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Antagonist molecules in the treatment of angina

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Abstract

Introduction—Management of chronic angina has evolved dramatically in the last few decades with several options for pharmacotherapy outlined in various evidence-based guidelines.

Areas covered—There is a growing list of drugs that are currently being investigated for treatment of chronic angina. These also include several herbal medications, which are now being scientifically evaluated as potential alternative or even adjunctive therapy for angina. Gene- and cell-based therapies have opened yet another avenue for management of chronic refractory angina in ‘no-option’ patients who are not candidates for either percutaneous or surgical revascularization and are on optimal medical therapy. An extensive review of literature using PUBMED, Cochrane database, clinical trial databases of USA and European Union was done and summarized in this review. This review will attempt to discuss the traditional as well as novel therapeutic agents for angina.

Expert opinion—Several pharmacological and non-pharmacological therapeutic options are now available for treatment and management of chronic refractory angina. Renewed interest in traditional therapies and cell- and gene-based modalities with targeted drug delivery systems will open the doors for personalized therapy for patients with chronic refractory angina.

1. ANGINA, A HISTORICAL PROSPECTIVE

Although often thought to be a modern disease, the history of angina could have started with an atypical presentation 330 years ago. A historical perspective of angina is outlined in an excellent treatise by Opie [1]. Heberden first described angina, in 1772, as a disorder of the breast in a lecture given to Royal College of Physicians. He was the first to describe the association of exertion to symptom exacerbation, and distribution of pain to left arm and left sub-sternal area. John Hunter described precipitation of angina by emotional crisis in 1793, and performed an autopsy on a patient who suffered from ‘a violent transport of anger’ who ‘fell down and expired immediately’. The two coronary arteries had become one piece of bone. Parry localized the syndrome to heart in 1799, where he linked it to poor blood flow. Alan Burns described the supply and demand hypothesis in 1809, and Virchow described ischemia in 1858. Osler described the coronary lesions as cause of angina ‘obliterative endarteritis’. Sir Thomas Lewis, in 1933, described the concept of absolute and relative ischemia and postulated ‘substance P’ as the origin of the muscular pain in claudication.

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Lauder Brunton first used amyl nitrate to treat angina in 1867. It was not until the mid-20th century when beta-blockers (BB) and calcium channel blockers (CCB) were first discovered and used to treat angina.

2. ANGINA – A GLOBAL ISSUE

Over the past century, the global burden of cardiovascular disease (CVD) has increased dramatically. The proportion of deaths attributable to ischemic heart disease was <10% at the turn of 20th century, increasing to approximately 30% of deaths worldwide and nearly 50% of deaths in the industrial world. Coronary artery disease (CAD) is the leading cause of death and disability worldwide, resulting in 7.2 million deaths per year [2]. CVD is the leading cause of death worldwide, accounting for around 16.7 million deaths each year, mainly from heart attacks and strokes [3]. This number is predicted to increase to approximately 25 million deaths by 2020, if the current trends continue [4]. Current estimates show that the global burden of CVD far exceeds that of its death toll, affecting an estimated 128 million people, or nearly eight times the number for cardiovascular mortality.

3. PATHOPHYSIOLOGY OF ANGINA

Understanding the basic pathophysiology of angina is paramount to appropriately treat the patients. By definition, myocardial ischemia results from an imbalance between myocardial energy supply, from insufficient sources of oxygen and substrate (glucose, free fatty acids (FFAs)), and myocardial oxygen demand. Mismatch of myocardial oxygen supply and demand is the common pathway which results in angina, however the mechanisms behind this mismatch are complex, involving substrate supply and utilization, enzymatic activities, and other variables involved in intermediary metabolism and mitochondrial function. These play important roles in the pathogenesis of myocardial ischemia in angina, acute coronary syndromes (ACS), and during reperfusion ischemic injury (Figure 1). Major determinants of myocardial oxygen demand are heart rate, blood pressure, and myocardial wall tension, in turn influenced by preload, afterload, and contractility. Physiological increases in myocardial oxygen needs are normally provided by rises in coronary blood flow. Ability of coronary arteries to increase flow to meet myocardial metabolic demand during exercise, called coronary flow reserve, is about four to six times the resting value at maximum dilatation of the coronary arteries [5, 6]. Coronary auto regulation is a complex phenomenon with many regulating variables, and detailed discussion is beyond the scope of this review [7]. Clinically, angina may be further subdivided according to common usage [8], as follows:

3.1 Chronic, stable

Chronic stable angina is generally due to one or more significant obstructive lesions in coronary arteries, defined as stenosis of 50% of the diameter of the left main coronary artery or stenosis of 70% of the diameter of a major epicardial vessel, and as stenoses are fixed, the angina is due to demand ischemia.

3.2 Decubitus

Attacks of decubitus angina occur upon recumbency, which raises end-diastolic volume, myocardial wall tension, and hence oxygen demand.

3.3 Nocturnal

Anginal discomfort awakens the patient, generally due to respiratory pattern changes, episodic tachycardia, hypoxia due to respiratory changes, or recumbency.

3.4 Refractory

Stable chronic angina is termed refractory when it is not controllable by a combination of maximal anti-anginal medication, angioplasty or coronary artery bypass surgery, or when the risks are unjustified.

3.5 Unstable (also called crescendo or rest)

Symptoms are recent onset, severe, and occur at rest or with minimal exertion, last >10 minutes, and follow a crescendo pattern. Unstable angina is an ACS, and when myocardial necrosis becomes evident from elevations in biomarkers, such as troponin I and troponin T, the applicable clinical term becomes non-ST-elevation myocardial infarction, or NSTEMI, in the absence of ST-segment changes. The European Society of Cardiology defines ACS as acute chest pain (ie, chest pain at rest >20 min within the prior 48 hours) together with electrocardiographic (ECG) changes suggesting myocardial ischemia and/or elevation of cardiac markers.

3.6 Microvascular (also called Syndrome X)

More common in women, angina-like pain, 'normal' or non-obstructive CAD by coronary angiograms, and positive exercise tests, sometimes with perfusion defects by stress imaging, are a basic diagnostic triad in microvascular angina [9]. Response to nitrates and other anti-ischemic agents is less reliable, and hormonal abnormalities, changes in pain perception with exaggerated sensitivity, insulin resistance, and psychological overlays may be modifying factors, just as in angina associated with obstructive CAD. Also as with obstructive CAD, most of these patients have varying degrees of endothelial dysfunction proportional to their atherosclerosis risk factor burden. Many have vascular smooth muscle dysfunction and/or even microvascular spasm. Again, similar to obstructive CAD patients, release of vasoactive substances, autonomic dysfunction, and loss of estrogen may all contribute. Chest pain may occur at rest, and/or under conditions of cardiac stress without evidence of ischemia. Gastroesophageal reflux disease (GERD) and esophageal motility and airway disorders are common comorbidities. In part, treatment is difficult because therapeutic responses may not be sustained and because the field lacks an evidence base of large, longer-term randomized controlled trials. Consequently, no guidelines exist to inform practitioners on the management of these patients.

3.7 Coronary artery spasm

Some forms (e.g., rest angina with ST segment elevation) are also called Prinzmetal's or variant angina, or angina inversa. This variant form of angina occurs at rest, often at night or

early morning hours, or with exertion. It is caused by focal or diffuse spasm of an epicardial coronary artery. Most often it is associated with a non-obstructive atherosclerotic lesion. Coronary spasm is a more common cause of chest pain and ACS than formerly believed, and may contribute to pathology with or without coexisting obstructive plaques, more frequently found in men. Over the years, coronary spasm has been linked to hypertension, Asian origin, low intracellular magnesium levels, hyperinsulinemia, defective focal nitric oxide production, and use of tobacco or cocaine as well as oral decongestants containing sympathetic amines.

3.8 Atypical angina

Patients with nonclassical symptoms and signs, such as absence of substernal location and character, exertional trigger, or typical relief with rest or nitroglycerin, are grouped under the term atypical angina. Atypical presentations are more frequent in women and diabetics, displaying variable pain intensity or thresholds, timing, and characteristics. Palpitations, sharp lancinating or back pain are confounding complaints.

3.9 Silent ischemia and anginal equivalents

In some patients, particularly diabetics and the elderly, myocardial ischemia may cause symptoms other than precordial discomfort. These may include dyspnea, diaphoresis, nausea and emesis, fatigue, weakness, altered sensorium, light headedness, and fainting. In the absence of chest pressure, heaviness, pain or sensorial cognition, ischemia is also called silent ischemia.

4. MANAGEMENT OF ANGINA – BASIC PRINCIPLES AND TRADITIONAL THERAPIES

Guidelines for the management of stable angina have been published by the American Heart Association (AHA), American College of Cardiology (ACC), and the European Society of Cardiology (ESC) [10–12]. The key to chronic management of patients with stable angina is treatment of underlying atherosclerotic disease and reduction of other established cardiovascular risks. This is critical to prevent future cardiac events and progression of CAD, which can worsen angina, even if there is complete revascularization [12–13]. One of the most effective treatments for reducing symptoms of angina is revascularization [14]. Several randomized trials, however, have demonstrated that revascularization does not improve the mortality in patients with stable chronic angina [15–19]. In a recently published meta-analysis of 10 prospective randomized controlled trials with a total of 6752 patients, no differences between percutaneous coronary intervention (PCI) versus medical therapy for all-cause mortality, cardiovascular mortality, angina relief at the end of follow-up were noted. PCI was not associated with reductions in all-cause or cardiovascular mortality, myocardial infarction (MI), or angina relief [20]. Surgical revascularization was in fact superior to percutaneous revascularization (BARI2D and FREEDOM) in reducing the death and MI in patients with diabetes [17–19, 21] and those with severe left main, proximal LAD disease or high syntax score (SYNTAX) [22]. These findings continue to support existing clinical practice guidelines that medical therapy be considered the most appropriate initial clinical management for patients with stable angina. Other non-pharmacological

interventions include cardiac rehabilitation, the alleviation of angina symptoms through training, and mechanical therapies, such as external enhanced counterpulsation, extracorporeal shockwave myocardial revascularization, spinal-cord stimulators, stellate-ganglion block, and coronary-sinus occluders and are beyond the scope of this review.

