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Therapy for Angina Pectoris Secondary to Coronary Disease

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1. Introduction

Ischemic heart disease is the world's leading cause of mortality and also causes widespread morbidity and limitation of life-style. Coronary artery disease (CAD) is the predominant cause of ischemic heart disease and generally results from fixed coronary artery obstruction that limits myocardial oxygen delivery relative to demand. Mortality associated with CAD is relatively high and was estimated at more than 1¼ million deaths in industrialized countries in 2001 (Lopez et al., 2006). Of note, CAD is projected to remain the primary basis of mortality at least through year 2030 (Mathers & Loncar, 2006). The impact of CAD on quality of life is even more impressive. The symptom that most commonly limits life-style in patients with CAD is angina pectoris. Angina pectoris is a symptom characterized by (1) substernal chest discomfort that is (2) predictably provoked by exertion or emotional stress, (3) lasts up to 20 minutes after the triggering activity is stopped, and (4) is relieved within minutes by nitroglycerin or rest. If all of these criteria are met, the symptom is called "typical angina pectoris"; if only 2 are met, the symptom is called "atypical angina". If one or none are met, the symptom probably is non-cardiac in origin (Diamond et al., 1983). Typical angina has several different causes but predominantly results from CAD. Indeed, the presence of typical angina predicts CAD with a likelihood of 90%, while the association of atypical angina with CAD is reported to be 50%. CAD with ischemia also can cause other symptoms, such as abnormal chest sensations that do not meet the criteria for angina, dizziness, palpitation, dyspnea, etc.

Angina pectoris is the presenting symptom in 50% of those with CAD (O'Rourke, 2010). Most often, this symptom is "stable", i.e., after its onset, it occurs at a relatively predictable workload, frequency and severity. By convention, stable angina manifests little change in these characteristics over 2 weeks, though some variation can be expected if change occurs in myocardial oxygen demand, physical stress or ambient temperature (Braunwald et al., 1994). In general, stable angina correlates with the stability or quiescence of an atherosclerotic plaque. Almost 20% of acute myocardial infarctions (MI) are preceded by chronic stable angina (Thom et al., 2006). This symptom must be distinguished from the less frequent "unstable angina", considered to occur when angina first is manifest ("new onset angina"), or when angina-like discomfort is present at rest (i.e., without the activity/

emotional stress trigger of typical angina), or when angina severity and frequency progress relatively rapidly. Most importantly, patients with unstable angina can be divided into low, intermediate or high short term risk of death or nonfatal MI (Gibbons et al., 1999). Patients at high and intermediate risk often have coronary artery plaques that have recently ruptured. Their risk of death is intermediate between that of patients with acute MI and patients with stable angina. Stable angina pectoris (hereafter denoted as "angina") is common and disabling, affecting 30,000 to 40,000 per 1 million people in Europe and United States (Julian, 1997). As of 2006, approximately 10.2 million patients had angina in the United States. Angina often seriously limits routine daily activities and frequently leads to premature retirement from work (Julian, 1997). Despite availability and application of multiple anti-anginal drugs and mechanical therapy, angina remains very common in patients with known CAD, affecting 30 to 50% of such individuals (Gehi et al., 2008). One in 3 patients with stable angina will have more than one episode per week. Epidemiologically, self reported angina substantially increases the risk of coronary events compared to its absence; this risk increases even more when angina is associated with exercise induced ischemia (Gehi et al., 2008). Regardless of the negative impact of angina on quality of life, in one study almost half of general practitioners considered angina in their patients to be optimally controlled in the face of persistent weekly symptoms (Beltrame et al., 2009).

This chapter will review therapies currently available and in development for relief of acute episodes of angina and, more importantly, for prevention of this symptom in its chronic stable form (Table 1). Because, angina from CAD develops from myocardial oxygen supply-demand imbalance, therapy for patients with CAD and angina is targeted to restore this balance. Indeed, the United States Food and Drug Administration will not approve a therapy for angina unless both the symptoms and the underlying ischemia are relieved in pre-approval testing because of concerns for patient safety if this symptomatic warning of ischemia is masked and the inciting activity continues. The major determinants of myocardial oxygen demand are heart rate (Fox et al., 2007; Heusch, 2008), systolic blood pressure and contractility. Indeed, experimentally, a twofold increase in any of these determinants of oxygen consumption requires approximately 50% increase in coronary blood flow if ischemia is to be avoided (Libby et al., 2008). The primary determinants of myocardial oxygen supply are coronary artery patency, perfusion pressure, arterial oxygen content and duration of diastole, when coronary flow occurs. Because of the high resting oxygen extraction by myocardial tissue, increase in myocardial oxygen consumption is primarily compensated by proportional increases in coronary flow and oxygen delivery.

In patients with CAD, comprehensive management focuses not only on prevention and relief of the symptom but also on prevention of other sequelae common in patients with angina, including myocardial infarction, heart failure and death. Importantly, however, most antianginal therapies, pharmacological and mechanical, have **not** been assessed for their impact on adverse outcomes in patients with chronic stable angina. Management of patients with angina include life style modifications to prevent symptoms as well as to minimize known risk factors for adverse events, medications to prevent angina or to relieve acute episodes, medications to relieve risk factors (cholesterol-lowering agents, antihypertensive drugs, etc.), medications known to prevent other sequelae of CAD (e.g., anti-platelet drugs, certain angiotensin converting enzyme inhibitors) and revascularization or other mechanical therapy to relieve angina if it is inadequately managed with drugs alone.

Anti-Anginal Therapy	Primary Pharmacological Effects	Putative Anti-ischemic Mechanism
Pharmacological Therapies		
Nitrates	Smooth muscle relaxation, vasodilatation (venodilation> arteriolardilation)	↓↓preload, ↓afterload, (↓ myocardial oxygen demand), ↑oxygen supply
Calcium Channel Blockers	Smooth muscle relaxation (all), ↓inotropy (some), ↓chronotropy (some), ?improved endothelial function	↓preload, ↓afterload, ↓ inotropy with ↓ contractility(some) (↓demand), ↑oxygen supply
Beta adrenergic blockers	↓chronotropy, ↓inotropy,	↓blood pressure ↓demand, ↑oxygen supply
Miscellaneous		
a. Direct metabolic enhancers		
1. Ranolazine	Inhibits fatty acid oxydation thus improving efficiency of oxydative metabolism, Na-channel inhibition thus decreasing calcium overload	Improved cellular metabolism
2. Trimetazidine	Inhibits palmitoyl-carnitine oxidation, inhibit fatty acid oxydation	Improved cellular metabolism
b. Novel unloading or HR lowering drugs		
1. Ivabradine	Inhibits I_f current, reduces HR, preserves LV inotropy and lusitropy, does not affect coronary vasomotion	↓ myocardial oxygen demand, ↑oxygen supply
2. Nicorandil	Opens ATP sensitive K channels, vasodilator,	↓preload, ↓afterload, (↓demand)

Anti-Anginal Therapy	Primary Pharmacological Effects	Putative Anti-ischemic Mechanism
	promotes endothelial NO synthase, reduces calcium toxicity	
3. Fasudil	Rho-kinase inhibitor, coronary vasodilatation/anti-spasmodic	↑oxygen supply
Mechanical Interventions	**Known effects**	
a. Revascularization		
1. Coronary artery bypass grafting 2. Coronary angio-plasty/stenting	Relieves mechanical obstructions to coronary arteries	↑oxygen supply
b. Enhanced external counterpulsation (EECP)	Alters hemodynamics to improve coronary perfusion	↑oxygen supply, ↓ myocardial oxygen demand
c. Spinal cord stimulation	Decreases pain and sympathetic tone	↑oxygen supply,↓ myocardial oxygen demand
d. Carotid sinus stimulation	Increases parasympathetic tone	↑oxygen supply,↓ myocardial oxygen demand
Biological Therapy	**Putative Actions**	
1. Transmyocardial laser revascularization	direct perfusion of myocardium, angiogenesis, placebo or myocardial denervation	↑oxygen supply
2. Angiogenic gene therapy	angiogenesis	↑oxygen supply

HR=heart rate, K=potassium, LV=left ventricle, NO=nitric oxide

Table 1. Antianginal anti-ischemic therapies, proven and putative

Therapies shown to be effective in relieving acute episodes are limited to rapid onset, short acting nitrates and, though seldom used today, carotid sinus or spinal cord stimulation, all reviewed in this chapter. Prevention of angina can be achieved with a variety of drugs, though those most frequently employed today are beta blockers, calcium channel blockers and long acting nitrates. These and the other newer drugs now available will also be reviewed below. The various mechanical options, including coronary artery bypass grafting surgery, percutaneous coronary angioplasty, enhanced external counterpulsation, and laser-mediated angiogenesis, will be summarized. Finally, the current status of approaches that

are not yet established but which hold promise for benefit and are under intensive study, including angiogenesis stimulated by growth factors directly or by gene insertions, and stem cell therapy, will be reviewed. Table 1 summarizes various approaches, pharmacological, mechanical and biological, now available or in relatively late stages of development.

2. Pharmacological therapy

2.1 Nitrates

Nitrates have been the staple of treatment for acute episodes of angina pectoris for almost 150 years, since the description of the effect of amyl nitrate for this condition in 1867 (Brunton, 1867). Indeed, such use of amyl nitrate was included in the Lillian Hellman play, "The Little Foxes", set just after the Civil War. Though the use of amyl nitrate has declined to application largely for diagnostic hemodynamic profiling for other conditions (e.g., idiopathic hypertrophic subaortic stenosis) other nitrates and, most particularly nitroglycerin, introduced by Murrell for this purpose in 1878 (Murrell, 1879), have gained enduring use, both for treatment of acute episodes and for prophylaxis.

