogenesis for refractory angina
67. Henry TD, Grines CL, Watkins MW, et al. Effects of Ad5FGF-4 in patients with angina: an analysis of pooled data from the AGENT-3 and AGENT-4 trials. *J Am Coll Cardiol.* 2007; 50:1038–1046. [PubMed: 17825712]
68. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation.* 2007; 115:3165–3172. [PubMed: 17562958]
69. Tse HF, Thambar S, Kwong YL, et al. Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). *Eur Heart J.* 2007; 28:2998–3005. [PubMed: 17984132]
70. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. *JAMA.* 2009; 301:1997–2004. [PubMed: 19454638]
71. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res.* 2011; 109:428–436. [PubMed: 21737787] Phase IIB trial which demonstrated that CD34+ improved angina symptoms in patients with refractory angina
72. Povsic TJ, Junge C, Nada A, et al. A phase 3, randomized, double-blinded, active-controlled, unblinded standard of care study assessing the efficacy and safety of intramyocardial autologous CD34+ cell administration in patients with refractory angina: design of the RENEW study. *Am Heart J.* 2013; 165:854–861. [PubMed: 23708155]
73. Wang JM. Meta-analysis of comparative study on guanxinling injection in the treatment of unstable angina pectoris. *Zhong Guo Yao Fang.* 2011; 22:1810–1812.
74. Zhang X, Wang H, Chang Y, et al. An overview of meta-analyses of danhong injection for unstable angina. *Evid Based Complement Alternat Med.* 2015; 2015:358028. [PubMed: 26539221]

Highlights

- Overview for the pathophysiology of angina
- Overlook for the traditional therapies for angina including beta-blockers, calcium antagonists, nitrates, and others
- Investigational therapies for angina
- Therapeutic angiogenesis and angina, challenges and future directions
- Herbal medications for angina, an unanswered knowledge gap

Figure 1.
Summary of the mechanism of action for the traditional and investigational therapies for angina.

Table 1

Guideline recommendations for the various pharmacological agents

	2013 ESC class/level of evidence	2012 ACC/AHA class/level of evidence
Traditional therapies:		
<i>Heart rate reduction:</i>		
Beta-adrenergic blockerstd	Class IA post MI and LV dysfunction *	Class IB in patients with MI for 3 years Class IIB in other patients
Ivabradine	Class IIa B *	Not approved in the US
<i>Late-sodium current inhibitor:</i>		
Ranolazine	Class IIa B	Class IIB
<i>Vascular smooth muscle relaxation:</i>		
Calcium antagonists	Class IA in patients intolerant to BBs	
Nitrates	Class IB short-acting in acute angina Class IIa B long acting	Class IB
Nicorandil	Class IIa B	Not approved in the US
Molsidomine	Approved as second line in some countries in Europe	Not approved
<i>Metabolic modulation:</i>		
Trimetazidine	Class IIa B	Not approved in the US
Investigational therapies:		
<i>Heart rate reduction:</i>		
Eleclazine	Not approved	Not approved
Amiodarone/Dronedaron	Not approved	Not approved
<i>Vascular smooth muscle relaxation:</i>		
Rho kinase inhibitors	Not approved	Not approved
Endogenous endothelin release	Not approved	Not approved
Phosphodiesterase-5 inhibitors	Not approved	Not approved
<i>Metabolic modulation:</i>		
Mildronate	Not approved	Not approved
Perhexiline	Not approved	Not approved
<i>Miscellaneous agents:</i>		
Allopurinol	Not approved	Not approved
Febuxostat	Not approved	Not approved
Testosterone	Not approved	Not approved

* Combination of metoprolol (beta-adrenergic blocker) and ivabradine is approved in Europe

ACC/AHA= American College of Cardiology/American Heart Association

ESC=European Society of Cardiology

LV= left ventricular

MI= myocardial infarction

Table 2

Summary of angina therapies and effect on symptoms and adverse events

	Impact on symptoms	Impact on adverse events
Traditional therapies:		
<i>Heart rate reduction:</i>		
Beta-adrenergic blockers	Moderate effect	In specific population *
Ivabradine	Moderate effect	No
<i>Late-sodium current inhibitor:</i>		
Ranolazine	Moderate effect	No
<i>Vascular smooth muscle relaxation:</i>		
Calcium antagonists	Moderate effect	No
Nitrates	Moderate effect	No
Nicorandil	Moderate effect	Maybe
Molsidomine	Mild effect	Unknown
<i>Metabolic modulation:</i>		
Trimetazidine	Moderate effect	No
Investigational therapies:		
<i>Heart rate reduction:</i>		
Eleclazine	Unknown	Unknown
Amiodarone/Dronedarone	Mild effect	No
<i>Vascular smooth muscle relaxation:</i>		
Rho kinase inhibitors	Mild effect	Unknown
Endogenous endothelin release	Unknown	Unknown
Phosphodiesterase-5 inhibitors	No	Unknown
<i>Metabolic modulation:</i>		
Mildronate	Mild effect	Unknown
Perhexiline	Moderate effect	Unknown
<i>Miscellaneous agents:</i>		
Allopurinol	Mild effect	Unknown
Febuxostat	Unknown	Unknown
Testosterone	Mild effect	Maybe harmful
Therapeutic angiogenesis	Mild effect	Unknown
Herbal medications	Unknown	Unknown

* Patients with reduced left ventricular ejection fraction or those with a recent myocardial infarction