4.1 Optimal medical therapy

as defined by COURAGE trial [15] includes: anti-platelet therapy with aspirin (81–325mg daily), or 75mg Clopidogrel if intolerant to aspirin; long acting beta-blocker (BB), calcium channel blocker (CCB) and a long acting nitrate alone or in combination; angiotensin-converting enzyme inhibitor (ACEi) or aldosterone receptor blocker (ARB) as tolerated; aggressive reduction of low density lipoprotein (LDL) to target of 65–85mg/dl using a statin alone or in combination with ezetimibe. Once LDL is at goal, target high-density lipoprotein (HDL) is above 40mg/dL and triglycerides below 150mg/dL. Lifestyle interventions include regular physical activity, complete cessation of tobacco use and exposure to tobacco smoke, and diet modifications to improve blood pressure, blood glucose levels, and serum lipid levels, along with control of diabetes and weight management [11, 23]. In pooled data including 5034 patients obtained from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) diabetes subgroup (n = 766 of 2287), the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (n = 2368), and the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial (n = 1900), the percentages of patients achieving the 1-year low-density lipoprotein cholesterol targets compared with baseline increased from 55% to 77% in COURAGE, from 59% to 75% in BARI 2D, and from 34% to 42% in FREEDOM. Although similar improved trends were seen for systolic blood pressure, glycemic control, and smoking cessation, only 18% of the COURAGE diabetes subgroup, 23% of BARI 2D patients, and 8% of FREEDOM patients met all four pre-specified treatment targets at 1 year of follow-up. These disappointing results suggest that a significant proportion of diabetic (and non-diabetic) CAD patients fail to achieve pre-specified targets for four major modifiable cardiovascular risk factors even in clinical trials with well-planned, guideline-based secondary prevention algorithms [24].

4.2 Traditional therapies

include BBs, nitrates, and CCBs. These agents work by reducing myocardial oxygen demand (by attenuation of the increase in heart rate, blood pressure, and contractility that occur during work activity), lowering ventricular preload, or improving blood supply by augmenting coronary vasodilatory capacity [25, 26].

4.2.1 Nitrates—produce direct, endothelium-independent vasodilatation and reduce myocardial ischemia by relaxation of venous smooth muscle, which lowers ventricular preload and oxygen demand [8]. Short-acting nitrates provide effective symptomatic relief and can be used as prophylaxis before physical exertion that might induce angina [27]. Long-acting nitrates available in multiple formulations are often used to prevent or reduce the frequency of angina in patients with CAD either as monotherapy or in combination with BB or CCB.

4.2.2 Beta-adrenergic receptor blockers—BBs are usually indicated as first-line therapy for patients with stable angina [11, 12]. These drugs reduce death and recurrent infarction in patients with previous myocardial infarction and in those with depressed left ventricular function, and also lower heart rate and systolic blood pressure by inhibition of β_1 and β_2 adrenergic receptors, which are activated by circulating endogenous norepinephrine and epinephrine in response to exercise or stress. The risk of suffering cardiovascular death or myocardial infarction was reduced by some 30% in post-MI trials with beta blockers [28] however, large BB studies in stable angina, the angina pectoris study in Stockholm ‘APSYS’ [29] and total ischemic burden European trial ‘TIBET’ [30] studies, did not show a significant difference in outcome between patients treated with BB or CCB.

4.2.3 Calcium channel blockers—Several clinical studies have demonstrated anti-anginal efficacy of CCBs [31–35]. The CCBs are all effective antihypertensive agents, a feature that is particularly helpful in the management of patients with both angina and hypertension. While CCBs have been used extensively in treatment of angina, their impact on cardiovascular outcomes in coronary artery disease and stable angina has not been systematically evaluated in randomized controlled trials. In the INVEST trial [36], no difference were noted in prevention of the outcome of all-cause mortality, nonfatal MI, or nonfatal stroke in patient with hypertension and CAD treated either with Verapamil or Atenolol based therapies. Furthermore, similar results were observed comparing the treatment strategies for all-cause mortality, cardiovascular death, cardiovascular hospitalization, and blood pressure control.

Information concerning the effect of the specific classes of anti-anginal therapy on long-term clinical outcome is limited. As such, there is little rationale, in many patients, to choose one class of anti-anginal over another based on a different effect of therapy on clinical outcome or events. ACC/AHA and ESC guidelines for management of chronic stable angina, recommend using BBs as initial therapy for relief of symptoms in patients with chronic stable angina. While BBs have been shown to reduce mortality after MI [28] and may be a valid treatment for patients with stable angina, recently published data from the REACH registry have questioned these benefits [37]. Among patients enrolled in the international REACH registry, BB use was not associated with a lower event rate of cardiovascular events at 44-month follow-up, even among patients with prior history of MI. CCBs or long-acting nitrates as stand alone agent(s) or as an adjunctive therapeutic agent are recommended for relief of symptoms when BBs are contraindicated or cause unacceptable side effects or when initial treatment with BBs is unsuccessful in patients with chronic angina.

5. SECOND-GENERATION ANTI-ANGINAL DRUGS

Over the past decade, several newer agents have been described and are being used increasingly in daily clinical practice.

5.1 Ranolazine

is an active piperazine derivative, which has been studied, in several placebo-controlled, randomized trials of stable angina, either as monotherapy [38] or when added to background therapy with β -adrenergic-receptor blockers, calcium-channel blockers, or nitrates [39,40].

Ranolazine reduced angina-attack frequency and nitroglycerin consumption, and increased exercise treadmill duration, time to onset of angina, and ischemic ST-segment depression on treadmill testing without a clinically significant change in heart rate or blood pressure [38]. Ranolazine is now approved for first-line therapy of angina in the United States. Ranolazine has additional clinical implications with emerging role in arrhythmias, heart failure and reduction of hemoglobin glycosylation [41].

5.2 Nicorandil

Nicorandil, a nicotinamide-nitrate ester [N-(2-hydroxyethyl)-nicotinamide nitrate], is the only clinically available potassium channel opener with antianginal effects, and with comparable efficacy and tolerability to existing antianginal therapy. The IONA (impact of nicorandil in angina) trial was carried out in the UK in which 5126 high-risk angina patients were randomly assigned to receive either placebo or nicorandil [42, 43]. Nicorandil reduced the risk of the primary composite end point (CHD death, nonfatal myocardial infarction [MI], or unplanned hospitalization with cardiac chest pain) by 17% ($p = 0.014$) over a mean follow-up of 1.6 years. Likelihood of deaths from all causes and fatal myocardial infarction was reduced by 35% in patients treated with nicorandil in a prospective observational study of a large cohort of patients who had angiographic evidence of CAD (Japanese Coronary Artery Disease Study) [44]. Nicorandil is not currently Food and Drug Administration (FDA) approved in the USA but is used in Europe and Japan. The ESC lists a class I indication for nicorandil (level of evidence C) for patients with intolerance or contraindications to BB or CCB, and a class IIa indication (level of evidence C) for patients in whom dual antianginal therapy with other classes of drugs is unsuccessful [12].

5.3 Bepridil

It was first approved by the FDA in 1990. It is a CCB, but it is often placed in a category of its own. Bepridil acts as a direct negative chronotrope, ionotrope and vasodilator and is thus able to provide angina relief. Another difference from commonly used CCBs is that bepridil inhibits receptor-operated, voltage-gated calcium channels as well as potassium currents and intracellular calcium/calmodulin complexes. This action results in decreased myocardial oxygen consumption, coronary vasodilation, and increased coronary blood flow. Bepridil helps to decrease the frequency of angina attacks, as measured by the use of nitrates. However, concerns regarding prolongation of the corrected QT interval and torsade de pointes have limited its use in North America [45].

5.4 Ivabradine

Heart rate reduction is a well-accepted and effective approach for the prevention of angina pectoris. Ivabradine decreases heart rate through selective inhibition of I_f , an inward potassium current that is activated by hyperpolarization over the diastolic range of voltages of myocytes in the sinoatrial node [46–49]. Ivabradine reduces the firing rate of the pacemaker cells in the sinoatrial node without affecting the duration of the action potential [47] and is most effective during tachycardia. Ivabradine is effective in the treatment of stable angina both as monotherapy and when given in combination with a BB [50–52].

5.5 Trimetazidine

During hypoxia, glucose oxidation is preferable to the oxidation of free fatty acids (FFA) for the generation of the ATP necessary for myocyte function. Modulation of cardiac metabolism by partial inhibition of the oxidation of FFA has been tested as a strategy to alleviate stable angina [53–55]. Of the numerous inhibitors of fatty-acid oxidation that have been developed, trimetazidine is the most widely used throughout Europe and Asia, but is not available in North America. Trimetazidine exerts no significant negative inotropic or vasodilatory properties at rest or during exercise [56–59]. The actual mechanism of antianginal effect is debatable with some research demonstrating a reduction in the rate of FFA oxidation accompanied by an increase in glucose oxidation rate during low-flow ischemia thought to be due to the inhibition of a key enzyme in the β -oxidation pathway [56]. Trimetazidine has been shown in several randomized, controlled trials to reduce symptoms of angina and to improve exercise capacity [53–55]. The Task Force on the Management of Stable Angina Pectoris of the ESC lists trimetazidine as a class IIb indication (level of evidence B) as adjunct or substitution therapy when conventional drugs are not tolerated [12].

5.6 L-Arginine

L-Arginine is the substrate for nitric oxide synthase. It has been shown that l-arginine administration improves endothelium dependent vasodilation in patients with risk factors for atherosclerosis, such as hypercholesterolemia, smoking, aging, and hypertension and in patients with coronary artery disease, microvascular angina pectoris, and peripheral arterial disease [60–65]. The clinical studies on oral l-arginine therapy as an antianginal are somewhat contradictory. No improvement in exercise tolerance in a group of 40 men with stable angina receiving l-arginine 5 mg was seen as compared to placebo [66]. However, a single-center, double-blind, placebo-controlled trial involving 22 patients with stable angina showed that treatment with l-arginine resulted in an increase in exercise duration and maximum workload during stress testing as well as an increase in the time to onset of ST-segment depression [67]. The FDA currently licenses l-arginine for use in the USA.