2.1.1 Pharmacological effects

Like all anti-anginal anti-ischemic drugs, nitrates act to improve the imbalance of myocardial oxygen supply and demand that underlies angina (Grayson et al., 1967). Nitrates are believed to induce vasodilatation by interacting with sulfhydryl groups on nitrate receptors on cell membranes (Goldstein, 1979). The prototype nitrate, nitroglycerin, combines with sulfhydryls within smooth muscle cells, where the resulting molecule is biotransformed to an active form, S-nitrosothiol, by mitochondrial aldehyde dehydrogenase (Abrams, 1980). This short-lived compound activates intracellular guanylate cyclase to produce cyclic guanosine monophosphate. This molecule directly initiates smooth muscle relaxation to cause vasodilatation by decreasing myocytic intracellular calcium, either by inhibition of calcium ion entry or by promotion of calcium exit (Ignarro et al., 1981). This pharmacological effect renders nitroglycerin a potent vasodilator. Experimental studies suggest that nitroglycerin's action as a venodilator may exceed that as an arterial and arteriolar dilator, though the drug acts on both sides of the circulation. It has been suggested that reduction in left ventricular (LV) preload, resulting from venous dilatation, is the primary basis for the drug-induced reduction in myocardial oxygen demand and, perhaps, the increase in myocardial oxygen supply observed with nitroglycerin and, thus, may be the primary basis for its anti-anginal anti-ischemic effect (Goldstein, 1979). However, reduction in LV outflow impedance due its arterial and arteriolar effects likely also is involved.

Experimental evidence suggests that nitrates also may act directly to increase myocardial oxygen supply by dilatation of coronary arteries and arterioles. Conversion to nitric oxide, a deficiency of which is the putative basis of "endothelial dysfunction" observed in many patients with CAD (Parker & Parker, 1998), provides potential for vasodilatation and enhancement of coronary blood flow. However, the practical importance of this effect is unclear, since the calcified state of many atherosclerotic coronary arteries is likely to limit potential for arterial dilatation. Experimental evidence also suggests nitroglycerin may preferentially affect collateral vessels within the myocardium to increase flow to ischemic regions. Finally, as a result of preload reduction, nitroglycerin reduces LV diastolic pressure potentially enhancing perfusion pressure during diastole when most coronary flow occurs. This effect is apparent primarily in the subendocardium, where flow is particularly

vulnerable, though little change in total myocardial perfusion appears to be associated with this effect (Bottcher et al., 2002). Finally, in experimental studies, nitroglycerin has antithrombogenic action, apparently mediated via stimulation of guanylate cyclase in platelets (Munzel et al., 2002). This effect would tend to minimize platelet aggregation. The clinical importance of this change, particularly for angina, is not known.

Irrespective of the underlying mechanisms, nitrates have been well demonstrated to increase exercise tolerance in patients with ischemic heart disease from CAD, while reducing ischemia as measured by increased time to ST segment depression during exercise in patients with chronic stable angina (Ben-Dor & Battler, 2007). Nitrates have additive effect when they are combined with beta-blockers or calcium channel blockers (Gibbons et al., 2003).

2.1.2 Clinical application

Nitroglycerin preparations are available as sublingual tablets, buccal spray and ointment (both in immediately available and prolonged release ["patch"] forms), the latter for prophylaxis rather than for treatment of acute episodes. Nitroglycerin tablets lose potency when exposed to light and, hence, are stored in dark containers. The sublingual preparation is the treatment of choice for acute episodes of angina because this mode of administration enables absorption without first pass metabolism in the liver, resulting rapidly in therapeutic concentrations in the circulation. (Buccal spray has a similar advantage.) From drug levels in the plasma, the half-lives of the compounds differ markedly, nitroglycerin having a half-life of 2-3 min, isosorbide dinitrate (ISDN) 20-30 min and isosorbide mononitrate (ISMN) 4-5 h (Olsson & Allgen, 1992). The beneficial clinical effect of nitroglycerin has a half-life of 30 minutes; its hemodynamic effects are seen even after 2 hours (Goldstein & Epstein, 1973).

Metabolism to inactive forms occurs in the liver. The usual dose of nitroglycerin for relief of an acute angina episode is 0.4 mg by the sublingual route, though smaller (and larger) doses are effective in some patients. Nitroglycerin spray dispenses 0.4 mg metered, aerosolized doses, which are better absorbed in patients with dry mucous membranes. There is evidence to show that when used in sublingual form, nitroglycerin is an effective antianginal and anti-ischemic agent that can abort an attack of established angina and, when taken prophylactically, prolong exercise tolerance (Aronow, 1973; Detry & Bruce, 1971; Goldstein et al., 1971). If symptoms persist after a single dose, additional doses can be given, usually at 5 minute intervals, though lack of relief with as much as 1.2 mg in a 15 minute interval suggests an acute coronary syndrome and should lead to emergency evaluation. Several long acting forms of nitrates have been developed. Their pharmacokinetics are such that they are not used for relief of acute angina episodes, but their persistence in the circulation and at active cellular sites can provide effective prophylaxis against angina. The most commonly employed are topical nitroglycerin ointment or nitroglycerin adherent to patches, oral ISDN and oral ISMN.

Topical cutaneous administration of nitroglycerin is possible either with an ointment or a polymer patch impregnated with the drug. Nitroglycerin ointment usually is applied in 0.5 – 2 inch doses, containing 15 mg of nitroglycerin per inch. The drug is effective for about 6 hours by this route. Absorption can be impeded if skin perfusion is minimized by hypotension or impaired cardiac output. Nitroglycerin patches release the drug at a rate of 0.1 to 0.8 mg/hour (depending on patch size) and are effective for approximately 12 to 18 hours. Tolerance generally is absent if the patch is used for no more than 12 to 14 hours

daily. Oral ISDN has relatively low bioavailability, undergoing rapid hepatic metabolism. It is usually administered in a dose of 30 mg 3 to 4 times daily. The antianginal effect lasts for 6 hours after the first dose, with decreased effect with each successive dose. Nitrate tolerance develops when it is administered four times daily. A dosing schedule permitting intermittent 10-12 hour nitrate free intervals helps to prevent tolerance.

ISMN is the active metabolite of ISDN. When administered orally, it doesn't undergo first pass metabolism and provides effective management of chronic stable angina. Steady state plasma concentration is achieved within 2 hours and its effect lasts for at least 8 hours. Tolerance is not reported when ISMN is administered once daily, but tolerance is common with twice daily dosing. A sustained release preparation is available in a dosage range from 30 to 240 mg daily. Nitroglycerin can also be used as an intravenous preparation with titration to symptoms and blood pressure. Though not strictly relevant for relief of chronic stable angina, this form has been used for patients with frequent ("unstable") angina at rest and requiring hospitalization (Frishman, 1985). It has also been used during acute coronary syndromes and has been effective in reducing ischemia during acute myocardial infarction (Borer et al., 1975) as well as in improving hemodynamics and reducing symptoms in heart failure, with or without infarction (Frishman, 1985).

2.1.3 Adverse effects

Most common adverse effects of nitrates and, specifically, of nitroglycerin, include headache, hypotension and flushing. These effects are due to vasodilatation. Methemoglobinemia is rare but reported after nitrate administration, most commonly after high doses of the intravenous form. Tolerance is reported with all forms of nitroglycerin. Tolerance to antianginal effects develops rapidly in humans during long-term, 4 times daily therapy with ISDN and continuous therapy with nitroglycerin patches (Crean et al., 1984; James et al., 1985; Parker & Fung, 1984; Reichek et al., 1984). The putative mechanism of tolerance is drug-induced generation of superoxide anions in the affected vessels, leading to impaired biotransformation and decreased responsiveness to nitric oxide (Gori & Parker, 2004). Tolerance can be best avoided by providing a nitrate free period, optimally of 10 to 12 hours. Development of tolerance is rarely a problem when nitroglycerin sublingual tablets are taken intermittently, either for relief of an acute symptom or for short-term prophylaxis before activities predictably associated with angina. Some studies have shown that angiotensin receptor blockers may prevent nitrate tolerance (Hirai et al., 2003). Patients can develop rebound symptoms after abruptly stopping nitrates. With the recent increase in the use of sildenafil, a phosphodiesterase inhibitor, the dangers of interaction with nitrates have been highlighted, leading to proscription of this combination to prevent severe and potentially lethal hypotension.

2.2 Calcium channel blockers

Calcium Channel Blockers (CCB) bind to and inhibit L-type calcium channels, reducing calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilatation in the peripheral and coronary beds and, in normal coronary arteries and perhaps diseased arteries, increased coronary blood flow. The 2 major subdivisions of CCBs are dihydropyridines (DHP) like nifedipine, amlodipine, felodipine, and nicardipine, and non-dihydropyridines which include verapamil and diltiazem.

2.2.1 Pharmacological effects

CCBs' main effect on angina is lowering myocardial oxygen demand by peripheral vascular smooth muscle relaxation. The result is to reduce blood pressure and impedance to LV outflow, in turn reducing myocardial wall tension, myocardial work load and oxygen consumption. However, they may cause dilatation of coronary arteries, as well, and thus may increase coronary blood flow/ myocardial perfusion. CCBs have been shown to be specifically and particularly effective in vasospastic angina pectoris (including "Prinzmetal's angina") and may be useful in effort-induced angina in part by relieving vasospasm associated with fixed obstructive lesions in some patients. In addition to vascular smooth muscle relaxation, the non-dihydropyridines also cause blockade of calcium entry into myocytes, leading to negative chronotropic effects due to action on the sinoatrial and atrioventricular nodal cells, and negative inotropic effects leading to depressed contractility due to action on ventricular myocytes.

Experimentally, calcium plays an integral role in the process of atherogenesis. Hence, it has been theorized that CCBs are anti-atherogenic. Some studies have shown that CCBs reduce the progression of atherosclerosis as measured by carotid intima-media thickness but there has been no difference in coronary atherosclerosis. The ENCORE I trial demonstrated that nifedipine improved coronary endothelial function in the most constricted segment (Azancot, 2003) and the ENCORE II study showed that nifedipine improved coronary endothelial function but had no effect on plaque volume (Luscher et al., 2009). The NICOLE study showed no effect of CCBs on reduction of angiographic progression of CAD (Dens et al., 2003). Thus, clinical studies to date provide equivocal evidence of anti-atherogenesis but stronger support for improvement of endothelial function.