5.7 Perhexiline

Perhexiline was first introduced in the 1970s as an anti-anginal agent effective at relieving symptoms of angina, improving exercise tolerance, and increasing workload needed to induce ischemia. The drug works in part by modifying myocardial substrate utilization from fatty acids to carbohydrates [68]. The use of perhexiline fell out of practice in mid 1980s due to reports of hepatotoxicity and peripheral neuropathy [69, 70]. These effects were later shown to occur in patients who were ‘slow hydroxylators’ secondary to a polymorphic variant of the cytochrome P-450 enzyme (CYP2D6) which metabolizes the drug [71]. Adverse effects of the drug are completely avoided by maintaining drug plasma concentration between 0.15 and 0.60 mg/L. In a large multicenter experience on the use of perhexiline in chronic heart failure and refractory angina using 151 patients in UK, perhexiline therapy was shown to provide symptomatic relief in the majority of patients with minimal side effects or toxicity [72]. Careful therapeutic level monitoring for dose titration is important to prevent acute and chronic toxicity. Patients with refractory angina were more

likely to be responders. In the UK, perhexiline is available off license, on a named patient and named consultant cardiologist basis. In some parts of the world, particularly Australia, perhexiline is quite widely used in the treatment of refractory angina and unstable angina, with excellent results [73].

6. NOVEL THERAPIES FOR ANGINA

6.1 Etoximir

It is similar to perhexiline, and is a potent carnitine phosphate transferase-1 inhibitor [74]. Etomoxir was initially introduced into the clinical market as a potential diabetic agent [75] and has shown potential as an antianginal agent in ex vivo research but is yet to be investigated in a randomized controlled trial [76]. An initial small, non-randomized study showed improvement in symptoms in heart failure [77]. Following this, the drug was withdrawn from the market because of side effects on the liver, which was detected in a larger, randomized study [78].

6.2 Omapatrilat

During myocardial ischemia, atrial and brain natriuretic peptides and bradykinin are released, all of which have anti-ischemic properties. These vasoactive peptides are inactivated by neprilysin, and bradykinin is also degraded by angiotensin-converting enzyme [79]. In a proof-of-concept study, omapatrilat, a potent vasopeptidase inhibitor with selective and competitive inhibitory activity of angiotensin-converting enzyme and neprilysin, was tested in 348 patients with stable angina [80]. Treatment with omapatrilat significantly increased total exercise capacity, time to onset of angina, and time to onset of ischemic ST-segment depression at peak plasma concentrations, with fewer patient reports of exercise-induced angina, compared with placebo. The beneficial effects were less evident 24 h after dosing. Omapatrilat is not commercially available, primarily due to concerns over angioedema.

6.3 Fasudil

The Rho-related GTP-binding proteins mediate intracellular signaling induced by activation of heterotrimeric G-protein-coupled receptors and growth receptors and regulate the sensitivity of vascular smooth muscle in the cardiovascular system to calcium, and have been shown in animal models of ischemic heart disease to reduce hypercontraction of vascular smooth muscle and ischemic ST-segment depression [53, 81]. Fasudil is a Rho kinase inhibitor. In a small double blind, placebo-controlled, randomized clinical trial using 84 patients with stable angina, fasudil was compared with placebo [82]. In this proof-of-concept trial, fasudil and placebo both tended to increase treadmill exercise time compared with baseline (by 118 s and 86 s, respectively), although the differences were not statistically significant. Fasudil did, however, significantly prolong the time to exercise-induced ischemic ST-segment depression compared with placebo.

6.4 DW1865

DW1865, a novel Rho kinase inhibitor, exhibited significant antihypertensive properties both in *in vitro* and *in vivo*, presumably via inhibition of intracellular Rho kinase activation [83].

In the rat heart-derived H9c2 cell line, DW1865 blocked angiotensin II-induced stress fiber formation and cellular hypertrophy. These cellular effects of DW1865 suggest that the beneficial effects of Rho kinase inhibition exceed blood pressure lowering to include potential reduction of hypertrophy in cardiomyocytes. DW1865 may be useful as an effective Rho kinase inhibitor in pharmaceutical or clinical applications in treatment of ischemic heart disease.

6.5 Allopurinol

Allopurinol inhibits xanthine dehydrogenase/oxidase, an enzyme required in the oxidation of hypoxanthine and xanthine, which produces uric acid. This agent has long been commercially available and, at therapeutic doses, results in a direct decrease in uric acid and an indirect decrease in purine synthesis by feedback inhibition of amidophosphoribosyltransferase, a rate-limiting enzyme. Recently, interest has grown in the possible antianginal effects of allopurinol. In a small, placebo-controlled, randomized trial of 65 patients with stable angina, high-dose allopurinol (300 mg twice daily) significantly increased total exercise duration, time to onset of angina, and ischemic ST-segment depression [84]. The exact mechanism of action is unknown, but inhibition of xanthine dehydrogenase/oxidase might reduce oxidative stress in ischemic myocardium. Additional randomized, placebo-controlled trials are required in larger series of patients to confirm these findings before allopurinol can be recommended as an effective antianginal therapy.

6.6 Testosterone

Testosterone has been shown to result in coronary artery dilation and increased blood flow in humans. The mechanism appears to be endothelium independent and may involve the ion channels on vascular smooth muscle cells [85]. Numerous cross-sectional case control studies report hypotestosteronaemia in patients with CAD [86, 87]. Several small studies have reported beneficial anti-ischemic effect of testosterone delivered via transdermal [88], intra-muscular [89] and chronic administration via oral therapy [90]. Acute administration of testosterone also provides rapid improvements in myocardial ischemia [91, 92] prompting the suggestion that testosterone may beneficially influence coronary vascular tone. This was confirmed in a subsequent study by Webb et al [93] in which intra-coronary infusion of physiological concentrations of testosterone increased coronary artery diameter and coronary blood flow in male patients with CAD, consistent with a direct coronary vasodilatory action. Although none of the patients experienced adverse prostatic or hematological effects, concern exists regarding possible health effects of long-term therapy with testosterone in the general male population.

6.7 Estrogen

Estrogen has also been investigated as an antianginal agent and has been shown to dilate coronary arteries and improve endothelial function [94]. A randomized, double blind, placebo-controlled trial involving 74 female patients with stable angina showed that estradiol and norethindrone therapy improved exercise duration and the time to onset of ST-segment depression [95]. There was also a reduction in the number of ischemic events in the treatment group. However, concern was raised in the Women's Health Initiative study, which showed that overall health risks exceeded benefits from use of combined estrogen plus

progesterin for an average 5.2-year follow-up among healthy postmenopausal US women [96]. These benefits, however, must be weighed against the potential for an initial increase in cardiac events caused by estrogen therapy in females with coronary artery disease. Given concerns about potential side effects, neither testosterone nor estrogen is recommended for treatment of refractory angina.

6.8 Molsidomine

Molsidomine or *N*-ethoxycarbonyl-3-morpholinomethyl-2-methyl-5-norbornene-2-carboxylate (SIN10) is a nitric oxide donating vasodilator [97] and has been used to treat angina. When compared with placebo, it reduced the incidence of anginal attacks, the use of sublingual nitrates, and increased exercise capacity in patients with stable angina [98]. Higher doses provided better protection from angina, although hypotension was a side effect [99]. This new drug is not yet in routine clinical use; however, it may serve as useful alternative or adjunct to conventional antianginal treatment. Further studies and longer follow-up will determine its place in patients with coronary artery disease.

6.9 Mildronate

Mildronate is a structural aza-analogue of the carnitine precursor gamma-butyrobetaine (GBB). It inhibits carnitine biosynthesis reversibly. The efficacy of mildronate has been shown to improve systolic function, improve arterial vascular tone, increase stress tolerance and reduce anginal symptoms [100, 101]. Dose dependent improvement in exercise tolerance in patients with stable angina treated with standard therapy was noted in a Phase II, placebo-controlled, double-blind randomized trial [102]. Mildronate is approved for clinical use in Latvia, Lithuania, Russia and Ukraine.

6.10 Phosphodiesterase inhibitors

The efficacy of phosphodiesterase type 5 inhibitors (PDE5I) in cardiovascular diseases appears to be related primarily to beneficial effects on endothelial function [103]. In fact, the PDE5I sildenafil was originally investigated for its potential in treating angina, however, the data from phase I trial for anti-anginal use was not encouraging. Recent studies suggest that the drug has powerful cardioprotective effect against ischemia/reperfusion injury, doxorubicin-induced cardiomyopathy and anti-hypertensive effect induced by chronic inhibition of nitric oxide synthase in animals [103].

6.11 Amiodarone

Combination therapy of amiodarone with conventional antianginal therapy is well tolerated and results in a significant improvement in exercise capacity and a mild reduction of symptoms in patients who have continued, limiting angina pectoris with conventional triple therapy [104].

6.12 Omecamtiv mecarbil

The cardiac myosin activator omecamtiv mecarbil has been studied in healthy volunteers in whom it produced dose-dependent and concentration-dependent increases in systolic ejection time, fractional shortening, and ejection fraction without increasing oxygen

consumption, thereby increasing myocardial efficiency [105, 106]. In a double-blind, placebo-controlled, crossover, dose-ranging, Phase II trial investigating the effects of omecamtiv mecarbil (formerly CK-1827452), given intravenously for 2, 24, or 72 h to patients with stable heart failure and left ventricular systolic dysfunction receiving guideline-indicated treatment, concentration-dependent increases in left ventricular ejection time (up to an 80 ms increase from baseline) and stroke volume (up to 9.7 mL) were recorded, associated with a small reduction in heart rate [107]. Angina was not noted in the study population despite increased chronotropy, and this may potentially be exploited as a novel agent for patients with angina and depressed LV function.