2.2.2 Clinical application

From multiple trials, CCBs decrease the frequency of angina, reduce the need for nitrates, extend treadmill walking time, and improve ischemic ST-segment changes on exercise testing and electrocardiographic monitoring (Gibbons et al., 2003; Heidenreich et al., 1999; Nissen et al., 2004; Rice et al., 1990). Amlodipine, in particular, may have some independent action in relieving diastolic dysfunction other than by a reduction in blood pressure (Tapp et al., 2010), potentially improving myocardial oxygen supply by enhancing perfusion pressure. CCBs are used in patients who cannot tolerate β-blockers or in combination with other anti-ischemic agents for additive benefit. Though clearly effective antianginal agents, CCBs have not been found to modify the natural progression of CAD and have no effect on cardiovascular or all cause mortality in patients with CAD. DHP tend to cause reflex tachycardia because of lowering of blood pressure; this effect can be blunted by concomitant use of β-blockers. If clinically needed, verapamil or diltiazem may be used with caution to lower heart rate or slow atrioventricular (AV) conduction further when ventricular function is preserved. In a case control study among enrollees of the Group Health Cooperative of Puget Sound, a link was reported between short-acting nifedipine and coronary events when the drug was used as primary therapy for hypertension (Psaty et al., 1995). However, short-acting nifedipine never has been approved by the FDA for use for this indication (i.e., its use was "off label"), and its application for this purpose by the Puget Sound group was an act of highly questionable judgment. Meta-analysis by Furberg et al showed that nifedipine is associated with dose related increase in mortality in patients with CAD, a study which included patients with acute coronary syndromes (ACS) (Furberg et al., 1995). However, the only trial included in the meta-analysis that involved patients with stable

angina was the International Nifedipine trial on Antiatherosclerotic Therapy (INTACT), which showed that patients on nifedipine had retardation of atherosclerotic disease by angiogram, though clinical symptoms were not reported (Lichtlen et al., 1990). A Coronary Disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) study reported that, in patients with stable angina and hypertension, long-acting nifedipine was acceptably safe (no increased incidence of myocardial infarction, heart failure or death), but there was no evidence of improvement in mortality or other major cardiac endpoints and no reduction in refractory angina in already maximally medically treated patients (Poole-Wilson et al., 2004; Sierra & Coca, 2008). In addition to vasodilatation, verapamil acts in part through its negative inotropic effect. Diltiazem has greater vasodilatory actions than verapamil. Both verapamil and diltiazem are contraindicated in patients with uncompensated heart failure because of their negative inotropic effects, whereas amlodipine and felodipine are relatively safe when LV dysfunction is present, particularly if compensated clinically (Sierra & Coca, 2008). Use of non-dihydropyridines after complex myocardial infarctions should be avoided, as well, because of the possibility of HF.

Although CCBs are effective anti-ischemic agents, they do not improve mortality in patients with ACS. DHP can also cause reflex tachycardia which can be deleterious in acute ischemia by increasing myocardial oxygen demand. In addition, DHP-induced hypotension may detrimentally lower coronary perfusion pressure. A meta-analysis of trials of CCBs and long acting nitrates did not show any difference in clinical outcomes between these types of agents (Heidenreich et al., 1999). Nifedipine is a potent, long-acting vasodilator that has proved highly efficacious in relieving angina caused by coronary vasospasm. In vivo, it exerts no myocardial depressant effects and has no antiarrhythmic properties. Nifedipine is available in doses of 10-30 mg given 3 times daily and in sustained release preparations in doses of 60 to 120 mg that can be administered once daily. Onset of action is 20 minutes after administration and half life is 2-5 hours. Steady state concentrations are reached in 48 hours. Immediate release formulation is not recommended for hypertension because of concerns of sudden hemodynamic compromise but it is still approved for coronary spasm and management of angina. Treatment with nifedipine can safely be combined with administration of a β receptor blocking agent.

Verapamil is usually started with 40 mg three times daily and titrated to a maximum dose of 480 mg daily. Sustained release preparations are available and can be given in doses of 120 mg daily to 480 mg daily. Onset of action of verapamil is in 30 minutes; elimination half life is 3-7 hours. Diltiazem is available in doses of 30-90 mg given up to four times daily. A sustained release or long-acting form usually is administered at a starting dose of 120 mg daily and can be increased to 360 mg daily. Its onset of action is within 30-60 minutes and it has a half life of 3-7 hours. It can take up to 2 weeks to achieve maximal effect of diltiazem.

2.2.3 Adverse effects

Common side effects of headache, dizziness, flushing and edema (particularly with DHP) are due to vasodilatation. Verapamil and diltiazem can interact with other negative chronotropic or negative inotropic agents to produce substantial bradycardia, conduction disturbances or clinically overt heart failure. CCBs may also suppress lower esophageal sphincter contraction and worsen gastroesophageal reflux. Particularly with verapamil and, to a lesser extent with diltiazem, bowel motility can be importantly reduced, causing constipation, a particularly frequent complaint in relatively elderly patients given these

drugs. CCBs inhibit the CYPA4 enzyme in the liver and, therefore, may raise levels of statins and other drugs, resulting in adverse effects of the drugs so affected (Furberg et al., 1978). By blocking the microsomal enzymes, the liver enzymes that metabolize CCBs, cimetidine and grapefruit juice may raise blood CCB concentrations. Since magnesium is a calcium antagonist, magnesium supplements may enhance the actions of CCBs, particularly nifedipine.

2.3 Beta-blockers

Adrenergic receptors are G-protein-coupled molecules stimulated by circulating catecholamines. These receptors are broadly classified into α and β groups. Effects of β-receptors are mediated by adenyl cyclase. β-receptors are further classified into β1 and β2 subtypes. β1 stimulation results in increased chronotropy, inotropy, automaticity, release of renin from juxtaglomerular cells and lipolysis. β2 effects include relaxation of bronchial, vascular and other smooth muscle, with dilatation of peripheral, coronary, and carotid arteries, and promotion of glycogenolysis and gluconeogenesis. β-blockers are effective in preventing angina because they lower heart rate, reduce blood pressure, and reduce contractility, thereby reducing myocardial oxygen demand (Gibbons et al., 2003). However, of these effects, current data indicate that the most important is reduction in heart rate, the primary determinant of myocardial oxygen demand (Andrews et al., 1993; Borer et al., 2003; Daly et al., 2010). Most antianginal effects of β-blockers result from β1 inhibition. Also, because of the heart rate reduction, β-blockers can enhance myocardial oxygen supply by prolonging diastole, when coronary perfusion occurs. However, by blocking β2 receptors that can mediate coronary vasodilatation, some β-blockers can allow unopposed α-adrenergic stimulation, leading to coronary vasoconstriction and mitigating the potentially beneficial effects of prolongation of diastole. β-blockers also have negative lusitropic (relaxation) effects on the myocardium, minimizing the rate at which LV pressure falls during diastole and, thus, minimizing the increase in perfusion pressure that otherwise might be expected during prolonged diastole that drives coronary flow.

2.3.1 Pharmacological effects

Some β-blockers are partial agonists, manifesting intrinsic sympathomimetic activity, blunting secondary preventive benefits (Freemantle et al., 1999). These generally are not used for angina prevention. Some newer β-blockers, such as labetalol, carvedilol, and bucindolol, also have partial α1-adrenergic blocking effects, causing vasodilatation. Others have antiarrhythmic effects – propranolol, metoprolol, and carvedilol have effects similar to "class I" (sodium-channel blockade) antiarrhythmics, while sotalol has a "class III" (potassium channel blockade) effect. Further, experimentally, carvedilol and its metabolites have antioxidant and antiproliferative properties that inhibit apoptosis. Most β-blockers are well absorbed. β-blockers that are lipid-soluble, such as propranolol and metoprolol, have short half-lives because they are metabolized by the liver. Hydrophilic β-blockers such as atenolol and nadolol are eliminated through kidney and have longer half-lives.

Atenolol is usually started with a dose of 50 mg daily and can be titrated to a suggested maximal dose of 200 mg daily. Metoprolol can be started with 50-100 mg daily and titrated for heart rate and blood pressure. When used to prevent angina, β-blockers generally are titrated to a resting heart rate of 50–60 bpm and an exercise heart rate 75% of the rate that precipitates ischemia. In patients with severe angina, target heart rates of 50 bpm are

sometimes used if neither symptoms (fatigue, lightheadedness) nor atrioventricular block supervenes.

2.3.2 Clinical application

β-blockers have been primary therapeutics for angina management since early after their development (Hoekenga & Abrams, 1984); indeed, slowing heart rate to prevent angina was the primary reason for their development, for which a Nobel Prize was awarded. Many β-blockers have been studied in chronic stable angina (Furberg et al., 1978; Jackson et al., 1978). β-blockers have been shown to reduce mortality in patients with relatively recent MI, primary angioplasty for ST elevation MI and CHF with LV dysfunction. However, no randomized trials ever have been performed to assess the effects of β-blockers on natural history outcomes in patients only with stable angina. Hence β-blockers are titrated for maximal symptom benefit with least adverse effects. No differences have been shown in antianginal effects of different beta blockers when they are titrated to similar heart rate reductions. β-blockers can be combined with nitrates, CCBs and other antianginals to enhance symptom relief.

2.3.3 Adverse effects

Absolute contraindications to β-blockers are severe bradycardia with or without conduction system disease, severe asthma or peripheral vascular disease with rest ischemia, depression, and acute decompensated heart failure (HF). β-blockers may cause dyslipidemia (increase in triglycerides and decrease in high-density lipoprotein cholesterol). The most common adverse effect is fatigue, a common complaint of patients receiving these agents. Mild depression, lack of motivation and erectile dysfunction have been well reported. β-blockers may blunt the tachycardic response to hypoglycemia in diabetics; worsening of hypoglycemia in diabetics on oral agents or insulin has been reported. β-blockers enhance insulin resistance, possibly accounting for the hyperglycemia. Patients with cocaine-induced coronary vasoconstriction may also react adversely when given β-blockers, with hypertension and seizures. Similarly, since β-adrenergic receptors may be up-regulated when patients are treated with β-blockers, these agents should not be abruptly discontinued, lest rebound vasoconstriction precipitate unstable angina or even MI or death (Miller et al., 1975; Psaty et al., 1990). Patients with asthma, claudication, or HF whose symptoms increase with β-blockers should be appropriately monitored and reevaluated for possible substitution with CCBs.

2.4 Ranolazine

Ranolazine is a piperazine derivative that has been shown to prevent stable angina pectoris. This agent was approved by FDA in 2006 for use in combination with other antianginals when angina is not adequately controlled with established therapies.

2.4.1 Pharmacological effects

The pharmacological effects most likely to underlie ranolazine's antianginal action are not fully elucidated. Several such effects have been suggested. Ranolazine has been shown to alter myocyte metabolism to favor oxidation of glucose over fatty acid by partial fatty acid oxidation (p-FOX) (Clarke et al., 1996). Less oxygen is required to metabolize glucose than fatty acids; consequently, ranolazine may improve efficiency of oxidative metabolism,

allowing more mechanical activity for a given oxygen supply. However, in formal clinical testing, though time to angina was increased with ranolazine versus placebo, no evidence was found that cardiac workload at angina was increased when angina occurred, thus casting doubt on improved metabolic efficiency as the underlying cause of the drug's benefit. Experimentally, ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I_{Na}) (Antzelevitch et al., 2004; Belardinelli L, 2004). Excess intracellular sodium activates the sodium-calcium exchanger and can result in intracellular calcium overload via reverse transport of the sodium calcium exchanger. Ranolazine appears to minimize the intracellular consequences of myocardial ischemia by reducing excess late sodium ion influx, thereby reducing calcium overload (Chaitman & Sano, 2007). Indeed, the drug is now labeled to indicate that sodium channel inhibition is the most likely basis of its activity. However, the drug also has modest alpha- and β-blocking properties. Ranolazine is extensively metabolized by cytochrome P450 (mainly the 3A4 enzyme) and excreted mainly in urine, predominantly as metabolites (Abdallah & Jerling, 2005; Chu N, 2003). The elimination half life in healthy individuals is 5.3 to 8.9 hours which is significantly increased in severe renal impairment (Jerling & Abdallah, 2005).

2.4.2 Clinical application

Ranolazine has been investigated in Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial, in which the drug was found to be well tolerated and effective in increasing exercise duration and time to ST segment depression in a dose dependent manner (Chaitman, 2002). In the Combination Assessment of Ranolazine in Stable Angina (CARISA) study, ranolazine was compared to placebo on a background of treatment with either atenolol 50 mg daily, amlodipine 5 mg daily, or diltiazem 180 mg daily. Ranolazine was effective in increasing exercise duration and mean time to onset of angina compared to placebo. There was also reduction in the frequency of angina as well as nitroglycerin use compared to placebo. In this trial, a higher dose of ranolazine (1000 mg twice daily) provided no extra benefit compared to the lower dose (750 mg twice daily) (Chaitman et al., 2004). In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, ranolazine was compared to a placebo on a background of amlodipine 10 mg daily. Again, ranolazine resulted in lower frequency of angina and nitroglycerin consumption and similar frequency of adverse effects (Stone et al., 2006). In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation (MERLIN-TIMI-36) trial, 6560 patients with acute coronary syndromes were randomized within 48 hours of symptom onset, to intravenous ranolazine or a placebo, in addition to standard therapy. Ranolazine was administered as a bolus of 200 mg over 1 hour and then continued as an infusion for 12 to 96 hours, followed by 1000 mg twice daily orally. After a median follow-up of 348 days, there was no difference in all-cause mortality, sudden cardiac death, or frequency of symptomatic arrhythmias between ranolazine and placebo. Though the trial failed to support ranolazine as a means of improving natural history in patients with CAD, it demonstrated the overall favorable safety profile of ranolazine, crucial for its FDA approval given prior concerns about drug-induced syncope and ECG QT prolongation with possible "pro-arrhythmia", while supporting its effectiveness in reducing angina (Morrow et al., 2007).

2.4.3 Adverse effects

Ranolazine is fairly well tolerated. Adverse effects (primarily dizziness, nausea, asthenia and constipation) appear to be dose related. Thus, in clinical trials, fewer than 8% of patients

discontinued ranolazine due to adverse effects; three quarters of these withdrawals occurred at the 1500 mg twice daily dose. Consequently, the approved starting dose is 500 mg twice daily, with possible up titration to 750 mg twice daily and 1000 mg twice daily if lower doses do not adequately prevent angina (Chaitman et al., 2004). An extended release (ER) oral preparation is also available. Ketoconazole and diltiazem can increase ranolazine plasma concentrations; ranolazine increases digoxin plasma concentration (Jerling & Abdallah, 2005; Chaitman et al., 2004). Ranolazine prolongs QTc interval in a dose related manner but, as noted above, MERLIN-TIMI 36 failed to demonstrate excessive sudden death with the drug (Scirica et al., 2007), nor were these suggested in earlier, shorter trials.

2.5 Ivabradine

The principle of heart rate slowing for prevention of angina is well established based on pathophysiological studies and clinical assessments of heart rate lowering drugs (Daly et al., 2010). Indeed, heart rate is the major determinant of myocardial oxygen demand and its increase is a precipating factor for ischemia or angina (Andrews et al., 1993; Borer et al., 2003; Daly et al., 2010; Fox et al., 2007; Heusch, 2008; Tardif et al., 2005). Heart rate also predicts outcome in epidemiologic studies of patients with CAD, as well as those with heart failure, hypertension, and, indeed, in unselected free living populations without apparent heart disease (Daly et al., 2010; Diaz et al., 2005; Fox et al., 2007; Fox et al., 2008; Fox et al., 2008; Tardif et al., 2009). For example, the Coronary Artery Surgery Study (CASS) registry showed after a 14 year follow-up that cardiovascular and overall mortality was directly related to heart rate at entry into the study (Diaz et al., 2005). Similar results were seen in the placebo group of the prospective BEAUTIFUL [morBidity-mortality EvAlUaTion of the *If* inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction] trial and in a retrospective assessment of the Treating to New Targets [TNT] study (Fox et al., 2008; Ho et al., 2010).

2.5.1 Pharmacological effects

As heart rate increases progressively myocardial oxygen demand increases (increase in myocardial work) and myocardial blood flow (and with it, potential myocardial oxygen supply) decreases because of reduction in the duration of diastole, when coronary flow occurs. When a threshold value is reached at which demand is greater than supply, ischemia results, often causing angina. Thus, Andrews et al showed that heart rate is a predictor of coronary ischemia in patients with stable CAD (Andrews et al., 1993). Ivabradine selectively inhibits the inward sodium–potassium I_f current, a relatively low amplitude primary modifier of the rate of spontaneous depolarization of the sino-atrial (SA) node myocytes (discovered in 1979 by DiFrancesco, et al (Brown et al., 1979; DiFrancesco & Camm, 2004)). Spontaneous depolarization, itself, is a function of other calcium and potassium currents. Ivabradine has no other known pharmacological actions on normal cardiovascular physiology. Therefore, it is considered a pure heart rate slowing drug (Thollon et al., 1994). Resting heart rate lowering by ivabradine is comparable to that achieved with β-blockers and is greater than that associated with CCBs (Pine et al., 1982; Tardif et al., 2005) for equal antianginal effect. The heart rate reduction is dose dependent (Borer et al., 2003; Thollon et al., 1994). Ivabradine is a selective and specific I_f inhibitor; it has no inotropic effect, no effect on relaxation (luisotropy), no impact on AV nodal conduction and no coronary vasoconstriction. Thus, ivabradine diminishes myocardial oxygen demand, increases

myocardial oxygen supply, maintains contractile force, preserves ventricular relaxation and allows coronary vasodilatation. The drug improves coronary perfusion and maintains cardiac performance better than alternative equieffective anti-anginal drug therapy.

2.5.2 Clinical application

The first placebo controlled trial of ivabradine for angina prevention (Borer et al., 2003) showed that increasing doses progressively reduced heart rate at rest and during exercise. With these changes, there was progressive increase in time to limiting angina and time to 1mm ST depression on bicycle exercise; the drug also reduced the number of diary-reported weekly angina episodes (Borer et al., 2003). The INITIATIVE (the INternatIonal TrIAl on the Treatment of angina with IVabradinE vs. atenolol) study compared ivabradine with atenolol ; ivabradine was non-inferior to the beta blocker in increasing treadmill exercise tolerance and preventing angina at doses selected to cause heart rate reduction approximately equivalent to that achieved with atenolol (Tardif et al., 2005). Indeed, ivabradine nominally improved exercise parameters to a greater extent than atenolol, though these differences did not reach statistical significance. Ivabradine also reduced spontaneous angina episodes compared with baseline and was again equivalent to atenolol in this effect (Tardif et al., 2005). Importantly, when the specific increment in exercise duration was assessed as a function of heart rate reduction ("anti-anginal efficiency") ivabradine was markedly and significantly more efficient than atenolol. When compared with amlodipine, ivabradine was non-inferior in improving exercise tolerance and preventing angina, and increasing time to 1 mm ST depression on exercise (Ruzyllo et al., 2007). Though some concern initially was raised about the combination of ivabradine and beta blockers because of the potential for profound heart rate lowering, the ASSOCIATE (Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina) trial of ivabradine versus placebo on a background of atenolol (Tardif et al., 2009) confirmed the experimental findings that ivabradine effect is « use dependent », i.e., the drug has its greatest rate-reducing effect at relatively high heart rates and has progressively less impact on heart rate as the pretherapy value decreases; more importantly, symptomatic bradycardia was rare with the combination, though significant antianginal efficacy was demonstrated with the combination compared with atenolol alone. When all clinical studies are considered, ivabradine has demonstrated consistent antianginal efficacy across all subpopulations, with reductions of 51% to 70% in the frequency of angina attacks (Tendera et al., 2009).