7. THERAPEUTIC ANGIOGENESIS AND ANGINA

Despite several options for medical management of angina, there are substantial numbers of patients who continue to have refractory symptoms lacking further treatment options. Therapeutic angiogenesis has become an important focus of cardiovascular research. The goal is to enhance neovascularization and arterial blood flow to myocardium, which in turn may relieve myocardial ischemia and improve regional and global ventricular function [108]. The natural process of angiogenesis is complex, with a large number of angiogenic growth factors, as well as inhibitors of angiogenesis, having been identified [109]. Clinical experience with protein growth factors and genes encoding for these growth factors to enhance myocardial angiogenesis primarily involves vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Protein alone, plasmid, and adenoviral vectors using a variety of delivery methods (intravenous, intracoronary, and intramyocardial) have been used in clinical trials of angiogenesis. Initial pre-clinical phase I trials were promising [110–113] and led to several phase II trials which had disappointing results. These data have been reviewed extensively in various publications [114, 115]. The clinical benefit of angiogenic therapy for refractory angina has been difficult to prove, in part because of heterogeneous patient populations, suboptimal patient selection, and placebo effects. The primary efficacy endpoint was also different in various trials and has included the assessment of anginal functional class, exercise tolerance time, improvement in myocardial perfusion, or freedom from cardiovascular events.

8. CELL-BASED THERAPIES

Several experimental and small to intermediate pre-clinical data suggest feasibility and safety of cell-based therapies in patients with ischemic cardiomyopathy [116–119]. To date, different autologous adult stem and progenitor cells, in particular several subtypes of bone marrow-derived cells, isolated adipose tissue-derived or cardiac derived stem/progenitor cells are under preclinical and clinical evaluation. Additionally, embryonic stem cells and induced pluripotent stem cells provide regenerative capacity and improve cardiac function after ischemia in animal models. Overview of cell types for cardiac repair in acute myocardial infarction and chronic ischemic cardiomyopathy is elegantly discussed in an extensive review by Templin et al [120] and Sequeira et al [121]. The best method for delivery of the stem cells is contentious. Several modalities with varying success and pitfalls have been described. These include peripheral infusion, intramyocardial injection during

bypass grafting, endocardial using various catheters as well as intracoronary infusion [120–124].

Few of the landmark studies on cell based therapy for chronic myocardial ischemia and angina are outlined in this section. In the randomized-controlled, double-blind trial conducted by van Ramshorst *et al* [125], intramyocardial application of BMCs resulted in a modest but significant improvement of myocardial perfusion as assessed by SPECT, angina severity, and quality of life during a 3-month follow-up in patients with severe angina (classes III–IV), despite optimal medical therapy, ineligible for myocardial revascularization, and evidence of myocardial ischemia at baseline. Similarly, 6 months after direct injection of autologous BMCs in patients with severe refractory angina, a significant improvement of exercise time, LV function, and NYHA functional class was observed in the PROTECT-CAD trial [126]. Significant improvements in angina frequency and exercise tolerance in patients with refractory angina who received intramyocardial injections of autologous CD34+ cells (10^5 cells/kg) was the high light of ACT34-CMI trial [127]. The G-CSF in Angina patients with Ischemic heart disease to stimulate Neovascularization (GAIN 1) trial sought to assess the safety and efficacy of an intracoronary infusion of CD133+ stem cells following pretreatment with G-CSF in patients with refractory angina. The rate of serious adverse events was significant, with numerous episodes of myocardial ischemia. While there was an improvement in a range of subjective angina parameters, there was no change in myocardial perfusion or ischemia detected by SPECT imaging or dobutamine echo. Furthermore, the addition of intracoronary CD133+ did not improve either subjective or objective parameters of myocardial ischemia [128].

The mechanism of therapy is not clearly understood. Improvements are mostly attributed to paracrine factors. These appear to contribute to cardiac repair possibly through neo-vascularization, angiogenesis, less inflammation, smaller infarct size, and decreased fibrosis. Paracrine secretions contribute to enhanced cardiomyocyte survival by decreasing apoptosis, while increasing cell proliferation and mobilizing other stem cells to the infarct zone [129, 130].

9. HERBAL MEDICINES IN TREATMENT OF CHRONIC ANGINA

Botanicals have been used widely in traditional Chinese and Indian medicine. These include hawthorn leaf and flower extract for heart failure and coronary insufficiency; garlic for atherosclerosis; *Ginkgo biloba* extracts for peripheral arterial occlusive disease; and horse chestnut extract for chronic venous insufficiency. Herbs such as *Salviae miltiorrhizae Radix* ('dan shen' in Chinese), *Notoginseng Radix* ('san qi'), *Chuanxiong Rhizoma* ('chuan xiong'), and *Crataegi fructus* ('shan zha') are common Chinese herbs used in the treatment of a wide range of cardiovascular conditions, including angina pectoris. Key botanicals used to treat stable angina pectoris, including their main active constituents and pharmacological actions are elegantly reviewed by O'Brien and Vitetta [131].

10. EXPERT OPINION

Chronic and refractory angina remains a global problem despite the availability of several options for management including revascularization, non-pharmacological tools like enhanced external counterpulsation, coronary sinus reducer stents, acupuncture, transcutaneous electrical nerve stimulation, spinal cord stimulation, transmyocardial revascularization as well as numerous drugs. As with the entire spectrum of coronary disease, optimal medical therapy and risk factor modification provides important prognostic and symptomatic benefit in these patients. A wide array of pharmacological armamentarium is now available to manage the patients with chronic stable angina as outlined in Table 1 [27, 31–36, 38–40, 42, 43, 45, 50, 51, 53, 54, 67, 72, 78, 80, 82–84, 87–92, 95, 97, 102, 107, 132–144].

Despite the fact that BBs have disease-modifying properties and exert favorable effects on arrhythmias, heart failure and prevention of sudden death, their use as first-line therapy of stable angina will likely be revisited given the data from REACH registry. There is a lack of evidence that CCBs are disease-modifying, and their therapeutic role will be probably reduced in the near future. Long-acting nitrates are used on an empirical basis as randomized controlled trials are lacking, and are therefore expected to be replaced by the newer anti-anginal treatments, particularly ranolazine, which will likely have more robust use in clinical practice for management of angina given several positive pleiotropic effects on arrhythmia suppression, heart failure as well as glycemic control besides anti-anginal properties.

Ivabradine and nicorandil are already indicated as second line options in patients inadequately controlled by first-line treatments or in whom such treatments are contraindicated or not tolerated. With more evidence coming in favor of these two molecules, their use is likely to become more global with acceptance in US markets. Several old drugs are being re-evaluated for their anti-anginal properties, in particular, amiodarone and sildenafil. Allopurinol is also getting attention and these agents offer exciting adjunct therapies for angina treatment. More recently, an increase in exercise capacity was described in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, who were treated with a novel soluble guanylate cyclase stimulator, riociguat [144, 145]. It will be interesting to see if there will be a role for this drug in patients with chronic angina. Several new drugs are being studied and offer additional therapeutic potentials (Table 2).

Cell and gene therapy continues to be a challenge. Although important progress is occurring in the use of stem cells for cardiac repair, the most optimal stem cell(s) for treatment of patients with infarcted myocardium has not yet been determined and requires identification. This will require comparison studies of human embryonic stem cells, bone marrow stem cells, allogeneic mesenchymal stem cells, circulating stem cells and umbilical cord blood cells in research animals and in patients. The ideal stem cell for cardiac repair should be non-toxic; not require immune suppression of the patient; create or stimulate healthy and functional cardiac muscle and blood vessels; improve heart function; and limit left ventricular remodeling. In addition, the optimal stem cell(s) should be easily harvested, readily propagated *ex vivo* in large numbers without neoplastic differentiation, and be

available as a standardized ‘off the shelf’ treatment for prompt cardiac repair in patients. Several trials using various cell types as well as delivery vehicles are currently being carried out, and outcomes from these studies will have the potential to completely revolutionize anti-anginal management (Table 2).

Trends of future medical care that may require advanced drug delivery systems include individualized therapy and the capability to automate drug delivery. Implantable drug delivery devices that promise to address these anticipated needs have been constructed in a variety of ways using micro- and nano-electromechanical systems (MEMS or NEMS)-based technology. These devices expand treatment options for addressing unmet medical needs related to dosing. Within the last few years, advances in several technologies (MEMS or NEMS fabrication, materials science, polymer chemistry, and data management) have converged to enable the construction of miniaturized implantable devices for controlled delivery of therapeutic agents from one or more reservoirs. Suboptimal performance of conventional dosing methods in terms of safety, efficacy, pain, or convenience can be improved with advanced delivery devices. In addition, innovative drug-medical device combinations may protect labile active ingredients within hermetically sealed reservoirs [146].

BIBLIOGRAPHY

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

1. Opie LH. Angina pectoris: the evolution of concepts. *J Cardiovasc Pharmacol Ther.* 2004; 9:S3–9. [PubMed: 15378128]
2. World Health Organization. World health reports 2004: changing history. Geneva: World Health Organization; 2004. Available at: http://www.who.int/whr/2004/en/report04_en.pdf [Last Accessed 6 August 2013]
3. Rosamond W, Flegal K, Friday G, et al. Heart Disease and Stroke Statistics—2007 Update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2007; 115:e69–e171. [PubMed: 17194875]
4. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA.* 2004; 291:2616–20. [PubMed: 15173153]
- 5*. Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. *Vasc Health Risk Manag.* 2010; 6:635–56. A comprehensive review on pathophysiology, diagnosis and risk stratification of patients with angina. [PubMed: 20730020]
6. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev.* 2008; 88(3):1009–86. [PubMed: 18626066]
7. Westerhof N, Boer C, Lamberts RR, Sipkema P. Cross-talk between cardiac muscle and coronary vasculature. *Physiol Rev.* 2006; 86(4):1263–308. [PubMed: 17015490]
- 8**. Kones R. Recent advances in the management of chronic stable angina II: anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization. *Vasc Health Risk Manag.* 2010; 6:749–74. A comprehensive review outlining various modalities for management of chronic stable angina. [PubMed: 20859545]
- 9**. Sharaf B, Pepine CJ, Kerensky RA. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). *Am J Cardiol.* 2001; 87:937–41. Landmark study outlining angiographic findings in women with ischemia. [PubMed: 11305981]

- 10**. Fihn SD, Gardin JA, Berra K, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive Summary. A Report 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; 126:3097–137. Guideline document. [PubMed: 23166210]
11. Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 Chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation*. 2007; 116:2762–72. [PubMed: 17998462]
- 12**. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J*. 2006; 27:1341–81. European Society of Cardiology guidelines for management of stable angina. [PubMed: 16735367]
13. Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. Endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006; 113:2363–72. [PubMed: 16702489]
14. Simoons ML, Windercker S. Chronic stable coronary artery disease: drugs vs. revascularization. *Eur Heart J*. 2010; 31:530–41. [PubMed: 20106842]
- 15**. Boden WE, O'Rourke RA, Teo KK, et al. COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007; 356(15):1503–16. Landmark trial on optimal therapy: medical vs. percutaneous revascularization. PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. [PubMed: 17387127]
16. Maron DJ, Boden WE, O'Rourke RA, et al. Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the COURAGE trial. *J Am Coll Cardiol*. 2010; 55:1348–58. [PubMed: 20338496]
- 17**. The BARI 2D Study Group. A randomized trial of therapy for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009; 360:2503–15. Pivotal clinical trial outlining management of CAD in patients with type 2 diabetes. [PubMed: 19502645]
18. Chaitman BR, Hardison RM, Adler D, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease. Impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation*. 2009; 120:2529–40. [PubMed: 19920001]
19. Chaitman BR, Hadid M, Laddu AA. Choice of initial medical therapy vs. prompt coronary revascularization in patients with type 2 diabetes and stable ischemic coronary disease with special emphasis on the BARI 2D trial results. *Curr Opin Cardiol*. 2010; 25:597–602. [PubMed: 20885315]
20. Thomas S, Gokhale R, Boden WE, Devereaux PJ. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in stable angina pectoris. *Can J Cardiol*. 2013; 29(4):472–82. [PubMed: 23010084]
- 21**. Farkouh ME, Domanski M, Sleeper LA, et al. for FREEDOM trial investigators. Strategies for multivessel revascularization in patients with diabetes. *New Eng J Med*. 2012; 367:2375–84. An important trial documenting superiority of CABG to PCI in patients with diabetes in that it significantly reduced rates of death and myocardial infarction, with a higher rate of stroke. [PubMed: 23121323]
- 22*. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomized, clinical SYNTAX trial. *Lancet*. 2013; 381:629–38. A follow up on patients enrolled in SYNTAX trial. CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores). For patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI is an acceptable alternative. [PubMed: 23439102]

23. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol.* 2011; 58:2432–6. [PubMed: 22055990]
- 24*. Farkouh ME, Boden WE, Bittner V, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. *J Am Coll Cardiol.* 2013; 61(15):1607–15. Important meta-analysis of three trials (BARI 2D, FREEDOM, and COURAGE) that focused on optimal medical therapy for diabetic patients with CAD. [PubMed: 23500281]
25. Abrams J. Clinical practice. Chronic stable angina. *N Engl J Med.* 2005; 352:2524–33. [PubMed: 15958808]
26. Abrams J, Thadani U. Therapy of stable angina pectoris: the uncomplicated patient. *Circulation.* 2005; 112:e255–e259. [PubMed: 16216965]
27. Kimchi A, Lee G, Amsterdam E, et al. Increased exercise tolerance after nitroglycerin oral spray: a new and effective therapeutic modality in angina pectoris. *Circulation.* 1983; 67:124–7. [PubMed: 6401172]
28. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA.* 1988; 260:2088–93. [PubMed: 2901501]
29. Rehnqvist N, Hjemdahl P, Billing E, et al. Effects of metoprolol vs. verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J.* 1996; 17:76–81. [PubMed: 8682134]
30. Dargie HJ, Ford I, Fox KM. Total Ischemic Burden European Trial (TIBET). Effects of ischemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. *Eur Heart J.* 1996; 17:104–12. [PubMed: 8682116]
31. Fox KM, Mulcahy D, Findlay I, et al. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur Heart J.* 1996; 17:96–103. [PubMed: 8682138]
32. Kawanishi DT, Reid CL, Morrison EC, Rahimtoola SH. 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; 19:409–17. [PubMed: 1732370]
33. Glasser SP, Gana TJ, Pascual LG, Albert KS. Efficacy and safety of a once-daily graded-release diltiazem formulation dosed at bedtime compared to placebo and to morning dosing in chronic stable angina pectoris. *Am Heart J.* 2005; 149:e1–e9.
34. Frishman WH, Glasser S, Stone P, et al. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. *Am J Cardiol.* 1999; 83:507–14. [PubMed: 10073852]
35. Kohli RS, Rodrigues EA, Hughes LO, et al. Sustained release verapamil, a once daily preparation: objective evaluation using exercise testing, ambulatory monitoring and blood levels in patients with stable angina. *J Am Coll Cardiol.* 1987; 9:615–21. [PubMed: 3102585]
- 36*. Pepine CJ, Handberg E, Cooper-DeHoff RM, et al. for the INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA.* 2003; 290:2805–16. A landmark trial comparing outcomes in older patients with hypertension on multiple drugs including trandolapril and hydrochlorothiazide, randomized to a nondihydropyridine calcium antagonist – verapamil and a non-calcium antagonist agent – atenolol. [PubMed: 14657064]
37. 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(13):1340–9. [PubMed: 23032550]
- 38*. 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; 43:1375–82. A landmark trial (Monotherapy Assessment of Ranolazine In Stable Angina

- (MARISA)) designed to determine the dose-response relationship of ranolazine on symptom-limited exercise duration, led to FDA approval of the drug. [PubMed: 15093870]
- 39*. 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; 291:309–16. CARISA trial: another critical trial on efficacy and dosing of ranolazine which showed twice-daily dosing increased exercise capacity and provided additional anti-anginal relief to symptomatic patients with severe chronic angina taking standard doses of atenolol, amlodipine, or diltiazem, without evident adverse, long-term survival consequences over 1 to 2 years of therapy. [PubMed: 14734593]
 40. 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; 48:566–75. [PubMed: 16875985]
 41. Vadanis DS, Wenger NK. Emerging clinical role of ranolazine in the management of angina. *Ther Clin Risk Manag*. 2010; 6:517–30. [PubMed: 21063462]
 42. The IONA Study Group. Trial to show the impact of nicorandil in angina (IONA): design, methodology, and management. *Heart*. 2001; 85(6):e9. [PubMed: 11359763]
 - 43*. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina (IONA) randomized trial. *Lancet*. 2002; 359:1269–75. An important study which demonstrated improvement in outcome due to a reduction in major coronary events by antianginal therapy with nicorandil in patients with stable angina. [PubMed: 11965271]
 44. 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(3):503–9. [PubMed: 20081320]
 45. Hollingshead LM, Faulds D, Fitton A. Bepiridil. A review of its pharmacological properties and therapeutic use in stable angina pectoris. *Drugs*. 1992; 44:835–57. [PubMed: 1280569]
 46. DiFrancesco D. The role of the funny current in pacemaker activity. *Circ Res*. 2010; 106:434–46. [PubMed: 20167941]
 47. Baruscotti M, Barbuti A, Bucchi A. The cardiac pacemaker current. *J Mol Cell Cardiol*. 2010; 48:55–64. [PubMed: 19591835]
 48. Savelieva I, Camm AJ. If inhibition with ivabradine: electrophysiological effects and safety. *Drug Saf*. 2008; 31:95–107. [PubMed: 18217787]
 49. DiFrancesco D. Cardiac pacemaker I(f) current and its inhibition by heart rate-reducing agents. *Curr Med Res Opin*. 2005; 21(7):1115–22. [PubMed: 16004681]
 - 50*. Tardif JC, Ford I, Tendera M, et al. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005; 26:2529–36. Clinical trial that showed that ivabradine is as effective as atenolol in patients with stable angina. [PubMed: 16214830]
 51. 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; 30:540–8. [PubMed: 19136486]
 52. Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and anti-ischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation*. 2003; 107:817–23. [PubMed: 12591750]
 53. Chaitman BR, Sano J. Novel therapeutic approaches to treating chronic angina in the setting of chronic ischemic heart disease. *Clin Cardiol*. 2007; 30(Suppl 1):I25–I30. [PubMed: 18373327]
 - 54*. Ciapponi A, Pizzarro R, Harrison J. Trimetazidine for stable angina. *Cochrane Database Syst Rev*. 2005 Oct 19;(4):CD003614. Meta-analysis: trimetazidine is effective in the treatment of stable angina compared with placebo, alone or combined with conventional anti-anginal agents. [PubMed: 16235330]
 55. Ribeiro LW, Ribeiro JP, Stein R, et al. Trimetazidine added to combined hemodynamic antianginal therapy in patients with type 2 diabetes: a randomized crossover trial. *Am Heart J*. 2007; 154:78.e1–78.e7. [PubMed: 17584555]