Almost uniquely among antianginal drugs, ivabradine has been demonstrated to exert a benefit on natural history end-points/cardiac events. Thus, in BEAUTIFUL, Fox et al showed that, among patients with chronic stable CAD, LV ejection fraction <40% and heart rate ≥70 bpm before therapy, heart rate reduction with ivabradine markedly and significantly reduced the incidence of fatal or non-fatal myocardial infarction, as well as the incidence of revascularization and non-MI acute coronary syndrome (Fox et al., 2008). In the BEAUTIFUL angina substudy (Fox et al, 2009) ivabradine not only reduced the frequency of angina, but it reduced the primary end-points of death, non-fatal myocardial infarction (both end-points similarly affected) or hospitalization for heart failure and improved quality of life. Among all patients in the subgroup (as well as those with pre-therapy heart rate ≥70 bpm), all cause mortality fell 10% (and 13%), fatal or non-fatal myocardial infarction incidence fell 42% (and 73%); hospitalization for heart failure and coronary

revascularization fell 30% and 59% respectively (Fox et al., 2009). Though the BEAUTIFUL angina substudy was a "post-hoc" assessment that cannot be considered definitive, nonetheless, it strongly suggests that, for patients with angina, for whom ivabradine is already approved for marketing throughout Europe and other parts of the world, heart rate slowing with this drug has additional benefits, beyond angina prevention, in reducing major coronary events. In this regard, ivabradine is almost unique among all currently available anti-anginal anti-ischemic pharmacological agents. Though not specifically related to angina, the SHIFT (the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial) study in patients with moderately severe to severe systolic heart failure demonstrated the usefulness of ivabradine in reducing mortality or hospitalization for HF (Bohm et al., 2010; Swedberg et al., 2010), irrespective of the etiology of HF. Since the study population of more than 6500 patients predominantly involved patients with ischemic etiology, SHIFT, together with BEAUTIFUL and the various antianginal trials, demonstrated the benefit of pure heart rate reduction by ivabradine in patients with CAD in all its manifestations.

2.5.3 Adverse effects

Ivabradine is safe in combination with β-blockers and causes only a relatively small excess risk of symptomatic or dose-limiting bradycardia. The drug is well tolerated; the primary side effect is relatively infrequent transient and reversible "phosphenes" (flashing scotomata), that are sufficient to cause cessation of therapy in less than 1% of patients (Fox et al., 2008). This symptom is attributed to blockade of the retinal h channels, similar to the SA nodal f channels, by ivabradine.

2.6 Nicorandil

Nicorandil is a coronary and peripheral vasodilator which reduces LV preload and afterload. It also affects potassium channels involved in ischemic preconditioning and, thus, is suggested to have cardioprotective effects. The drug has been used in Europe for angina relief in patients with angina already receiving "conventional' antianginal drugs.

2.6.1 Pharmacological effects

Nicorandil is structurally a nicotinamide ester derivative. It enhances potassium ion conductance by opening adenosine triphosphate (ATP)-sensitive potassium channels, in turn activating the enzyme guanylate cyclase. Nicorandil also has a nitrate moiety and promotes expression of endothelial NO synthase, thus sharing nitrate smooth muscle relaxing properties. Consequently, the drug enhances dilatation of arterial, venous and epicardial coronary arteries, resulting in reduced preload, afterload and myocardial oxygen demand while possibly increasing myocardial oxygen supply (Jahangir et al., 2001). Nicorandil may be associated with improved myocardial function during ischemia-reperfusion, cardioprotective action during ischemia, shortened action potential duration, and prevention of intracellular calcium toxicity (Jahangir & Terzic, 2005; Jahangir et al., 2001; John et al., 2003; Zingman et al., 2007).

2.6.2 Clinical application

Nicorandil has antianginal efficacy similar to that of β-blockers, nitrates and calcium channels blockers. In the Impact Of Nicorandil in Angina (IONA) randomized trial, nicorandil 20mg twice daily showed a 17% relative risk reduction (Hazard ratio of 0.83,

P=0.014) in hospitalization for chest pain, MI, and cardiac death when added to standard antianginal therapy (Ford, 2002). However, the result was driven by effects of nicorandil on "hospital admission for cardiac chest pain", and the risk reduction for cardiac death or non-fatal MI during 1.6 years of treatment was non significant. Thus the value of the treatment has been disputed (Fox et al., 2006). Several small randomized trials have shown that Nicorandil prolongs the time to onset of ST-segment depression and exercise tolerance during treadmill exercise testing in patients with stable angina (Di Somma et al., 1993; Meeter et al., 1992; Raftery et al., 1993). Markham et al also have shown that nicorandil prolongs time to the onset of angina, time to 1 mm ST depression, improves exercise duration and reverses ischemia-related impairment in regional wall motion during exercise (Markham et al., 2000). In a multicenter, randomized trial (197 patients) comparing it to isosorbide mononitrate, nicorandil was found to be both safe and effective in preventing angina (Doring, 1992). A dose of 10–40 mg twice daily controls symptoms in 70%–80% of patients with chronic stable angina; the effect of a single administration is maintained for about 12 hours (Meeter et al., 1992).

2.6.3 Adverse effects

In the IONA trial, the drop out-rates were about 10%, mainly due to headache in the nicorandil group. Nicorandil is not yet approved for use in the United States, but is widely available for angina therapy in Europe and other countries.

2.7 Fasudil

Fasudil is a Rho-kinase inhibitor and a vasodilator. Rho–kinase has been identified as one of the effectors of the small GTP-binding protein, Rho. The Rho/Rho-kinase pathway plays an important role in various cellular functions including vascular smooth muscle cell contraction, actin cytoskeleton integrity and gene expression. As a Rho-kinase inhibitor, fasudil has been utilized in cerebral vasospasm, pulmonary hypertension and, recently, in angina.

2.7.1 Pharmacological effects

The Rho molecules are small GTP-binding proteins that mediate intracellular signaling by activation of G-protein-coupled receptors and growth factor receptors. The Rho/Rho-kinase signaling pathway is known to be involved in the pathogenesis of coronary artery spasm (Shimokawa & Takeshita, 2005). Rho molecules are known to modulate Ca^{2+}-sensitization of vascular smooth muscle cells and may act by inhibiting myosin phosphatase activity (Fukata et al., 2001). As a Rho-kinase inhibitor, fasudil is a vasodilator.

2.7.2 Clinical application

Fasudil can increase coronary artery diameter to an extent greater than that achievable with nitroglycerin in patients with documented vasospasm (Otsuka et al., 2008). Vasospastic angina precipitated by acetylcholine can be prevented by intracoronary infusion of fasudil (Mohri et al., 2003). When used as monotherapy, fasudil doses ranging from 5 mg three times daily to 40 mg three times daily have increased maximum exercise time and time to the onset of ST segment depression compared with baseline. Fasudil is well tolerated, with minimal effects on blood pressure and heart rate at rest or during exercise (Shimokawa et al., 2002). In a double blind, placebo controlled randomized clinical trial of 84 patients with

chronic stable angina, both placebo and fasudil increased exercise time on treadmill testing compared to baseline, but the difference between active drug and placebo was not statistically significant, though time to onset of ischemic ST segment depression during exercise was significantly prolonged compared to placebo (Vicari et al., 2005). Fasudil is not yet approved for use in United States. An intravenous formulation is approved in Japan to prevent cerebral vasospasm after subarachnoid hemorrhage.

2.7.3 Adverse effects

Vicari et al reported adverse effects in 41 patients and compared them to those reported with placebo. Overall incidence of adverse effects were similar in the 2 groups. The common organ systems reported to be involved were skin, subcutaneous tissue and the vascular system. Common disorders reported (incidence <20%) were allergic dermatitis, bruising, diaphoresis, facial erythema, facial flushing, hypotension or hypertension and a Raynaud-like phenomenon. The majority of adverse events were classified as mild to moderate. No deaths were reported (Vicari et al., 2005).

2.8 Trimetazidine

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) is a prototype of a group of antianginal agents thought to act by affecting myocardial metabolism directly.

2.8.1 Pharmacological effects

As for most if not all antianginal drugs, the mechanism of action of trimetazidine is not fully clear. The proposed mechanism is direct enhancement of myocardial energy metabolism, resulting in cytoprotective effects (Harpey, 1989; Kay et al., 1995). Fantini et al showed that in isolated rat heart mitochondria, trimetazidine has an inhibitory effect on palmitoyl-carnitine oxidation, with no significant effect on pyruvate oxidation (Fantini et al., 1994). This suggests that trimetazidine inhibits fatty acid oxidation in the heart. It has been shown that high fatty acid oxidation rates are detrimental in the setting of ischemia because of inhibition of the more energy efficient glucose oxidation, resulting in exacerbation of ischemic injury and a decrease in cardiac efficiency during reperfusion. Kantor et al demonstrated that trimetazidine suppresses fatty acid oxidation secondary to inhibition of long-chain 3-ketoacyl CoA thiolase, resulting in an increase in glucose oxidation. As a result, switching energy substrate preference from fatty acid oxidation to glucose oxidation may explain the antianginal properties of trimetazidine (Kantor et al., 2000). Unlike several other antianginals, trimetazidine has no effect on vascular smooth muscle and thus has been termed a "cellular anti-ischemic agent".

2.8.2 Clinical application

The European Collaborative Working Group has demonstrated that trimetazidine is equivalent to propranolol in its antianginal efficiency, but is devoid of measurable hemodynamic effects (Detry et al., 1994). Similar results were reported in comparison with nifedipine (Dalla-Volta et al., 1990). Additive antianginal effects were observed when trimetazidine was combined with diltiazem (Levy, 1995; Manchanda & Krishnaswami, 1997), while the benefits of combination with metoprolol were demonstrated in the TRIMPOL II (Szwed et al., 2001) trial.

2.8.3 Adverse effects

Trimetazidine is relatively safe and is very well tolerated; there are few known drug interactions. Because of its safety profile, compliance has been quite good. In one uncontrolled trial, 2.4% of patients had adverse events during an 8-week treatment period. Nausea was the most frequent adverse event (0.4%) (Makolkin, 2003).

3. Non-pharmacological therapy

Despite maximized pharmacological therapy and life style modification, many patients with CAD continue to suffer from angina, including so-called "refractory angina", which is defined as Canadian Cardiovascular Society (CCS) class III or IV angina with marked limitation during ordinary physical activity or inability to perform ordinary physical activity without discomfort (Gowda et al., 2005). Patients with refractory angina typically experience poor general health status, psychological distress, impaired role functioning, activity restriction, and inability to manage their living situation (Brorsson et al., 2002; Erixson, 1997; McGillion et al., 2007). Refractory angina is debilitating and its treatment is challenging. In the past several decades, a number of nonpharmacological treatments have been developed to help resolve this problem. These therapies will be outlined in this section.

3.1 Mechanical therapy
3.1.2 Revascularization

Coronary angiography and possible revascularization should be considered in patients with refractory angina. Revascularization includes percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery.

3.1.2.1 Percutaneous coronary intervention

PCI, initially involving balloon angioplasty and later generally comprising balloon angioplasty plus stent placement to support and maintain the new channel, was developed for the relief of angina in patients refractory to medication. This remains one of the few data-supported applications of the technique.

3.1.2.1.1 Evidence

A comparison of balloon angioplasty with pharmacological therapy in treating patients with single vessel CAD (ACME) showed that angioplasty resulted in a greater proportion of patients free of angina at 6 months and greater improvement in treadmill exercise duration than did pharmacological therapy (Parisi et al., 1992). This study predated the routine use of stents and manifested a high rate (20%) of PCI failure but nonetheless supported the superiority of mechanical angioplasty to drug therapy alone for angina prevention. The multicenter Randomized Intervention Treatment of Angina (RITA) 2 trial was one of the largest trials prospectively assessing the impact of balloon angioplasty vs medical therapy on angina. Angina was of relatively mild severity (CCS 0-2) in 80 % of patients (Chamberlain, 1997). Angina frequency, exercise time and quality of life all improved in both groups. However, the subgroup of patients with CCS≥2 derived significantly greater symptom-relieving benefit from PCI than from pharmacological therapy during a 1 year follow-up interval. By 3 years, this advantage was lost, though interpretation of this finding is confounded by a relatively high (23%) crossover rate of medically treated patients to PCI. The Atorvastatin versus Revascularization Treatment (AVERT) trial assessed patients with angina CCS class 0-2. In this study, half the PCI

group received stents as well as balloon angioplasty (Pitt et al., 1999). Patients in the PCI group evidenced greater improvement than those receiving pharmacological therapy. Bucher et al conducted a systematic review of 6 trials from 1979 through1998, including a total of 1904 patients with stable single vessel CAD and normal LV function (4). Balloon angioplasty was associated with a significant improvement in angina compared with pharmacological therapy alone. There was no difference of mortality or myocardial infarction between PCI and drug therapy (Bucher et al., 2000). Recently, 2 trials, MASS (Medicine, Angioplasty or Surgery Study) II (Hueb et al., 2004) and COURAGE (Clinical Outcomes utilizing Revascularization and Aggressive Drug Therapy) (Boden et al., 2007) compared PCI versus pharmacological therapy in stable CAD. MASS-II included 611 patients; after 1 year of follow up, 79% of patients in PCI group, 88% of patients in surgery group and 46% in medical therapy group were free of angina, though no difference was found in mortality rates among the groups. COURAGE compared initial PCI with "optimal medical management". At baseline, 43% of patients either did not have symptoms or had Class 1 angina. After 5 years follow up, 74% of patients in the PCI group and 72% patients in the medical therapy group were free of angina. By this time, one-third of patients had crossed over from medical therapy to PCI group. No evidence of benefit was found in terms of mortality or major morbidity when the groups were analyzed according to intention to treat.

3.1.2.1.2 Conclusion

The decision to perform PCI for symptom relief in patients with angina remains complex and needs to be individualized based on analysis of goals and risks. The relevant trials performed to date have important limitations for extrapolation to current decisions including the possible impact of recent improvements in PCI techniques, changes in pharmacology and alterations in the populations at risk, in part because of drug therapy that can modify atherosclerosis. Most trials show that PCI results in greater symptom relief and better exercise tolerance than drug therapy but suggest that this advantage is of relatively limited duration, requiring adjunctive or additional therapy to maintain anti-anginal benefits. However, for patients with angina refractory to pharmacological therapy, current evidence clearly supports PCI as an appropriate therapy for symptom improvement. Nonetheless, because of the rapidly changing landscape of therapy noted above, the appropriate approach to achieve optimal symptom prevention is a moving target, and more studies would be useful.

3.1.2.2 Coronary artery bypass grafting (CABG) surgery

CABG is an important therapeutic modality for millions of patients with CAD. Surgery has evolved over the more than 4 decades since its introduction, both in terms of duration of benefit (open arteries) and in reduction of peri-operative complications.

3.1.2.2.1 Evidence

Early trials included the European Coronary Surgery Study (ECSS) (Varnauskas, 1988), Veterans Cooperative Study (Detre, 1984) and Coronary Artery Surgery Study (CASS) (Killip, 1983). These studies were designed to assess the benefits of CABG for survival and prevention of major morbidity, but provided information about angina prevention, as well. In each of these studies, CABG was compared with medical therapy in patients with stable CAD and angina. Yusuf et al conducted a meta-analysis of earlier surgery trials which

included a total of 2649 patients in which outcomes were evaluated at 5 and 10 years (Yusuf et al., 1994). CABG improved survival compared with pharmacological therapy. Importantly, though, CABG also produced greater freedom from symptoms and less use of antianginal medications than pharmacological therapy during a 5 year follow-up. Not surprisingly, benefits were greatest among those with the most severe disease at randomization, those with left main or multivessel disease and those with one or two vessel disease involving the proximal left anterior descending artery. Survival benefits were greater among patients with at least moderately subnormal LV ejection fraction than among those with normal LV performance. Bypass Angioplasty Revascularization Investment (BARI) trial was the largest (1829 patients) randomized study comparing balloon angioplasty versus CABG in symptomatic multivessel CAD (Alderman, 1996). After 10 years of follow up, angina rates in the two groups were similar. There were higher subsequent revascularization rates in balloon angioplasty group than in those who were randomized to CABG. Also, as noted above, MASS-II showed that 88% of patients in surgery group, 79% of patients in PCI group and 46% in medical therapy group were free of angina at pre-specified follow-up (Hueb et al., 2004). Bravata et al did a meta-analysis of 23 trials which included a total of 9963 patients, indicating that angina was relieved at 5 years in 79% of PCI patients and 84% of CABG patients (Bravata et al., 2007). Data also indicate that approximately 80-90% patients who are symptomatic on medical therapy become symptom free following CABG. This benefit has been shown to extend even to low-risk patients in whom mortality benefit with surgery has not been shown (Yusuf et al., 1994).

3.1.2.2.2 Conclusion

Both CABG and PCI are effective in relieving angina but CABG achieves this benefit with less need for repeat procedures than does PCI. In addition, though not specifically relevant to angina relief, several subsets of patients with chronic stable CAD can anticipate survival benefit from CABG; no parallel data are available for PCI. However, many of the relevant data were obtained with techniques and devices that have been superseded in this rapidly developing area. Thus, more data with the most up-to date techniques would be useful, on a background of the most modern pharmacological therapy to beneficially alter CAD progression. Nonetheless, as suggested by data from matched cohorts from the New York State coronary surgery database (Hannan et al., 2005), even as PCI techniques develop, CABG remains superior in terms of survival but the effects of newer approaches on angina remain to be defined.

3.1.3 Enhanced External Counterpulsation

Enhanced External Counterpulsation (EECP) is a non-invasive treatment that has been studied and employed with variable success for more than 30 years (Amin et al., 2010). EECP is carried out by placing compressible cuffs around the calves and lower and upper thighs, inflating them sequentially during diastole and deflating them simultaneously at the onset of systole. Throughout this process, the patient is connected to an electrocardiogram (ECG) and a finger plethysmograph. The R wave of the ECG is used to gate inflation and deflation. Treatment typically involves 35 sessions, each lasting 1 hour, undertaken over a 7-week interval (Sinvhal et al., 2003). EECP is believed to improve coronary perfusion pressure through diastolic augmentation while decreasing cardiac workload by reducing aortic impedance during systole.

3.1.3.1 Evidence

EECP is generally considered acceptably safe and is without specific contraindications. The few adverse effects associated with EECP generally are related to the physical characteristics of the equipment and its application, e.g., leg and back pain, abrasion of skin, bruising, blistering, edema and paresthesia (Arora et al., 1999). The effectiveness of EECP for refractory angina has been investigated in several studies over the last two decades. In the only published randomized clinical trial (Arora et al., 1999), the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), which involved 139 patients with angina and documented CAD, patients were randomised to either 35 h of active counterpulsation (300 mm Hg maximal cuff pressure) or inactive counterpulsation (75 mm Hg maximal cuff pressure) over a 4–7 week-period. Exercise duration increased in both groups to a similar degree (p > 0.3) and nitroglycerin use did not differ between groups (P>0.7). However, time to ≥1-mm ST segment depression (exercise-induced ischemia) increased significantly from baseline in active counterpulsation compared with inactive counterpulsation (p = 0.01). More active counterpulsation patients saw a decrease and fewer experienced an increase in angina episodes as compared with inactive counterpulsation patients (p < 0.05). The investigators concluded that EECP reduced angina and extended time to exercise-induced *ischemia* in patients with symptomatic *CAD*. Treatment was relatively well tolerated and was free of limiting side effects in most patients. The limitations of this trial include fairly stringent patient selection criteria precluding simple extrapolation of the data, the preponderance of patients with only Class I or II symptoms, and the lack of data about natural history outcomes. Also, there were more withdrawals due to adverse effects in active EECP group than in the control group.

To further assess EECP effects on both exercise tolerance and cardiac function, Urano et al (Urano et al., 2001) examined 12 stable patients with CAD and evidence of exercise-induced myocardial ischemia despite conventional medical or surgical therapies. These investigators found that, compared with baseline values, EECP improved all exercise test parameters, reduced exercise-induced reversible perfusion defects by thallium scintigraphy, and improved diastolic filling and LV end-diastolic pressure. These hemodynamic improvements were associated with decreased plasma brain natriuretic peptide levels. The investigators concluded that EECP definitely was effective in patients with CAD.

To clarify the mechanism underlying EECP benefits, Shechter et al (Shechter et al., 2003) investigated the influence of short-term EECP on vascular endothelial function in patients with CAD. They used high-resolution ultrasound to assesse endothelium-dependent brachial artery flow-mediated dilation (FMD) and endothelium-independent nitroglycerin-mediated vasodilation before and after EECP therapy. EECP resulted in significant improvement in post-intervention FMD but no significant effect on nitroglycerin-induced vasodilation. EECP significantly reduced angina as assessed by mean daily sublingual nitrate consumption and mean CCS angina class. The investigators concluded that EECP improved vascular endothelial function and angina in patients with CAD and refractory angina pectoris, suggesting a causal relation.

Few studies have evaluated the long-term effects of EECP. Loh et al (Loh et al., 2008) used the International EECP Patient Registry (IEPR-1) that enrolled consecutive patients treated with EECP in more than 100 centers; follow-up duration was 3 years. These investigators found that immediately post-EECP, the proportion of patients with severe angina (CCS III/IV) was reduced from 89% to 25% (p<0.001). The benefit was sustained in 74% during

follow-up. This is the longest follow-up from IEPR-1 to date and tends to confirm the safety and immediate benefits of EECP as well as suggesting that sustained symptomatic and quality of life benefit can be achieved in most patients for up to 3 years. However, this observational study lacked a control group, weakening the conclusions. Further, the results are impaired by patient selection and survival bias. Other non- randomized studies (Barsheshet et al., 2008; Holubkov et al., 2002; Shechter et al., 2003; Urano et al., 2001) have been difficult to interpret. All assessments need to be treated with considerable caution due to selection bias and absence of blinding (McKenna et al., 2009).

3.1.3.2 Conclusion

With its development, it was hoped that EECP would be a viable adjunct for patients with CAD patients and angina inadequately responsive to medication and revascularization. To date, results from well-designed clinical trials are relatively few. However, these data provide a suggestion of no more than limited clinical effectiveness. Issues of adverse effects and cost-effectiveness have limited application of EECP therapy. Finally, evaluation in a truly refractory population with predominantly Class III/IV patients has not been undertaken. The ACC/AHA 2002 guideline update for the management of patients with chronic stable angina assigns EECP therapy a level of evidence of Class IIB (the usefulness/ efficacy is less well established by evidence/opinion). This suggests there may be some benefit, but additional clinical trial data are needed before EECP can be recommended definitively (Gibbons et al., 2003). EECP was not mentioned in the 2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients with Chronic Stable Angina (Fraker et al., 2007). Thus, additional data from randomized controlled trials are needed with regards to exercise tolerance, angina frequency and nitroglycerin use, ischemia reduction and, if possible, long term benefit on quality of life, as well as mortality or major morbid cardiovascular events.

3.1.4 Carotid Sinus Nerve Stimulation

Fifty years ago, carotid sinus nerve stimulation (CSNS) to slow heart rate and, to a lesser extent, to lower blood pressure was conceived (Lown & Levine, 1961) as an alternative treatment for refractory angina. Stimulation of the carotid sinus nerves reflexly reduces the frequency of sympathetic efferent impulses which, in turn, results in reduction in arterial pressure, myocardial contractility, and heart rate; as a consequence, myocardial oxygen demand is diminished and angina is relieved. Small, non-randomized studies demonstrated that CSNS relieved angina and allowed patients to perform more exercise without developing angina (Braunwald et al., 1967; Epstein et al., 1969; Rotem, 1974). However, due to the need for invasive implantation of the stimulator using the somewhat crude methods of the time, CSNS never was broadly applied. Nonetheless, it proved the principle that angina relief could be achieved directly by altering certain hemodynamic variables.

3.1.5 Spinal Cord Stimulation

Spinal cord stimulation (SCS), also called dorsal column stimulation or neurostimulation, is a neuromodulation therapy to alleviate pain by electrically activating pain-inhibiting neuronal circuits in the dorsal horn and inducing paresthesia that masks the original pain sensations. Local anesthesia is used during SCS implantation, via an incision at the level of thoracic vertebrae 6-8, an electrode is inserted into the epidural space and guided via X-ray monitoring up to the level of the thoracic 1-2 vertebrae. Its location is adjusted until the

patient experiences paresthesiae within the area of the anginal pain. An extension wire is then tunneled subcutaneously via an incision to the left flank, where it is connected to a subcutaneous pulse-generator below the left costal arch. The stimulation intensity is then fine-tuned post-operatively. The patient can regulate the strength of the actual stimulation using a remote control (Borjesson et al., 2008). SCS has been successfully reported to relieve pain in a number of chronic conditions including neuropathic pain and peripheral vascular disease (Kemler et al., 2000; Kumar et al., 2007; Lee & Pilitsis, 2006). Since the late 1980s, SCS has been used to treat patients with chronic refractory angina who are not responsive to conventional medical therapy and revascularization (Murphy & Giles, 1987). Although the underlying mechanism is not fully elucidated, it has been proposed that SCS exerts beneficial effects by decreasing pain and sympathetic tone, yielding reductions in myocardial oxygen consumption and improved myocardial microcirculatory blood flow (Latif et al., 2001).

3.1.5.1 Evidence

Published evidence supports SCS as effective and acceptably safe for patients with refractory angina who are unresponsive to medical and surgical intervention (Bondesson et al., 2008; de Vries et al., 2007; Diedrichs et al., 2005; Dyer et al., 2008; Eddicks et al., 2007; Lapenna et al., 2006; McNab et al., 2006). Recently, a meta-analysis of 7 randomized controlled trials involving 270 patients (Taylor et al., 2009) found benefits similar to those of CABG and percutaneous myocardial laser revascularization (PMR). Compared to the control, there was some evidence of improvement in all outcomes following SCS implantation with significant gains observed in pooled exercise capacity and health related quality of life. However, the trials were small and varied considerably in quality. The healthcare costs of SCS appeared to be lower than CABG at 2-years follow up. One particular challenge of SCS evaluation is the difficulty in patient blinding, as the therapy produces paresthesia in the area of the pain if SCS is effective. In addition, the implantation procedure might produce a placebo effect, but sham operations are ethically difficult to justify (Van Zundert, 2007). Further high quality trials and cost effectiveness evidence is needed before SCS can be accepted as a routine treatment for refractory angina.

3.1.5.2 Conclusion

SCS has been used for treatment of refractory angina in Europe for 20 years. In the European Society of Cardiology guidelines on management of angina (Fox et al., 2006), SCS is accepted as a "well established method" for the management of refractory angina. Patients experience a favorable analgesic effect and positive effects on symptoms from SCS, though long-term effects are unknown. The ACC/AHA guidelines for the management of patients with chronic stable angina (Fraker et al., 2007; Gibbons et al., 2003) provided a class II b recommendation, suggesting that SCS should only be used in patients who cannot be managed adequately by medical therapy and who are not candidates for revascularization.

3.1.6 Transmyocardial revascularization

Transmyocardial revascularization (TMR) applies high-energy laser beams to create non-transmural endomyocardial channels. These channels can be generated surgically, using an epicardial approach, or percutaneously (PMR), via catheter, an endocardial approach. The basis for angina prevention with TMR is unclear. The initial hypothesis was that the channels provided oxygenated blood from the LV to directly perfuse the myocardium; support for this mechanism is not compelling; more recently, it has been proposed that

clinical improvement may be secondary to angiogenesis, placebo effect, or myocardial denervation (Huikeshoven et al., 2002). TMR also has been combined with administration of angiogenic growth factors and/or angiogenic gene vectors introduced via the channels to stimulate angiogenesis (see Biological Therapy, below).

3.1.6.1 Evidence

Since its initial application in association with CABG in 1983, surgical TMR has been considered an alternative for patients with refractory angina who were not amenable to conventional revascularization (Smith et al., 1995). However, though several preliminary studies demonstrated a decrease in angina severity in most patients (Cooley et al., 1996; Horvath et al., 1996), subsequent randomized controlled trials (RCT) have reported contradictory results (Aaberge et al., 2000; Burkhoff et al., 1999; Campbell et al., 2001; Jones et al., 1999; March, 1999; van der Sloot et al., 2004). Briones et al (Briones et al., 2009) conducted a Cochrane systematic review to assess the efficacy and safety of TMR versus optimized drug therapy in alleviating angina and improving survival and heart function. The 7 RCTs included in the review involved 1137 patients of whom 559 were randomized to TMR. Overall, 43.8% of patients in the treatment group decreased two angina classes, compared to 14.8% in the control group (95% confidence interval 3.43 to 6.25). Mortality analyzed on an intention-to-treat basis was similar in both groups at 30 days (4.0% in the TMR group vs. 3.5% in the control group) and at one year (12.2% in the TMR group vs. 11.9% in the control group). However, the per protocol 30-day mortality was 6.8% in the TMR group compared to 0.8% in the control group (OR 3.76 [95% CI, 1.63 to 8.66]). The authors concluded that evidence is insufficient to support the presumption that clinical benefits of TMR outweigh the potential risks. Importantly, the observed improvement in angina was not measured using blinded methods and is therefore subject to significant potential bias, and there was no difference in survival.

PMR is less invasive than TMR, utilizing a fiberoptic catheter inserted through a femoral artery under conscious sedation to carry the laser energy to the endocardial surface. Laser firing is synchronized during systole to create a series of nontransmural channels in targeted regions (Oesterle et al., 1998). Recently McGillion et al (McGillion et al., 2010) conducted a meta-analysis to assess the effectiveness of PMR versus optimized drug therapy for reducing angina and improving health-related quality of life (HRQL), and exercise performance. Seven RCT trials, involving 1,213 participants, were included. At 12-month follow-up, the PMR group had more than 2 CCS class symptom reductions as well as improvements in HRQL, disease perception and physical limitations. However, PMR had no significant impact on all-cause mortality. In the secondary analyses, in which the data were from a single trial that employed a higher-dose laser group, the result showed no significant overall impact of PMR across outcomes.

3.1.6.2 Conclusion

When applied in carefully selected patients with refractory angina, TMR can provide durable reduction in self-reported angina and improvement in quality of life compared to drug treatment alone. However, evidence of improvement in exercise tolerance, the "objectification" of angina, is less strong, and impact on survival has not been demonstrated. For PMR, evidence is insufficient to demonstrate efficacy for angina prevention (and, therefore, of benefit to risk relation). Long-term outcomes of PMR are not clear. PMR devices have not been approved by the FDA due to lack of adequate evidence of

efficacy in their use. ACC/AHA guidelines (Eagle et al., 2004; Gibbons et al., 2003) recommend TMR as a Class IIa procedure, stating that TMR alone or in combination with CABG is reasonable in patients with angina refractory to medical therapy who are not candidates for PCI or CABG but does not recommend PMR, noting that it should still be considered experimental.

3.2 Biological therapy
3.2.1 Angiogenic gene therapy
Angiogenesis is the biological process involving formation of new blood vessels from pre-existing vessels under physiological or pathological conditions. In patients with chronic CAD, angiogenesis in response to repeated myocardial ischemia can provide collateral blood flow to muscle distal to sites of coronary stenoses. Theoretically, stimulation of angiogenesis presents an attractive approach for the treatment of CAD. Attempts at therapeutic angiogenesis have employed molecules (growth factors) shown experimentally to improve jeopardized blood supply, thereby relieving myocardial ischemia, improving regional and global LV performance, lessening angina, and improving clinical outcomes (Simons & Ware, 2003). A number of growth factors have been demonstrated to stimulate blood vessel growth in humans and are the focus of recent angiogenic gene therapy studies. These include several fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs) and granulocyte/macrophage colony stimulating factor (GM-CSF) (Zachary & Morgan, 2011).

3.2.1.1 Evidence

How to effectively and safely deliver growth factors to the target tissue remains a major problem in therapeutic angiogenesis trials. The accepted consensus is that effective angiogenic intervention will require the presence of the therapeutic agent at the desired site of action for as long as four to six weeks. In early experience, delivery of growth factors was achieved either by systemic infusion or intracoronary infusion, but results were disappointing, perhaps because of short residence time of the infused proteins in target tissues. Repeated administration or the use of sustained release polymers may prove more effective, but remains to be tested. Introduction of angiogenic genes into the myocardium offers a theoretical alternative approach to delivery that might obviate the need for repeated administrations of short-lived proteins, and avoid the potential risks of short-term systemic exposure to relatively high concentrations of proteins (Simons et al., 2000). Introduction of angiogenic genes with both plasmid and adenoviral vectors has been associated with improvements in heart function and perfusion in different animal models of myocardial ischaemia (Hammond & McKirnan, 2001). Several clinical gene therapy trials of angiogenic growth factors have been conducted using either plasmid or adenoviral vectors. Effects of intramyocardially delivered plasmid VEGF were assessed in two randomised, double-blinded, placebo-controlled trials, EUROINJECT-ONE (Kastrup et al., 2005) and NORTHERN (Stewart et al., 2009) involving, respectively, 80 and 93 patients with severe stable ischemic heart disease (CCS III/IV). Neither trial demonstrated alteration in the primary end point, change in myocardial perfusion, by therapy, despite the use of a high plasmid dose (2 mg) in the NORTHERN study. There was a trend toward improvement in exercise treadmill time and angina reduction, but again no significant differences were observed. Another RCT, REVASC (Stewart et al., 2006) employed an adenoviral vector (AdVEGF121) delivered into the myocardium at surgery in 67 patients with refractory

angina. In this study, a statistically significant increase in the primary end point, time to 1 mm ST-segment depression on treadmill exercise, was observed at 26 weeks in the active treatment group. Another RCT, KAT (Hedman et al., 2003), compared AdVEGF165 with either plasmid VEGF or placebo for effect on myocardial perfusion in 103 patients. In this trial, the vectors were administered by intracoronary injection at angioplasty. There was no significant difference in the rates of restenosis between treatment groups at 6 months, but myocardial perfusion improved in the AdVEGF165 group compared with plasmid VEGF. In an 8-year follow-up study of the KAT trial, the incidence of major adverse cardiovascular events, cancer or diabetes did not differ between the treatment groups (Hedman et al., 2009). A series of AGENT trials investigated the safety and efficacy of intracoronary injections of an adenoviral-encoded FGF-4 gene. The AGENT-1 trial (Grines et al., 2002) enrolled 79 patients and found a trend toward improved exercise time at four weeks in treatment group compared to the placebo group; when only patients with baseline exercise time ≤10 minutes were considered, exercise time increased significantly. The subsequent AGENT-2 trial of 52 patients with AdFGF-4 found a nonsignificant reduction in the size of the ischemic defect on perfusion imaging between treatment and placebo (Kapur & Rade, 2008). However, two large double-blind phase III trials of Ad-FGF4 (AGENT-3 and AGENT-4) were negative for their primary end point although a post-hoc analysis suggested a benefit in a certain population of middle aged women (Henry et al., 2007).

3.2.1.2 Conclusion

Though therapeutic angiogenesis theoretically is an attractive option for improving the quality of life in chronic ischemic heart disease, no large clinical trial yet has shown substantial clinical benefit. However, efforts are ongoing to improve delivery and expression and biological efficacy of the angiogenic genes (Zachary & Morgan, 2011).

3.2.2 Stem cell therapy

Hematopoietic stem cells are bone marrow-derived cells capable of differentiating into a variety of cell types. Such cells may be obtained directly from the bone marrow or, using apheresis techniques, from peripheral blood, usually after stimulation with granulocyte-colony stimulating factor (G-CSF). Cardiac stem cell therapy has been evaluated clinically during the past 10 years. Many clinical trials have been conducted on treatment for heart failure (Menasche et al., 2008; Stamm et al., 2007) and acute MI (Martin-Rendon et al., 2008) but the study of stem cell therapy for refractory angina is in early stages of development. The mechanisms of potential benefit remain uncertain. The initial hypothesis of transdifferentiation into cardiomyocytes no longer is generally accepted (Murry et al., 2004). The currently favored hypothesis is that increased angiogenesis is stimulated by angiogenic growth factors released by bone marrow cells, particularly by the CD34+ fraction (Menasche, 2011).

3.2.2.1 Evidence

Losordo et al (Losordo et al., 2007) showed the efficacy of intramyocardial transplantation of autologous G-CSF-mobilized peripheral blood CD34+ stem cells for prevention of angina. Twenty-four patients with CCS class III or IV angina who were undergoing optimized medical treatment and who were not candidates for mechanical revascularization were enrolled in a double-blind, randomized (3:1), placebo-controlled dose-escalating study. CD34+ progenitors were collected following GCSF-induced cell mobilization and apheresis.

Electromechanical mapping was performed to identify ischemic but viable regions of myocardium for injection of cells (versus saline). The intramyocardial injection of cells or saline did not result in cardiac enzyme elevation, perforation, or pericardial effusion. Neither ventricular tachycardia nor ventricular fibrillation occurred during the administration of G-CSF or intramyocardial injections. Efficacy parameters including angina frequency, nitroglycerin usage, exercise time, and CCS class showed trends that favored CD34+ cell–treated patients versus placebo-treated controls. A phase II b study in a larger population is currently under way.

A recent RCT of intracoronary infusion with autologous bone marrow CD34+ stem cells involved 112 patients with intractable angina (Wang et al., 2010). No myocardial infarction or other major adverse event was observed during the procedure. Investigators found significantly greater reduction in angina frequency by diary at 3 and 6 months after active treatment than after control. Other efficacy parameters, such as nitroglycerin use, exercise time and the CCS class, also were improved by active treatment versus control, as was myocardial perfusion imaging assessment of ischemia.

3.2.2.2 Conclusion

Stem cell therapy is an investigational technique that has reduced angina frequency and severity by several measures in small populations with refractory angina. However, additional studies are required to determine the magnitude, consistency and durability of anti-anginal benefit, as well as the long-term safety of this approach for treatment of patients with angina due to CAD.

4. Acknowledgment

5. References

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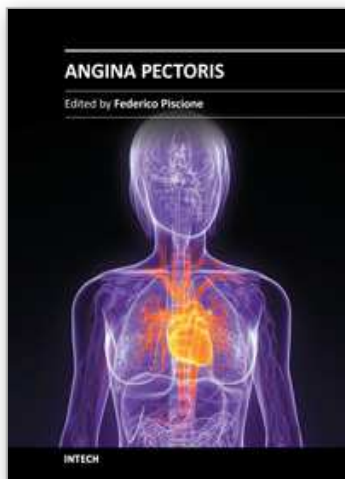
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