56. MacInnes A, Fairman DA, Binding P, et al. The antianginal agent trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res.* 2003; 93:e26–e32. [PubMed: 12869391]
57. Marazzi G, Wajngarten M, Vitale C, et al. Effect of fatty acid inhibition on silent and symptomatic myocardial ischemic in diabetic patients with coronary artery disease. *Int J Cardiol.* 2007; 120:79–84. [PubMed: 17134770]
58. Pornin M, Harpey C, Allal J, et al. Lack of effects of trimetazidine on systemic hemodynamics in patients with coronary artery disease: a placebo-controlled study. *Clin Trials Metaanal.* 1994; 29(1):49–56. [PubMed: 10150185]
59. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res.* 2000; 86(5):580–8. [PubMed: 10720420]
60. Casino PR, Kilcoyne CM, Quyyumi AA, et al. Investigation of decreased availability of nitric oxide precursor as the mechanism responsible for impaired endothelium-dependent vasodilation in hypercholesterolemic patients. *J Am Coll Cardiol.* 1994; 23(4):844–50. [PubMed: 8106688]
61. Campisi R, Czernin J, Schoder H, et al. L-arginine normalizes coronary vasomotion in long-term smokers. *Circulation.* 1999; 99(4):491–7. [PubMed: 9927394]
62. Chauhan A, More RS, Mullins PA, et al. Aging-associated endothelial dysfunction in humans is reversed by L-Arginine. *J Am Coll Cardiol.* 1996; 28(7):1796–1800. [PubMed: 8962569]
63. Tentolouris C, Tousoulis D, Toutouzas P, Davies G. Effects of acute L-arginine administration in coronary atherosclerosis. *Circulation.* 1999; 99(12):1648–9. [PubMed: 10096992]
64. Tentolouris C, Tousoulis D, Davies GJ, et al. Serum cholesterol level, cigarette smoking, and vasomotor responses to L-arginine in narrowed epicardial coronary arteries. *Am J Cardiol.* 2000; 85(4):500–3. [PubMed: 10728960]
65. Egashira K, Hirooka Y, Kuga T, et al. Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary arteriograms. *Circulation.* 1996; 94(2):130–4. [PubMed: 8674170]
66. Walker HA, McGing E, Fisher I, et al. Endothelium-dependent vasodilation is independent of the plasma L-arginine/ADMA ratio in men with stable angina: lack of effect of oral L-arginine on endothelial function, oxidative stress and exercise performance. *J Am Coll Cardiol.* 2001; 38(2): 499–505. [PubMed: 11499744]
67. Ceremuzynski L, Chamiec T, Herbaczynska-Cedro K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. *Am J Cardiol.* 1997; 80(3):331–3. [PubMed: 9264427]
68. Abozguia K, Shivu GN, Ahmed I, et al. The heart metabolism: pathophysiological aspects in ischemia and heart failure. *Curr Pharm Des.* 2009; 15:827–35. [PubMed: 19275646]
69. Roberts RK, Cohn D, Petroff V, Seneviratne B. Liver disease induced by perhexiline maleate. *Med J Aust.* 1981; 2:553–4. [PubMed: 7321956]
70. Bouche P, Bousser MG, Peytour MA, Cathala H. Perhexiline maleate and peripheral neuropathy. *Neurology.* 1979; 29:739–43. [PubMed: 220563]
71. Morgan MY, Reshef R, Shah RR, et al. Impaired oxidation of debrisoquine in patients with perhexiline liver injury. *Gut.* 1984; 25:1057–64. [PubMed: 6479680]
- 72*. Phan TT, Shivu GN, Choudhary 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(9): 881–6. An important retrospective study which showed that perhexiline therapy provides symptomatic relief in the majority of patients with minimal side effects or toxicity and that patients with refractory angina were more likely to be responders. [PubMed: 19656806]
73. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol.* 2002; 18:439–42. [PubMed: 11992140]
74. Lopaschuk G, Wall S, Olley P, Davies N. Etomoxir, a carnitine palmitoyltransferase I inhibitor, protects hearts from fatty acid-induced ischemic injury independent of changes in long chain acylcarnitine. *Circ Res.* 1988; 63(6):1036–43. [PubMed: 3197271]

75. Reaven GM, Chang H, Hoffman BB. Additive hypoglycemic effects of drugs that modify free-fatty acid metabolism by different mechanisms in rats with streptozocin-induced diabetes. *Diabetes*. 1988; 37(1):28–32. [PubMed: 3275556]
- 76*. Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischemic heart disease, a novel approach to treatment. *Eur Heart J*. 2004; 25(8):634–41. Four metabolic anti-anginal drugs are reviewed: perhexiline, trimetazidine, ranolazine, and etomoxir. [PubMed: 15084367]
77. Schmidt-Schweda S, Holubarsch C. First clinical trial with etomoxir in patients with chronic congestive heart failure. *Clin Sci (Lond)*. 2000; 99:27–35. [PubMed: 10887055]
78. Holubarsch CJ, Rohrbach M, Karrasch M, et al. A double-blind randomized multicentre clinical trial to evaluate the efficacy and safety of two doses of etomoxir in comparison with placebo in patients with moderate congestive heart failure: the ERGO (etomoxir for the recovery of glucose oxidation) study. *Clin Sci (Lond)*. 2007; 113:205–12. [PubMed: 17319797]
79. Trippodo NC, Fox M, Natarajan V, et al. Combined inhibition of neutral endopeptidase and angiotensin converting enzyme in cardiomyopathic hamsters with compensated heart failure. *Pharmacol Exp Ther*. 1993; 267(1):108–16.
- 80*. Chaitman BR, Ivleva AY, Ujda M, et al. Antianginal efficacy of omapatrilat in patients with chronic angina pectoris. *Am J Cardiol*. 95(11):1283–9. Study revealed the anti-anginal efficacy of omapatrilat in patients with chronic angina pectoris.
81. Satoh K, Fukumoto Y, Shimokawa H. Rho-kinase: important new therapeutic target in cardiovascular diseases. *Am J Physiol Heart Circ Physiol*. 2011; 301:H287–H289. [PubMed: 21622831]
- 82*. Vicari RM, Chaitman B, Keefe D, et al. Fasudil Study Group. Efficacy and safety of fasudil in patients with stable angina: a double blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol*. 2005; 46(10):1803–11. Clinical trial on efficacy and safety of fasudil. [PubMed: 16286163]
83. Kwang-Seok O, Oh BK, Park CH, et al. Cardiovascular effects of a novel selective Rho kinase inhibitor, 2-(1*H*-indazole-5-yl) amino-4-methoxy-6-piperazino triazine (DW1865). *Eur J Pharmacol*. 2013; 702:218–26. [PubMed: 23376156]
84. Noman A, Ang DS, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomized, placebo controlled crossover trial. *Lancet*. 2010; 375:2161–7. [PubMed: 20542554]
85. Chou TM, Sudhir K, Hutchison SJ, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation*. 1996; 94(10):2614–9. [PubMed: 8921808]
86. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis*. 1996; 125:1–13. [PubMed: 8831922]
87. English KM, Mandour O, Steed RP, et al. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J*. 2000; 21:890–4. [PubMed: 10806012]
88. 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(16):1906–11. [PubMed: 11034937]
89. Jaffe MD. Effect of testosterone cypionate on post-exercise ST segment depression. *Br Heart J*. 1977; 39:1217–22. [PubMed: 337982]
90. Wu SZ, Weng XZ. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chinese Med J*. 1993; 106:415–8.
91. Webb CM, Adamson DL, Dezeigler D, Collins P. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol*. 1999; 83:437–9. [PubMed: 10072236]
92. Rosano GM, Leonardo F, Pagnotta P, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circ*. 1999; 99:1666–70.
93. Webb CM, McNeil JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999; 100:1690–6. [PubMed: 10525487]

94. Magness RR, Rosenfeld CR. Local and systemic estradiol-17 beta: effects on uterine and systemic vasodilation. *Am J Physiol Endocrinol Metab*. 1989; 256(4):E536–42.
95. Sanderson EJ, Sanderson J, Haines CJ, et al. Anti-ischemic action of estrogen-progestogen continuous combined hormone replacement therapy in postmenopausal women with established angina pectoris: a randomized, placebo-controlled, double-blind, parallel-group trial. *J Cardiovasc Pharmacol*. 2001; 38(3):372–83. [PubMed: 11486242]
- 96*. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288(3):321–33. Important document on hormonal replacement therapy and cardiovascular risks. [PubMed: 12117397]
97. Nitz RE, Fiedler VB. Molsidomine: alternative approaches to treat myocardial ischemia. *Pharmacotherapy*. 1987; 7:28–37. [PubMed: 3554158]
98. Van Hove C, Carreer-Bruhwyler F, Géczy 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]
99. 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]
100. Sesti C, Simkhovich BZ, Kalvinsh I, Kloner R. Mildronate, a novel fatty acid oxidation inhibitor and antianginal agent, reduces myocardial infarct size without affecting hemodynamics. *J Cardiovasc Pharm*. 2006; 47(3):493–9.
101. Dzerve V, Matisone D, Pozdnyakov Y, Oganov R. Mildronate improves the exercise tolerance in patients with stable angina: results of a long term clinical trial. *Sem Cardiovasc Med*. 2010; 16(3):1–8.
102. Dzerve V, MILSS I Study Group. A dose dependent improvement in exercise tolerance in patients with stable angina treated with Midronate: a clinical trial "MILSS I". *Medicina*. 2011; 47(10): 544–51. [PubMed: 22186118]
103. Schwartz BG, Jackson G, Stecher VJ, et al. Phosphodiesterase type 5 inhibitors improve endothelial function and may benefit cardiovascular conditions. *Am J Med*. 2013; 126:192–9. [PubMed: 23410557]
104. Meyer BJ, Amann FW. Additional antianginal efficacy of amiodarone in patients with limiting angina pectoris. *Am Heart J*. 1993; 125:996–1001. [PubMed: 8465772]
105. Teerlink JR, Clarke CP, Saikali KG, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study. *Lancet*. 2011; 378:667–75. [PubMed: 21856480]
106. Shen YT, Malik FI, Zhao X, et al. Improvement of cardiac function by a cardiac myosin activator in conscious dogs with systolic heart failure. *Circ Heart Fail*. 2010; 3:522–7. [PubMed: 20498236]
107. Cleland JGF, Teerlink JR, Senior R, et al. The effects of cardiac myosin activator, omecamtiv mecarbil on cardiac function in systolic heart failure: a double blind, placebo controlled, crossover, dose-ranging phase 2 trial. *Lancet*. 2011; 378:676–83. [PubMed: 21856481]
108. Simons M, Ware JA. Therapeutic angiogenesis in cardiovascular disease. *Nat Rev Drug Discov*. 2003; 2:1291–7.
- 109*. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med*. 2000; 6:389–95. A good review on biology of angiogenesis. [PubMed: 10742145]
110. Henry TD, Abraham JA. Review of preclinical and clinical results with vascular endothelial growth factors for therapeutic angiogenesis. *Curr Interv Cardiol Rep*. 2000; 2:228–41. [PubMed: 11096672]
111. Udelson JE, Dilsizian V, Laham RJ, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 improves stress and rest myocardial perfusion abnormalities in patients with severe symptomatic chronic coronary artery disease. *Circulation*. 2000; 102:1605–10. [PubMed: 11015335]

112. Hendel RC, Henry TD, Rocha-Singh K, et al. Effect of intracoronary recombinant human vascular endothelial growth factor on myocardial perfusion: evidence for a dose-dependent effect. *Circulation*. 2000; 101:118–21. [PubMed: 10637195]
113. Henry TD, Rocha-Singh K, Isner JM, et al. Intracoronary administration of recombinant human vascular endothelial growth factor to patients with coronary artery disease. *Am Heart J*. 2001; 142:872–80. [PubMed: 11685177]
114. Attanasio S, Schaer G. Therapeutic angiogenesis for management of refractory angina: current concepts. *Cardiovasc Ther*. 2011; 29:e1–e11.
115. Mitsos S, Katsanos K, Koletsis E, et al. Therapeutic angiogenesis for myocardial ischemia revisited: basic biologic concepts and focus on latest clinical trials. *Angiogenesis*. 2012; 15:1–22. [PubMed: 22120824]
116. Landmesser U, Wollert KC, Drexler H. Potential novel pharmacological therapies for myocardial remodeling. *Cardiovasc Res*. 2009; 81:519–27. [PubMed: 19019834]
117. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. 2006; 355:1210–21. [PubMed: 16990384]
118. Schachinger V, Erbs S, Elsasser A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J*. 2006; 27:2775–83. [PubMed: 17098754]
119. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. *Nature*. 2008; 451:937–42. [PubMed: 18288183]
120. Templin C, Luscher TF, Landmesser U. Cell-based cardiovascular repair and regeneration in acute myocardial infarction and chronic ischemic cardiomyopathy—current status and future developments. *Int J Dev Biol*. 2011; 55:407–17. [PubMed: 21553380]
- 121** *. Sequeira C, Park K, Pepine CJ, Cogle C. Stem and progenitor cell therapies for cardiovascular disease. *J Cell Sci Ther*. 2011:S1–S9. A good review on stem cell therapy principles for cardiac diseases. [PubMed: 23483082]
122. Mozid AM, Arnous S, Sammut EC, Mathur A. Stem cell therapy for heart disease. *Br Med Bull*. 2011; 98:143–59. [PubMed: 21596713]
123. Wu KH, Mo XM, Han ZC, Zhou B. Stem cell engraftment and survival in the ischemic heart. *Ann Thorac Surg*. 2011; 92:1917–25. [PubMed: 21955573]
124. Strauer BE, Steinhoff G. 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart from the methodological origin to clinical practice. *J Am Coll Cardiol*. 2011; 58:1095–104. [PubMed: 21884944]
125. 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]
- 126**. 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. A landmark trial that showed direct endomyocardial implantation of autologous BM cells significantly improved exercise time, LVEF, and NYHA functional class in patients with severe CAD who failed conventional therapy. [PubMed: 17984132]
127. Losardo DW, Henry TD, Davidson C, et al. ACT34-CMI Investigators. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. 2011; 109:428–36. [PubMed: 21737787]
128. Kovacic J, Macdonald P, Feneley M, et al. Safety and efficacy of consecutive cycles of granulocyte-colony stimulating factor, and an intracoronary CD133⁺ cell infusion in patients with chronic refractory ischemic heart disease: The G-CSF in Angina patients with IHD to stimulate Neovascularization (GAIN 1) trial. *Am Heart J*. 2008; 156:954–63. [PubMed: 19061712]
129. Gneocchi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res*. 2008; 103:1204–19. [PubMed: 19028920]
130. Ceradini DJ, Kulkarni AR, Callagan MJ, et al. Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. *Nat Med*. 2004; 10:858–64. [PubMed: 15235597]

131. O'Brien KA, Vitetta L. The potential role of herbal medicines in the treatment of chronic stable angina pectoris: a review of key herbs, and as illustration, exploration of the Chinese herbal medicine approach. *Botanics: Targets and Therapy*. 2013; 3:1–17.
132. Lievre M, Cucherat M. Aspirin in the secondary prevention of cardiovascular disease: an update of the APTC meta-analysis. *Fundam Clin Pharmacol*. 2010; 24:385–91. [PubMed: 19678849]
133. Bhatt D, Fox AA, Fox MB, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006; 354:1706–14. [PubMed: 16531616]
134. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. *Lancet*. 2010; 376:1670–81. [PubMed: 21067804]
135. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000; 342:145–53. [PubMed: 10639539]
136. Bakris GL, Fonesca V, Katholi RE, et al. Metabolic effects of carvedilol vs. metoprolol in patients with type 2 diabetes mellitus and hypertension. A randomized controlled trial. *JAMA*. 2004; 292:2227–36. [PubMed: 15536109]
137. Weiss R, Ferry D, Pickering E, et al. Effectiveness of three different doses of carvedilol for exertional angina. Carvedilol Angina Study Group. *Am J Cardiol*. 1998; 82:927–31. [PubMed: 9794346]
138. van der Does R, Hauf-Zachariou U, Pfarr E, et al. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. *Am J Cardiol*. 1999; 83:643–9. [PubMed: 10080412]
139. Hauf-Zachariou U, Blackwood RA, Gunawardena KA, et al. Carvedilol versus verapamil in chronic stable angina: a multicentre trial. *Eur J Clin Pharmacol*. 1997; 52:95–100. [PubMed: 9174677]
140. Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. *Am J Cardiol*. 2007; 100:1254–62. [PubMed: 17920367]
141. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007; 269:201–7.
142. 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; 15:162–8. [PubMed: 18651401]
143. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Eng J Med*. 1998; 338:520–31.
144. Ghofrani HA, Gahe N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Eng J Med*. 2013; 369:330–40.
145. Ghofrani HA, Gahe N, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Eng J Med*. 2013; 369:319–29.
146. Staples M. Microchips and controlled-release drug reservoirs. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*. 2010; 2(4):400–17. [PubMed: 20564466]

Figure 1.
Pathophysiology of chronic stable angina.

Table 1

Pharmacological agents for management of chronic stable angina.

Drugs/Class	Mechanism of Action	ACC/AHA class/level of evidence	ESC class/level of evidence	Key references, trials
Aspirin	Irreversible cyclooxygenase inhibitor, reduces thrombotic events	Class 1A	Class 1A	APTC meta-analysis [132].
Clopidogrel	Adenosine diphosphate P2Y ₁₂ inhibitor. No additional benefit, increase risk of bleeding	Class 1B indicated in patients with ASA intolerance.	Class IIB	CHARISMA trial [133].
Statins	HMG Co~A reductase inhibitors	Class 1A	Class 1A	Baigent et al [134].
ACE inhibitors		Class 1A	Class 1A	HOPE [135].
Beta-adrenergic blockers 1 Cardioselective 2 Non Cardioselective	Competitive catecholamine inhibition via β_1 and β_2 receptor blockade. Increased diastolic filling. Reduces oxygen demand via negative inotropic effect, decrease HR and BP.	Class 1B started and continued for 3 years in all patients with normal LV function after MI or ACS. Class IIB for all other patients.	Class 1A post MI or with CHF	GEMINI [136], CAS [137–141]
Nebivolol	Selective β_1 antagonist, vasodilator via nitric oxide generation	FDA approved for hypertension	Approved for HTN	[142]
Calcium channel blockers 1 Dihydropyridine: Nifedipine, Amlodipine, Felodipine, Nicardipine 2 Nondihydropyridine: Verapamil and Diltiazem.	Inhibition of L-type calcium channel. Increased vasodilation Decreased inotropy. Dihydropyridines contraindicated in heart failure.	Class IIB, for relief of symptoms when BB are contraindicated or cause unacceptable side effects	No evidence to support the for prognostic reasons in uncomplicated stable angina, rate lowering CCB may be used as an alternative to BB post MI in patients without heart failure who do not tolerate BB.	[31–36]
Nitrates	Indirect nitric oxide donor Block calcium entry in smooth muscle cells and promote their relaxation through production of cyclic guanosine monophosphate (cGMP). Reduce preload Redistribution of coronary blood flow from healthy to ischaemic areas	Class 1B for symptom relief.	No prognostic benefit, used for symptom relief only	[27, 143]
Ranolazine	Late Na current inhibitor Prevents Ca overload Improves myocardial perfusion.	Class IIB	Not licensed to use	MARISA, CARISA and ERICA [38–40]
Nicorandil	Potassium channel opener	Not approved in USA	Class I C for patients with intolerance or contraindications to BB or CCB, and a class IIC for patients in whom dual antianginal therapy with other classes of drugs is unsuccessful	IONA study group [42, 43]
Bepridil	Negative chronotrope, ionotrope and vasodilator. Inhibits receptor-operated, voltage-gated calcium channels as	Approved by FDA for chronic angina in 1990,		[45]

Drugs/Class	Mechanism of Action	ACC/AHA class/level of evidence	ESC class/level of evidence	Key references, trials
	well as potassium currents and intracellular calcium/calmodulin complexes. Causes decreased myocardial oxygen consumption, coronary vasodilation, and increased coronary blood flow.	however not used in routine practice due to increased incidence of torsades des pointes and agranulocytosis		
Ivabradine	Blocks sinoatrial node I_f entry currents. Decrease HR.	Not approved in the USA	Class IIB, BB intolerant patients	INITIATIVE [50], ASSOCIATE [51].
Trimetazidine	Metabolic modulator, partially inhibit β -oxidation and increase glucose oxidation	Not approved in the USA	Class IIB	[53, 54], TACT [144]
L-Arginine	Substrate for nitric oxide synthase. Improves endothelium-dependent vasodilation.			[67]
Perhexiline	Modifies myocardial substrate utilization from fatty acids to carbohydrates	Not approved	Available off license in the UK	[72]
Etoximir	Fatty acid metabolism modulator	Not approved	Not approved	ERGO [78]
Omapatrilat	Vasopeptidase inhibitor with selective and competitive inhibitory activity of ACE	Not approved	Not approved	[80]
Fasudil	Rho kinase inhibitor	Not approved	Not approved	[82]
DW1865	Rho kinase inhibitor	Not approved	Not approved	[83]
Allopurinol	Xanthine oxidase inhibitor	Not approved	Not approved	[84]
Testosterone	Endothelium-independent vasodilation	Not approved	Not approved	[87–92]
Esgtrogen	Vasodilation and endothelial function improvement	Class III	Not approved	[95]
Molsidomine	Nitric oxide donor			[97]
Mildronate	Inhibits carnitine biosynthesis. Improves systolic function, arterial vascular tone, stress tolerance and reduces anginal symptoms		Approved for clinical use in Latvia, Lithuania, Russia and Ukraine.	[102]
Omecamtiv mecarbil	Cardiac myosin activator			[107]

ACE: Angiotensin-converting enzyme; ASA: Aspirin; BB: Beta-blockers; BP: Blood pressure; CCB: Calcium channel blockers; cGMP: Cyclic guanosine monophosphate; CHF: Congestive heart failure; FDA: Food and Drug Administration; HR: Heart rate; MI: Myocardial infarction.

TABLE 2

Current open trials for various pharmacological therapeutic modalities for management of angina.

Trial	Condition	Objective	Outcomes	Principal Investigator
Cell Therapy in Severe Chronic Ischemic Heart Disease (MiHeart) NCT01727063	Chronic ischemic heart disease Coronary artery disease Angina pectoris	Phase II/III, multicenter, randomized, double-blind, placebo-controlled study of the efficacy of intramyocardial injection of autologous bone-marrow cells in patients with severe, chronic ischemic heart disease undergoing coronary bypass surgery	Increase in myocardial perfusion, improvement in LV function and in angina class	Luis Henrique W Gowdak, Heart Institute, Sao Paulo, Brazil
Intracardiac CD133+ cells in patients with no-option resistant angina (Regent Vsel Study) NCT01660581	Stable angina	A randomized, prospective, double-blind study to evaluate intracardiac injections of bone marrow, autologous CD133+ cells (electromechanical mapping based) in patients with resistant angina and no effective revascularization option	Improvement of myocardial perfusion and function, and on decrease of occurrence of symptomatic angina	Wojciech Wojakowski, Katowice-Ochojec, Silesian, Poland
Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina (RENEW), NCT01508910	Chronic myocardial ischemia Refractory angina pectoris (advanced) coronary heart disease	Phase III, prospective, randomized, double-blinded, active-control and unblinded SOC controlled study to determine the efficacy and safety of targeted intramyocardial delivery of autologous CD34+ cells (auto-CD34+ cells) for increasing exercise capacity during standardized exercise testing in subjects with refractory angina pectoris and chronic myocardial ischemia	Change from baseline in total exercise time on exercise tolerance test, angina frequency and MACE	Adel Nada, Baxter Healthcare Corp.
Efficacy and Safety of Ad5FGF-4 for Myocardial Ischemia in Patients With Stable Angina Due to Coronary Artery Disease – ASPIRE. NCT01550614	Stable angina	Randomized, controlled, parallel group, multicenter Phase III study to evaluate the efficacy and safety of Ad5FGF-4 using SPECT myocardial perfusion imaging in patients with stable angina	Change in reversible perfusion defect size, angina frequency, quality of life and functional class using CCS angina classification	Ivan Gordeev, Municipal Hospital #15, Moscow, Russia
Endocardial VEGF-D Gene Therapy for the Treatment of Severe Coronary Heart Disease - A Phase I Single-blinded Placebo-controlled Phase I Clinical Trial, NCT01002430	Angina pectoris myocardial infarction	Phase I single-blinded placebo-controlled trial	Assessments for safety and tolerability as measured as the acute and late adverse effects, laboratory parameters, biodistribution of the vector, anti-adenovirus antibodies and VEGF-levels before and in several time points after the gene transfer	Juha Hartikainen, Kuopio, Finland.
VM202 in Subjects With Chronic Refractory Myocardial Ischemia, NCT01002495	Myocardial ischemia	A Phase I/II open-label, dose-escalation study to assess the safety and tolerability of VM202 in subjects with chronic	Evaluate safety and tolerability of a catheter-based, endocardial injection of different doses of VM202, assessment of	ViroMed Co., Ltd. and VM Biopharma

Trial	Condition	Objective	Outcomes	Principal Investigator
		refractory myocardial ischemia	angiogenic potential. Efficacy measures include exercise treadmill test, SPECT, cardiac MRI and change in use of anti-anginal medications	
NIRVANA – Nebivolol for the Relief of Microvascular Angina in Women, NCT01665508	Microvascular angina	Phase IV, open-label study	Seattle angina questionnaire score, peak VO2 measurement	Nandita S Scott and Malissa J Wood, MGH, Boston, MA, USA
Research on Nicorandil Treatment of Patients Diagnosed as Coronary Heart Disease With Stable Angina, NCT01396395	Stable angina Coronary disease	A Phase IV randomized, placebo-controlled, double-blind, cross-over study	Number of ischemic attacks measured by 24-hour Holter monitoring	Yong Huo, Peking University, Beijing, China
Comparative Study to Assess the Efficacy of Nicorandil+Atenolol vs Atenolol in Treatment naïve Patients of Chronic Stable Angina, NCT01397994	Chronic stable angina	Phase IV, open-label, randomized, parallel arrangement, safety/efficacy study	Changes in perfusion will be evaluated in each arm at week 4 and comparison between the two study arms will be made to document the anti-ischemic effects of nicorandil using Ex-SPECT MPI	Tariq Ashraf, National Institute of Cardiovascular disease, Karachi, Pakistan
The Influence of Febuxostat on Coronary Artery Endothelial Dysfunction in Participants With Chronic Stable Angina, NCT01763996	CAD	Randomized, double blind, crossover assignment, phase IV efficacy study	Change in coronary artery flow from rest to isometric handgrip using MR	Takeda Global Research and Development Center, Inc
Effect of Molsidomine on the Endothelial Dysfunction in Patients With Stable Angina Pectoris Undergoing a Percutaneous Coronary Intervention, MEDCOR, NCT01363661	Stable angina pectoris Atherosclerosis	Phase IV, randomized, double-blind, placebo-controlled, parallel assignment efficacy study	Change versus baseline in the score of endothelial function by reactive hyperemia in the two groups after one year of treatment	Emanuele Barbato, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium
Phase III Trial of Dantonic® (T89) Capsule to Prevent and Treat Stable Angina (CAESA) - NCT01659580	Angina pectoris	Phase III, randomized, double-blind, confirmatory safety/efficacy study of Dantonic® (T89), a botanical drug consists of extracts of Danshen (Radix Salviae Miltiorrhizae) and Sanqi (Radix Notoginseng) with borneol in a capsule form	Change in symptom limited total exercise duration	Henry He Sun, Tasly Pharmaceuticals
Testosterone Therapy on Angina Threshold and Atheroma in Patients With Chronic Stable Angina, NCT00131183	Angina	Phase IV, randomized, double-blind, safety/efficacy study	Change in time to ST-segment depression of > 1mm during exercise testing.	Kevin S Channer, Sheffield, South Yorkshire, UK
YM758 in subjects with stable angina, EUCTR2005-002456-18-SK	Angina	A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and preliminary efficacy of a 4-week treatment with YM758, a novel hyperpolarization-activated inward current inhibitor which has been shown to prolong the AH intervals	Safety and tolerability of different oral doses of YM758 in subjects with stable angina.	Astellas Pharma Europe

Trial	Condition	Objective	Outcomes	Principal Investigator
		when given during atrial burst pacing [130]		
Clinical efficacy of Pentalong® in stable Angina patients after 12 Weeks of routine administration: a randomised, double-blind, placebo-controlled trial. – CLEOPATRA, EUCTR2008-007093-37-DE	Stable, effort-induced angina pectoris	A randomized, double-blind, placebo-controlled multi-center study designed to demonstrate the anti-anginal efficacy of PETN 80 mg b.i.d. (morning and midday) as compared with placebo on top of anti-anginal background treatment. Pentaerithrityltetranitrate (PETN), brand name Pentalong® is a long acting NO donor and has recently been described as an organic nitrate ester that (in contrast to other nitrate acid esters) does not induce oxidative stress	Change in Total Exercise duration from baseline after 12 weeks of treatment with PETN 80 mg b.i.d.	Actavis Deutschland GmbH
Effects of Sildenafil on Signs and SYmptoms of Ischemia, Myocardial BlooD Flow, and Markers of ANgiogenesis in Patients with REfractory CoronarY Artery Disease – SYDNEY, EUCTR2010-023375-26-AT	Refractory angina	Randomized, double-blind, placebo-controlled study designed to prospectively investigate if intermittent phosphodiesterase 5 inhibition for 15 weeks improves myocardial perfusion by angiogenesis in patients with therapy refractory myocardial ischemia due to CAD	Total exercise duration	Rudolf Berger, Waehringer Guertl 18–20, 1090 Vienna, Austria
Effects of Inorganic Nitrite on cardiac and skeletal muscle: Physiology, pharmacology and therapeutic potential in patients suffering from Angina (UKCRN ID 13271).	Angina	Single center randomized, double-blind, placebo-controlled study on patients with chronic stable angina (>2 months duration) who are on no background antianginal therapy other than short-acting nitrates	Increase in the time to onset of angina using a modified Bruce exercise test	M P Frenneaux, University of Aberdeen, UK
Danhong injection in treatment of angina, NCT01681316	Chronic stable angina	Phase IV, randomized, multi-center, double-blind, placebo-controlled trial designed to evaluate the effect of Danhong Injection on the relief of angina	Change in angina-frequency score on the Seattle Angina Questionnaire	Zhong Wang, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences