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Evaluation of Anti-Ischemic Therapy in Coronary Artery Disease: A Review

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1. Introduction

Myocardial ischemia, or lack of oxygen, is caused by an imbalance between oxygen supply and oxygen demand in the heart. This imbalance is usually due to an inability to increase coronary blood flow in response to increased myocardial oxygen consumption. The inability to increase coronary blood flow is often related to atherosclerosis of the large coronary arteries, which leads to a progressive narrowing of the blood vessel lumen and a reduction in coronary blood flow. Coronary blood flow may also be restricted by either focal or generalized intense vasoconstriction (i.e. vasospasm) in the major coronary arteries. Antianginal drugs may effectively relieve or prevent acute ischemic episodes by increasing myocardial oxygen supply, decreasing myocardial oxygen demand, or both.

2. Conventional antianginal

2.1 Nitrates (short and long acting) and nitrites

Sir Thomas Lauder Brunton first used amyl nitrite in the treatment of angina pectoris in 1867. As a medical student, Brunton had became aware of prior clinical findings of Benjamin Ward Richardson that inhaled amyl nitrite rapidly increased the action of the heart (Richardson, 1864), and also the unpublished observations of Arthur Gamgee demonstrating that amyl nitrite greatly lessened 'arterial tension' in both animals and man (Brunton, 1867**). At the same time** William Murrell, began using the organic nitrate; glyceryl trinitrate (GTN), in the treatment of angina pectoris (Murrell, 1879). With GTN therapy, patients would obtain relief from angina with some patients also reporting that their angina could be aborted by taking the drug at the onset of symptoms. In the 1920s, Richard Bodo used the Starling's heart–lung preparation to determine the effects of two nitrite preparations on coronary flow (Bodo, 1928) as earlier work in myocardial studies demonstrated that nitrite preparations produced vasorelaxation (Francois-Frank, 1903; Schloss, 1913; Cow, 1910). By the 1930s, nitrites and nitrate esters were established treatments for angina and hypertension. Contro and colleagues observed a paradoxical action following inhalation of amyl nitrite in patients with coronary artery disease, in that electrocardiograph changes resembling myocardial ischemia would occur after administration of amyl nitrite due to a sudden drop in blood pressure followed by coronary insufficiency (Contro et al., 1952). Finally, the authors suggested that the nitrite could be used as a diagnostic test in patients

with borderline or questionable history of coronary artery disease. The nitrites/nitrates are classified as agents that directly relax vascular smooth muscle, but can also relax other smooth muscles such as bronchial, ureteral, and uterine smooth muscle (Chen et al., 2001; Dong et al., 1998; Facchinetti et al., 1996; Yallampalli et al., 1993).

2.1.1 Mechanisms of action

It is generally believed that the therapeutic effect of these drugs involves the release of nitric oxide (NO) from nitrite, the activation of guanylyl cyclase, and relaxation of blood vessels. Interactions with nitroglycerin (GTN) and sulfhydryl-containing receptors are necessary for vascular smooth muscle relaxation and repeated administration of GTN produces sulfhydryl depletion and the development of tolerance. Subsequent studies have demonstrated the release of NO following the decomposition of an intermediate S-nitrosothiol. Additional studies suggest that an enzymatic mechanism may be responsible for the bio-activation of GTN.

2.1.2 Cardiovascular pharmacological effects

The most commonly nitrites and nitrates agents at this time include isosorbide dinitrate, isosorbide-5-mononitrate, and GTN which are effective in reducing ventricular preload by increasing peripheral venous capacitance. These drugs can also decrease pulmonary and systemic vascular resistances, but require higher doses than those needed for the increase in venous capacitance. These agents can reduce ventricular filling pressure, wall stress and myocardial oxygen consumption, and may also improve systolic and diastolic ventricular function by improving coronary flow in patients with ischemic cardiomyopathy. However, there is, as yet, no convincing evidence that organic nitrates improve mortality in patients with acute myocardial infarction. The limitations of this class of agents are well known and potentially include adverse hemodynamic effects, drug tolerance, lack of selectivity, and limited bioavailability. Nitrates are recommended by the ACC/AHA guidelines as part of the initial management of ST elevation myocardial infarction (STEMI) and unstable angina (UA)/non-ST elevation myocardial infarction (NSTEMI). Nitrates can provide symptomatic relief in acute coronary syndrome (ACS) but are not associated with a survival benefit in younger ACS patients. However, nitrate use in the elderly ACS patients is associated with a reduction in mortality, heart failure, and left ventricular dysfunction at 6 months follow-up. The antianginal properties of nitrates can be attributed to the augmentation of coronary flow and to the decrease in the heart's oxygen consumption that they cause. Nitrates induce coronary vasodilatation, leading to better myocardial perfusion. They also produce venodilatation, leading to decreased venous return, and thus to reduced cardiac preload. Glyceryl trinitrate also exerts antiplatelet effects in patients with stable angina pectoris. Short-acting GTN is used sublingually to relieve symptoms of angina. Long-acting nitrates can be used in combination with a beta blocker if monotherapy has proven unsuccessful or in combination with calcium channel antagonist if beta blockade leads to unacceptable adverse drug reactions. During exercise, nitrates increase the delay before the onset of angina and the time to 1 mm ST segment depression (TST), but their effects are improved when used in combination with another antianginal agent. Nitrates should be administered intermittently, with 8 to 12 hours of nitrate-free intervals, to prevent pharmacologic tolerance. However, a rebound phenomenon with anginal symptoms is possible during

these intervals. Short acting nitrates control angina most effectively when administered in the morning. In contrast, long acting nitrates are designed for once per day dosing and should normally be administered at bedtime to maintain a therapeutic concentration in the plasma throughout the night and the subsequent vulnerable morning hours**.** The most frequent side effect of nitrates is headache, reported by up to 82% of patients in placebo-controlled trials in a dose-related fashion, with about 10% of patients reporting severe symptoms leading to discontinuation of the treatment (Thadani & Rodgers, 2006). Hypotension is frequent and usually asymptomatic, although syncope can rarely occur. The tolerance phenomenon associated with the chronic use of long-acting nitrates imposes the need for an 8–12 hour nitrate-free interval every day, which can occasionally lead to angina attacks at night during this period. Nitrates are contraindicated in patients with severe aortic stenosis or hypertrophic obstructive cardiomyopathy. Furthermore, concomitant use of nitrates and sildenafil can provoke severe potentially life-threatening hypotension, making this combination an absolute contraindication. Indeed, patients should be warned never to use sildenafil within 24 hours of nitrate consumption.

2.2 β-adrenoceptor blockers

β-blockers differ in physicochemical, pharmacokinetic and pharmacodynamic properties. Current drugs vary in their selectivity for β_1-, β_2- and β_3-adrenoceptors, and some, such as carvedilol and labetalol, are also α_1-adrenoceptor antagonists. Some have partial agonist activity or intrinsic sympathetic activity (ISA), local anaesthetic properties (membrane-stabilising activity), potassium (K^+) channel blocking activity or antioxidant properties. The number of β-blockers available rapidly increased and became the major first-line therapy for hypertension. Improvements in the symptomatic management of angina were followed by improvements in mortality in acute myocardial infarction and long-term when given post-myocardial infarction. β-blockers also reduce arrhythmias after both cardiac and non-cardiac surgery. Thus, β-blockers now have important role in improving both mortality and symptom control in ischaemic heart disease, arrhythmias and hypertension (Table 1) (Hollenberg, 2005). In patients with stable angina who also manifest congestive heart failure symptoms with reduced left systolic function, β-blockers are particularly beneficial and reduce heart failure related mortality by approximately 35% (Klein et al., 2003).

2.2.1 Properties of β-blockers

1. Subtype selectivity. The prototypical β-blocker propranolol has similar affinity for β1- and β2- adrenoceptors and lower affinity for β3-adrenoceptors. However, even the 'cardioselective' β-blockers, a nomenclature based on their selectivity for β1-adrenoceptors, are not, because none in clinical use are that selective (13-fold at most) (Baker, 2005; Schnabel, 2000). Although bisoprolol and nebivolol are the most β_1-selective and carvedilol having slight β_2-selectivity, it is not possible to predict what level of selectivity. Most currently available β-blockers (including propranolol) have low affinity for the β_3-adrenoceptor. There are, however, a subset of drugs comprising oxprenolol, carazolol, pindolol, nadolol, tertatolol, carteolol, arotinolol and nebivolol that have agonist effects at the β_3-adrenoceptor that could be responsible for the nitric oxide (NO)-mediated vasodilator properties observed with nebivolol (Baker, 2010). Even SR59230A, claimed to be selective for β_3-adrenoceptors, has a similar potency at all 3 subtypes (Baker, 2010, Michel, 2010).

2. Intrinsic sympathomimetic activity (ISA) and partial agonism. Some β-blockers are traditionally described as having ISA (Table 2). These drugs block the stimulatory effects of high-efficacy agonists, such as catecholamines, but stimulate agonist responses of their own. This is evident at both the cellular and tissue level with acebutolol, carteolol, penbutolol, pindolol, bucindolol and xamoterol, for which it is claimed that bradycardia and bronchoconstriction are less than for other β-adrenoceptor antagonists. However, drugs with ISA are less advantageous in the management of heart failure and migraine.
3. Low-affinity state of the β_1-adrenoceptor. Some β-adrenoceptor antagonists stimulate β_1-adrenoceptor function by interacting with a low-affinity state of the β_1-adrenoceptor (Molenaar, 2003) and the β_3-adrenoceptor (Baker, 2003). Activation of this low-affinity state of the β_1-adrenoceptor has been demonstrated in whole animals (Cohen, 2000) and humans (Kaumann and Molenaar, 1997). β-adrenoceptor antagonists with similar properties include oxprenolol, alprenolol, carazolol, pindolol and carvedilol. These ligands either stimulate agonist responses at concentrations much higher than those required to fully occupy and block the conventional catecholamine β_1-adrenoceptor site, or have biphasic concentration–response curves. However, there is currently no therapeutic use for this property of β-adrenoceptor antagonists.
4. Inverse agonism. Many β-adrenoceptor antagonists, at least at the β_2-adrenoceptor, are in fact inverse agonists (i.e. rather than just occupying the binding site and thus blocking the actions of agonists, they are associated with conformations of the receptor that turn off signalling) (Swaminath, 2005).
5. Other properties of β-blockers. Local anaesthetic or membrane-stabilising activity is shown by some β-adrenoceptor antagonists, notably propranolol and acebutolol and to a lesser extent pindolol and labetalol. This property is unlikely to be important in the therapeutic effects of β-blockers because it occurs at much higher concentrations than those normally encountered clinically. Individual (rather than class effect) properties of certain β-blockers include lipophilicity, K^+ channel blockade and antioxidant properties. Propranolol, timolol and metoprolol are somewhat lipophilic. Sotalol can block K^+ channels independently of its β-blocking properties. Carvedilol blocks α_1- and β-adrenoceptors, inhibits apoptosis and possesses antioxidant and free-radical-scavenging actions. Nebivolol causes NO-dependent vasodilation. These properties might contribute to their efficacy in cardiac failure.

2.2.2 Hemodynamic effects of β-blockers

β-adrenoceptor antagonists competitively inhibit the binding of endogenous catecholamines to β_1-adrenoceptors in the heart and most evidence strongly suggests that their anti-ischemic effects are due to cardiac depression. Myocardial oxygen demand is determined in large part by heart rate and cardiac contractility. Increased heart rate and contractility result in increased myocardial oxygen consumption and, conversely, reductions in heart rate and contractility lead to a decrease in oxygen consumption. By inhibiting the actions of norepinephrine and epinephrine on the heart, the β-adrenoceptor antagonists exert their negative dromotropic and intropic effects, and thereby attenuate the myocardial response to sympathetic nervous system stimulation that occurs, for example, with increased stress or exercise. Though most β-adrenoceptor antagonists lower resting heart rate to some extent, the effect on exercise-induced tachycardia is much more pronounced. Thus, for a given

degree of physical activity, myocardial oxygen consumption is diminished. It is important to note that the β-adrenoceptor antagonists do not change the point of imbalance between myocardial oxygen supply and consumption at which angina occurs; rather, they reduce the likelihood that this point is reached. By mechanisms that remain poorly understood, β-adrenoceptor antagonists also decrease peripheral vascular resistance, which leads to a reduction in arterial blood pressure and afterload (Hoffman, 2007). Reduced afterload results in decreased left ventricular wall tension, which is another major determinant of myocardial oxygen demand. This beneficial effect of the β-adrenoceptor antagonists may be partially offset, however, by an increase in left ventricular end-diastolic volume that occurs due to increased cardiac filling during diastole, but the net effect is to lessen oxygen demand. On the other hand myocardial oxygen supply is a function of both oxygen delivery (the heart is almost exclusively dependent on aerobic metabolism and an adequate supply of oxygen is critical to sustained cardiac activity) and oxygen extraction from the blood. Since oxygen extraction from coronary blood is near maximal at rest, there is little reserve to meet increased demand due to increased cardiac activity (Tune et al., 2004). Thus, the most important determinant of myocardial oxygen supply is total coronary blood flow. β-adrenoceptor antagonists have little propensity to increase coronary blood flow and myocardial oxygen supply, in fact β-adrenoceptor antagonists may increase coronary vascular resistance by inhibiting the β_2-adrenoceptor-mediated vasodilator effects of endogenous catecholamines and leaving α-adrenoceptor-mediated vasoconstriction unopposed. Thus, the anti-ischemic effects of the β-adrenoceptor antagonists are largely due to their ability to reduce myocardial workload and decrease oxygen consumption, rather than to improve myocardial oxygen supply.

Propranolol	Hypertension, ischaemic heart disease, arrhythmias, portal hypertension, anxiety, essential tremor, migraine, thyrotoxicosis
Acebutolol	Hypertension, ischaemic heart disease, arrhythmias
Atenolol	Hypertension, ischaemic heart disease, arrhythmias, migraine
Betaxolol	Glaucoma
Bisoprolol	Hypertension, ischaemic heart disease, heart failure
Carteolol	Glaucoma
Carvedilol	Hypertension, ischaemic heart disease, heart failure
Celiprolol	Hypertension
Esmolol	Arrhythmias (short-term)
Labetolol	Hypertension
Levobunolol	Glaucoma
Metipranolol	Glaucoma
Metoprolol	Hypertension, ischaemic heart disease, arrhythmias, migraine
Nadolol	Hypertension, ischaemic heart disease, arrhythmias, migraine, thyrotoxicosis
Nebivolol	Hypertension, heart failure
Oxprenolol	Hypertension, ischaemic heart disease, arrhythmias, anxiety
Pindolol	Hypertension, ischaemic heart disease
Sotalol	Arrhythmias
Timolol	Glaucoma, hypertension, ischaemic heart disease, migraine

Table 1. Current indications for β-blockers from the British National Formulary September 2010 (www.bnf.org)

Generation	Drugs	Specifications
First	Propranolol, Timolol	Non-cardioselective
Second	Metoprolol	Cardioselective, short acting
	Atenolol, Bisoprolol, Betaxolol	Cardioselective, sustained release
Third	Labetalol	Non-cardioselective, vasodilation (Higher affinity for α_1 receptor (α_1 receptor blockade) than β_1 and β_2)
	Carvedilol	Cardioselective, vasodilation (β_1 selective, decerased selectivity at higher doses, α_1 receptor blockade, increases insulin sensitivity, antioxidant properties)
	Nebivolol	Cardioselective, vasodilation (Higher β_1 selectivity; endothelium-dependent vasodilation *via* the L-arginine/nitric oxide pathway)

Table 2. Classification of beta blockers that used for treatment of chronic stable angina

2.2.3 Clinical application of β-blockers in angina

β-adrenoceptor antagonists are a mainstay in the treatment of chronic stable angina**.** While coronary blood flow (i.e. oxygen supply) may be sufficient to meet myocardial oxygen requirements at rest in patients with fixed atherosclerotic lesions, the obstruction prevents blood flow from increasing during periods of increased oxygen demand. Under these conditions coronary blood flow is already at a maximal level in most patients, thus any increase in myocardial work can trigger an episode of acute angina. Precipitating factors include physical exertion, emotional stress or excitement, and temperature extremes. By decreasing heart rate, myocardial contractility, and afterload, β-adrenoceptor antagonists reduce myocardial workload and oxygen consumption at rest as well as during periods of exertion or stress. Oral β-adrenoceptor antagonists are widely used in long-term maintenance therapy to prevent acute ischemic episodes. Prophylactic use of these agents reduces the frequency and severity of acute anginal attacks. Because of their slow onset of action, oral β-adrenoceptor antagonists are not appropriate for terminating an acute attack of angina once it has begun; sublingual nitroglycerin is the agent most frequently used under these conditions. Several β-adrenoceptor antagonists, including propranolol, metoprolol, and atenolol, have cardioprotective effects and have been shown to decrease mortality after myocardial infarction (Bunch et al., 2005). In patients with variant (Prinzmetal's) angina, the major underlying cause of angina is vasospasm of one or more coronary arteries. Intense vasoconstriction decreases coronary blood flow, thereby reducing myocardial oxygen supply. Coronary vasospasm can occur in arteries with little or no atherosclerotic plaque and is not associated with an increase in myocardial oxygen demand. Indeed, variant angina may strike at any time of the day or night, including during periods of rest or sleep. In contrast to stable angina, variant angina is most often the result of an

abrupt decrease in myocardial oxygen supply (i.e. coronary blood flow) rather than an increase in myocardial oxygen demand. Unlike nitrates and calcium channel blockers, β-adrenoceptor antagonists do not directly dilate coronary arteries to increase coronary blood flow. Moreover, blockade of vascular β-adrenoceptors inhibits the vasodilator actions of endogenous catecholamines and may exacerbate α-adrenoceptor-mediated vasoconstriction in coronary arteries. Thus, β-adrenoceptor antagonists may worsen coronary vasospasm and are not indicated for treatment of vasospastic angina. β-adrenoceptor antagonists may reduce the risk of progression to acute myocardial infarction in patients with unstable angina (Braunwald et al., 2002).The pathophysiology of this condition is often complex and may involve several underlying factors superimposed upon one another, including rupture of atherosclerotic plaques and thrombus formation, constriction of coronary arteries, and increased myocardial oxygen demand. In these patients, the beneficial effects of the β-adrenoceptor antagonists are likely due to a reduction in myocardial oxygen consumption. If coronary vasospasm is the major underlying problem, nitrates or calcium channel blockers would be more effective and β-adrenoceptor antagonists should be used with caution. When used concurrently, β-adrenoceptor antagonists can inhibit the baroreceptor-mediated reflex tachycardia and positive inotropic effects that may sometimes occur with organic nitrates. Alternatively, organic nitrates increase venous capacitance and can thereby offset β-adrenoceptor antagonist-mediated increases in left ventricular end-diastolic volume. Moreover, organic nitrates are coronary vasodilators and, as such, may prevent the increase in coronary vasomotor tone that may potentially result from blockade of vascular β-adrenoceptors. Dihydropyridine calcium channel blockers are also potent coronary vasodilators and provide similar advantages with regard to coronary vascular resistance in patients treated simultaneously with β-adrenoceptor antagonists. As with nitrates, dihydropyridines may also cause reflex tachycardia that can be alleviated by β-adrenoceptor antagonists. Concurrent use of β-adrenoceptor antagonists with the non-dihydropyridine calcium channel blockers, verapamil and diltiazem, is much more limited due to the potential for severe cardiac depression and must be used with great caution. In the long-term management of ischemic heart disease, β-adrenoceptor antagonists, with their antianginal effects, may also be combined with vasculoprotective drugs such as anti-platelet agents (aspirin, clopidogrel), angiotensin-converting enzyme inhibitors, and HMG-CoA reductase inhibitors to reduce the risk of ischemic vascular events.

2.3 Calcium entry blockers (CEBs)

The mode of action of most conventional antianginal agents involves hemodynamic changes, such as a reduction in systemic vascular resistance or coronary vasodilatation or negative inotropism, which improve the imbalance in myocardial oxygen supply and demand. CEBs bind to and inhibit L-type calcium channels, reducing calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow. The less selective, nondihydropyridine (DHP) CEBs, verapamil and diltiazem, also slow sinoatrial (SA) and atrioventricular (AV) nodal conductions to lower heart rate and depress contractility under physiological conditions. All the CEBs are effective coronary vasodilators. DHPs lower blood pressure and myocardial wall tension to reduce myocardial oxygen consumption. A rise in coronary blood flow further contributes to correct myocardial oxygen imbalance. These drugs lower 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. Amlodipine, in particular, may have some independent action in relieving diastolic dysfunction other than a reduction in blood pressure. CEBs find clinical use in patients who cannot tolerate β-blockers, when they are ineffective, and in combination for additive anti-ischemic effects. Although they are effective antianginal agents, they do not modify the natural progression of the disease. The large International Verapamil-Trandolapril Study (INVEST) trial reported a reduction in number of patients with angina from about 65%–25% using verapamil as compared with atenolol, with no difference in mortality over a 2-year period (Pepine et al., 2003). When DHPs are used in combination with β-blockers, reflex tachycardia from the CCBs is blunted. Long-acting DHPs are preferred. If clinically needed, verapamil or diltiazem may be used with caution to lower heart rate or slow AV conduction further when ventricular function is preserved. In patients with stable angina and hypertension, β-blockers in combination with amlodipine and long-acting nifedipine, nicardipine, isradipine, or felodipine offer an advantage. Of all agents available, the greatest clinical experience has been with amlodipine and felodipine. Short-acting nifedipine has been linked to an increase in myocardial infarction (MI) and should be avoided in unstable angina or ACS. The A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) study showed that long-acting nifedipine (gastrointestinal therapeutic system) safely relieved angina and prolonged event-free survival in patients with stable angina and hypertension (Poole-Wilson et al., 2004; Sierra and Coca, 2008). Verapamil acts chiefly through a negative inotropic action, with less associated reflex tachycardia; diltiazem has greater vasodilatory actions than verapamil. Both verapamil and diltiazem are contraindicated in patients with uncompensated heart failure (HF) because of their negative inotropic effects; amlodipine and felodipine appear safe when left ventricle (LV) dysfunction is compensated. Use of non-DPHs after complex MIs should be avoided because of the possibility of HF as well (Packer et al., 1996; Goldstein et al., 1991). DHPs, particularly nifedipine, are effective in managing Prinzmetal's variant angina along with long-acting nitrates. Although CCBs are effective anti-ischemic agents, in patients with UA/ STEMI, they do not improve mortality. Diltiazem and verapamil are contraindicated in patients with STEMI accompanied by systolic LV dysfunction and HF. Immediate release forms of DHPs-CCBs are contraindicated in STEMI because reflex tachycardia increases myocardial oxygen demand and hypotension potentially lowers coronary perfusion pressure. Also, they should not be used in UA/STEMI without a β-blocker. Common side effects of headache, dizziness, flushing, and edema are due to vasodilation. Interaction with other negative chronotropic or inotropic agents to produce bradycardia, heart block, or HF has been reported. CCBs may also suppress lower esophageal sphincter contraction and worsen symptoms of gastroesophageal reflux disease. CEBs inhibit the CYPA4 enzyme in the liver and, therefore, may raise levels of statins and many other drugs, which may be overlooked (Kones, 2010). Cimetidine and grapefruit juice may raise the effective level of CEBs. Since magnesium is a calcium antagonist, magnesium supplements may enhance the actions of CEBs, particularly nifedipine. **Chronotherapy** with CCBs has been designed to achieve the highest plasma concentration during the most vulnerable time period while maintaining an adequate therapeutic dose throughout the remainder of the 24 hour period and has been marketed in the US since 1996. A variety of CCBs delivery formulations (e.g., with controlled-onset and/or extended release) have been approved by the FDA, and may be beneficially prescribed to lower blood pressure, heart rate and rate-pressure product between 6:00 A.M. and noon depending on the time of

administration. Another study demonstrated an improvement in the duration of exercise with evening doses of this diltiazem preparation *versus* morning dosing.

3. Novel antianginal

New drugs based on novel mechanisms of action have emerged (Chaitman, 2005).

3.1 Ranolazine

Ranolazine (approved by the US Food and Drug Administration) is a unique anti-ischaemic drug that does not significantly affect haemodynamic parameters (Siddiqui et al., 2006). It was originally believed to modify the use of substrate by the ischaemic myocardium from lipids to glucose, thereby increasing metabolic efficiency. However, recent studies suggest that it inhibits the late sodium current (I_{NA}) and the accumulation of intracellular sodium and congruent cellular calcium overload *via* the sodium/calcium exchanger. As opposed to treatment with calcium channel antagonists and β-blockers, the ranolazine-induced improvement in diastolic function occurs without a decrease in systolic function. Clinical studies of the anti-ischaemic effect of ranolazine monotherapy in patients with stable angina showed a significant increase in exercise duration and an improved 1 mm ST-segment depression compared with atenolol. As an adjunct to standard doses of anti-ischaemia drugs (atenolol, amlodipine, diltiazem), ranolazine had an additional antianginal and anti-ischaemic effect, without causing significant hemodynamic changes. The ERICA study addressed the incremental benefit of adding ranolazine to maximal amlodipine regimen. Ranolazine significantly reduced the frequency of angina and GTN consumption compared with placebo. It also has another potentially favorable effect-namely, a dose-related reduction in haemoglobin (Hb_{A1c} %) concentrations in diabetic patients. More comparative trials of ranolazine with other antianginal agents and studies of its effects on long-term morbidity and mortality are needed. So far, results indicate that ranolazine may serve as a useful alternative or adjunct to conventional antianginal treatment. Adverse effects include constipation, nausea, and dizziness. Postural hypotension due to α-adrenergic receptor blocking has also been reported. Increases in QT- interval were observed but not associated *torsade de points*.

3.2 Trimetazidine

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) selectively inhibits the mitochondrial long chain 3-ketoacyl coenzyme A thiolase. It is widely used for the prophylactic treatment of episodes of angina pectoris at recommended daily doses ranging from 40–60 mg. Trimetazidine is a pure metabolic agent that induces the myocardium to shift from free fatty acids to predominantly glucose utilisation in order to increase adenosine triphosphate (ATP) generation per unit oxygen consumption. The antianginal properties of trimetazidine were previously shown in acute and chronic experimental conditions in which the cardioprotective effects were related to the positive effects on energy metabolism, hydroionic balance, coronary microcirculation, and oxidative stress. Efficacy studies reported that trimetazidine reduced ischemia during exercise stress tests, but there was no improvement in outcome. In a Cochrane meta-analysis of 23 studies including 1378 patients, trimetazidine was associated with a significant reduction in weekly angina episodes and

improved exercise time to 1 mm ST-segment depression compared to placebo (Ciapponi et al., 2005). In patients with stable angina who experienced concomitant erectile dysfunction, trimetazidine plus sildenafil was both safe and more effective in controlling episodes of ischaemia during sexual activity than nitrates alone. These data indicate that trimetazidine is safe and effective for the treatment of symptoms of stable angina, either as monotherapy or adjunctive treatment. The Di Napoli study (2005) indicated that trimetazidine added to usual treatment improved the functional status of patients with ischaemic dilated cardiomyopathy, as shown by their distribution in the NYHA class after 18 months of treatment. Compared with control patients maintained with their usual treatment, trimetazidine treated patients' functional improvement was associated with a significant increase in left ventricle ejection fraction and a significant effect on ventricular remodelling. These effects were significant starting from 12 months and were maintained after 18 months of treatment. Bonello et al., (2007) demonstrates that pretreatment with a 60 mg acute oral loading dose of trimetazidine before elective percutaneous coronary intervention limits myocardial damage, as shown by a lower total amount of troponin (cTnI) release after coronary angioplasty.

3.3 Ivabradine

Few agents were developed for I_f inhibition in the past; the first of which is Alinidine, a clonidine derivative, that was soon abandoned due to its relative inotropic action (Ogiwara et al., 1988). Later, zetabradine, a benzazepinone derivative also went out of contention due to unacceptable ocular side effects and QTc prolongation (Frishman et al., 1995; Frishman et al., 2003). Ivabradine, a unique specific I_f current inhibitor, was first described by Thollon et al., more than two decades ago (Thollon et al., 1994). The I_f current inhibitor ivabradine was approved for the treatment of stable angina pectoris by the European Medicines Agency (EMEA) in 2005. Ivabradine is an inhibitor of the selective cardiac pacemaker hyperpolarized-activated I_f current, one of the most important pacemaker currents in the sinoatrial node (DiFrancesco & Camm 2004; Zaza & Rocchetti 2005). Ivabradine has no negative inotropic or hypotensive effects and is therefore a pure heart rate-lowering agent, in contrast to beta blockers. The pure heart rate-reducing effect of ivabradine offers the advantage of not disturbing hemodynamic parameters or left ventricular systolic and diastolic functions. Moreover, the increase in the duration of diastole is greater with ivabradine than with atenolol for a given heart rate (Colin et al. 2003), a beneficial phenomenon considering that most of the coronary perfusion occurs during diastole. Double-blind trials showed that ivabradine treatment increased exercise time to 1 mm ST-segment depression and limited angina compared to placebo, and had similar clinical effects to atenolol or amlodipine—namely, a two-third reduction in the number of anginal episodes and an increase in total exercise duration. Ivabradine offers clear therapeutic benefit for a whole range of patients with stable angina, including those with contraindication or intolerance to β-blockers; however, its effect on survival remains to be explored. Visual symptoms and sinus bradycardia are the main adverse reactions observed with the use of ivabradine. The visual symptoms are mainly ***phosphenes,*** which are episodes of enhanced brightness in limited areas of the visual field frequently triggered by abrupt changes in light intensity. They include photopsia, stroboscopic effect, and non-typical blurred vision, among others. However, the symptoms are generally transient, mild, and do not affect daily living activities. The visual symptoms are probably caused by the interaction of ivabradine

with retinal hyperpolarization-activated *h* channels, responsible for responses to bright light stimuli, which are similar to the *f* ion channel located in the sinoatrial node (Demontis et al. 2002; Savelieva & Camm 2006). Sinus bradycardia has been reported by 4.6% of patients treated with ivabradine 7.5 mg twice daily (Tardif et al. 2005; Ruzyllo et al. 2007). Severe bradycardia (defined as a heart rate less than 40 beat/minute) has been shown to occur in 0.1% of patients. The QTc-interval was not increased in ivabradine recipients compared with atenolol.

3.4 Fasudil hydrochloride

[1-(5-isoquinolinesulfonyl)-homopiperazine] is a potent Rho-kinase (an intracellular signalling molecule involved in the vascular smooth muscle contractile response) inhibitor and vasodilator, used for the treatment of cerebral vasospasm, which is often due to subarachnoid hemorrhage, as well as to improve the cognitive decline seen in stroke victims. It has been found to be effective for the treatment of pulmonary hypertension. It was demonstrated in February 2009 that Fasudil could also be used to enhance memory and improve the prognosis of Alzheimer's patients**.** In patients with stable angina, fasudil treatment led to a significantly greater time to >1 mm ST-segment depression, but showed no difference from placebo in decreasing the time to angina, frequency of angina, or GTN use. In phase 2 dose-finding trials conducted in Japanese patients with stable effort angina, fasudil monotherapy at doses ranging from 5 mg three times daily to 40 mg three times daily increased maximum exercise time and time to the onset of ≥ 1 mm ST-segment depression compared with baseline. Fasudil was well tolerated, with minimal effects on blood pressure or heart rate at rest or during exercise (Shimokawa et al., 2002). Intracoronary fasudil ameliorate myocardial ischemia induced by intracoronary injection of acetylcholine in patients with cardiac syndrome X or microvascular angina (angina with normal coronary arteriogram) (Mohri et al., 2003).

3.5 Molsidomine

Molsidomine is a nitric oxide donating vasodilator. When compared with placebo, it reduced the incidence of anginal attacks and use of sublingual nitrates, and increased exercise capacity, in patients with stable angina. Higher doses provided better protection from angina, although hypotension was a side effect. These new drugs are not yet in routine clinical use; however, they may serve as useful alternatives or adjuncts to conventional antianginal treatment. Further studies and longer follow-up will determine their place in preventing death or myocardial infarction.

3.6 Potassium channel openers (KCOs)

Potassium-ATP (K_{ATP}) channels serve as endogenous homeostatic transducers balancing cellular resources in response to altered demand. In the heart, K_{ATP} channels protect against the metabolic insult of ischemia, and contribute as molecular mediators in the adaptive response to distress. Moreover, K_{ATP} channels regulate vascular tone, and thereby the delivery of metabolic resources to match demand.The possible smooth muscle relaxation mechanisms associated with K_{ATP} channels in the coronary artery are; in the endothelial cells the K_{ATP} channels are activated by adenosine and α_2-adrenoceptor stimulation and contribute to generation of nitric oxide, in the sympathetic neurons opening of presynaptic

K_{ATP} channels attenuates noradrenaline release. KCOs would enhance these exo-smooth muscle actions of the K_{ATP} channels and dilate the coronary artery. KCOs are chemically diverse, and belong to a number of structural classes. These include:

- Benzopyrans (levcromakalim, bimakalim)
- Benzothiadiazines (diazoxide)
- Cyanoguanidines (pinacidil)
- Cyclobutenediones (WAY-151616)
- Nicotinamides (nicorandil)
- Pyrimidines (minoxidil)
- Tertiary carbonoles (ZD-6169)
- Thioformamides (aprikalim)
- Dihydropyridine-like structures (ZM-244085)

3.7 Nicorandil

Nicorandil exerts dual actions: it increases the opening of ATP-gated K^+ channels, thereby relaxing smooth muscle and contributing to coronary vasodilatation; and it has a nitrate-donating moiety. As well as anti-ischaemic effects, nicorandil may have a cardioprotective action. Nicorandil may mimic the natural process of ischemic preconditioning, which involves ATP-dependent potassium channels. Several small randomized trials of patients with stable angina have shown that nicorandil prolongs the time to onset of ST-segment depression and exercise duration during stress testing and improves myocardial perfusion at rest and with exercise. In patients, nicorandil has been shown to be useful in the management of both stable and unstable angina with minimum adverse effects (Simpson et al., 2004). Nicorandil attenuated rest and effort angina, prolonged the duration of exercise and the time to onset of angina or ischemic ST-T changes (Markham et al., 2000). Long-term use of nicorandil was associated with reduction in cardiovascular events and the combined endpoints of death, myocardial infarction and hospitalization due to chest pain in patients with stable angina [The IONA Study Group, 2001]. Nicorandil is an effective anti-anginal agent at a dose of 10 to 40 mg twice a day, controlling stable chronic angina in 70 to 80 percent of patients (Simpson et al., 2004). The response to nicorandil is maintained for 12 hours, with an efficacy that compares favorably with that of nitrates, β-adrenoceptor and CEBs. In patients with unstable angina, nicorandil, when added to aggressive anti-anginal treatment, reduces transient myocardial ischemia, and arrhythmias when compared to placebo (Patel et al., 1999). In vasospastic angina, nicorandil, with potent vasospasmolytic activity, relieves both ergonovine-evoked and spontaneous coronary spasm, attenuates episodes of variant angina, suppresses ST-segment changes and improves perfusion defects. In MI, nicorandil improves ischemia-induced regional wall motion abnormalities, and perfusion in infarct-related areas. In the IONA trial of 5126 patients, the administration of nicorandil in addition to standard treatments reduced the primary end point (coronary death, MI, or hospitalisation for angina) by 17% after a mean follow-up of 1.6 years. There was also a significant reduction in the incidence of ACS and all cardiovascular events (IONA Study Group et al., 2002). In patients undergoing angioplasty, nicorandil preconditions the heart, improves coronary hemodynamics, dilates stenotic and non-stenotic segments, and ameliorates the “no-reflow” phenomenon (Yasuda et al., 2001). Intravenous nicorandil, in conjunction with coronary angioplasty, preserves

microvascular integrity and myocardial viability in patients with acute myocardial infarction (Simpson et al., 2004). Nicorandil also reduces preload and afterload, enhances cardiac endothelial nitric oxide synthase expression and has antiplatelet, fibrinolytic and antioxidant properties (Simpson et al., 2004). Unlike GTN, no development of tolerance to the antianginal effect of nicorandil has been reported (Simpson et al., 2004). Main side-effects include headache, gastrointestinal disturbances and dizziness, mucosal ulceration, including stomatitis and mouth and anal ulcerations. No evidence of proarrhythmia, conduction disturbance, exacerbation of myocardial ischemia, infarction, abrupt withdrawal syndrome, symptomatic decrease in blood pressure or change in heart rate has been observed (Simpson et al., 2004;The Lona Study Group, 2001). Also, no adverse interaction has been reported in patients on oral anticoagulants or hypoglycemic agents. The pharmacokinetics of nicorandil is unaltered in the elderly or patients with renal or hepatic insufficiency (Simpson et al., 2004). Other KCOs like **Levcromakalim, aprikalim and KRN4884** relax conduit arteries (internal mammary and gastroepiploic arteries) used as coronary artery bypass grafts and could be useful in preventing spasm of bypass grafts in patients undergoing surgery for atherosclerotic heart disease.

3.8 Antiplatelets

Antiplatelet agents are the cornerstone of treatment for patients with ACS undergoing percutaneous coronary intervention (PCI).

3.8.1 Acetylsalicylic acid (Aspirin)

Platelet activation and aggregation after vulnerable plaque rupture with resultant thromboses of varying degrees are key components in the pathophysiology of ACS. Acetylsalicylic acid (ASA), causes irreversible acetylation of serine 529 of cyclooxygenase (COX-1) in platelets and the endothelium, thereby preventing thromboxane A_2 (TXA_2) production and resultant platelet aggregation. Studies have shown that ASA reduces the risk of angina, death, or MI by approximately 30% in patients with coronary artery disease (Collaborative overview of randomised trials of antiplatelet therapy-I, 1994; Antithrombotic Trialists' Collaboration, 2002). Although ASA is beneficial for preventing and treating vascular disease, ASA does not prevent all thrombotic events from recurring. Patients who have an ischemic event and are taking aspirin actually may have worse outcomes than do patients who are not taking aspirin (Alexander et al., 1999). This observation that led to the concept of "aspirin resistance (Bhatt and Topol, 2003; Patrono, 2003), a term that has been used when ASA is ineffective for protecting patients from thrombotic complications, for prolonging bleeding times, or for decreasing TXA_2 production. Potential causes of aspirin resistance include inadequate dosing, drug interactions, genetic polymorphisms of COX-1 and other genes involved in TXA_2 production, and upregulation of non-platelet sources of TXA_2 production (Hankey and Eikelboom, 2006). Unfortunately, the optimal treatment for aspirin resistance, if any, is unknown. The Altering aspirin therapy after a laboratory finding of aspirin resistance could be both safe and helpful (Michelson et al., 2005). Aspirin has been shown to be beneficial in the primary prevention, secondary prevention, and treatment of ACS because of the important role of platelets in thrombus formation. One study suggested that prior aspirin use by those who develop an ACS may actually predispose to worse outcomes than those not previously taking aspirin (i.e. **aspirin paradox**) (Santopinto et al., 2001).

From the Thrombolysis In Myocardial Infarction (TIMI) trials database of 66,443 patients, Rich et al., (2010) demonstrated that prior aspirin use is associated with a high-risk cohort of patients but not associated with increased mortality after an ACS, emphasizing that it is likely more a marker as opposed to a pathophysiologic factor related to an increased risk. Prior aspirin use was associated with an increase in the risk of recurrent myocardial infarction and the composite end point of death/recurrent myocardial infraction/ischemia requiring urgent revascularization/recent ischemia requiring hospitalization/stroke. This may be attributable to confounders that cannot be corrected for, aspirin resistance, or both.

3.8.2 Thienopyridines

Thienopyridines, such as **ticlopidine, clopidogrel**, and the newer agent **prasugrel**, block P2Y12 receptor signaling to prevent production of adenyl cyclase, thereby inhibiting platelet activation through adenosine diphosphate (ADP). They also limit ADP-mediated conversion of glycoprotein receptor (GPIIb/IIIa) to its active form. Their mechanism of action is independent of and complementary to that of aspirin, and the combination of agents is superior to aspirin alone. Because thienopyridines take longer than aspirin to cause irreversible antiplatelet effects, a loading dose usually is administered. The thienopyridines are prodrugs that must be metabolized *in vivo* into active form. Both prasugrel and clopidogrel require CYP450 metabolism for the generation of active metabolites, but the pathways leading to conversion to the active metabolites differ between the prodrugs.

3.8.2.1 Ticlopidine

A 1st-generation thienopyridine, in combination with ASA, is associated with reducing rates of vascular death and MI by 46% in NSTEMI patients (Balsano et al., 1990). It has also been shown to be superior to oral anticoagulants in preventing thrombotic complications after coronary stent placement (Urban et al., 1998). However, it is used less frequently than the newer thienopyridines in current clinical practice because of its potential for side effects primarily rash, nausea, neutropenia, and thrombocytopenia (Love et al., 1998).

3.8.2.2 Clopidogrel

Second generation thienopyridine, is the most widely studied and used ADP-receptor-blocking agent. Initial data regarding clopidogrel are derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study [1996] which reported a 9% relative risk reduction in adverse cardiovascular events (vascular death, MI, or ischemic stroke) without a significant increase in bleeding. Also this study showed that the risk of the primary composite endpoint (cardiovascular death, MI, or stroke) was reduced 20% with the use of clopidogrel compared to aspirin. Clopidogrel has demonstrated considerable success in reducing thrombotic complications of ACS and/or PCI compared to aspirin alone and is standard of care for the management of patients with ACS and when added in patients undergoing PCI. In elderly STEMI patients who receive thrombolytics, a loading dose of clopidogrel is not recommended due to increased risk of intracerebral hemorrhage. Loading dose of clopidogrel is recommended in elderly STEMI patients only if primary PCI is performed**.** In UA/NSTEMI patients with a history of gastrointestinal bleeding, ASA and clopidogrel should be given with other agents, such as proton pump inhibitors (PPIs) that minimize the risk of recurrent gastrointestinal bleeding. Clopidogrel therapy must also be stopped 4 to 7 days before elective coronary artery bypass grafting (CABG), to prevent

excessive intraoperative and post-operative bleeding (Mehta et al., 2006; Chu et al., 2004). As a result, clinicians might have to delay giving clopidogrel to patients who are undergoing early coronary angiography (within 48 hr of hospital admission) until it is clear that these patients will not undergo a coronary artery bypass graft surgery (CABG) procedure within the next several days. However, there is growing evidence to support broad variability among individual patient responses to clopidogrel. This clopidogrel resistance is associated with a higher risk of recurrent ischemic complications (Serebruany et al., 2005). The mechanisms underlying the variability of response to clopidogrel may be related to poor patient compliance, differences in clopidogrel dosing, gastric absorption problems, and varying availability and clearance of the active metabolite (O'queli et al., 2007). Genetic factors including polymorphisms of hepatic CYP3A—have received special attention (Frere et al., 2008). There have been reports of concerns that proton pump inhibitors (PPIs) may interfere with clopidogrel's ability to inhibit platelet aggregation, thereby increasing the risk of rehospitalization or death in association with ACS (Li et al., 2004; Juurlink et al., 2009; Ho et al., 2009). Combined use of clopidogrel and PPIs was associated with an increased risk of death from or rehospitalization for ACS when compared with use of clopidogrel alone (Ho et al., 2009).

3.8.2.3 Prasugrel

It is an orally administered P2Y12 receptor antagonist that is more potent, more rapid in onset, and more consistent in its inhibition of platelet aggregation than clopidogrel. In clinical studies, prasugrel has consistently demonstrated greater and more rapid platelet inhibition than clopidogrel in healthy subjects, patients with stable coronary artery disease and acute coronary syndrome, and those undergoing percutaneous coronary intervention. In addition, subjects who are poor responders to clopidogrel respond adequately to prasugrel (Brandt et al., 2007; Weerakkody et al., 2007a; 2007b). In the Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Throm-bolysis in Myocardial Infarction (TRITON-TIMI 38) trial, prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal MI, or non-fatal stroke by 19%, when compared with clopidogrel (Wiviott et al., 2007). Prasugrel also reduced MI by 24%, the need for urgent revascularization by 34%, and stent thrombosis by 52% (Wiviott et al., 2008). However, the beneficial effect also was associated with a 0.5% absolute increase in non-CABG-related TIMI major bleeding and life-threatening bleeding and a 0.3% absolute increase in fatal bleeding (Wiviott et al., 2007). TRITON-TIMI 38 trial showed that patients with a history of transient ischemic attack or stroke, those who were 75 years or older, and those who weighed less than 60 kg were especially at risk of bleeding mainly during the maintenance phase (Wiviott et al., 2008; Murphy et al., 2008).

3.8.3 Nonthienopyridine antiplatelet agents

Cangrelor and Ticagrelor are direct and reversible inhibitors of the platelet P2Y12 receptor. **SCH 530348** is an oral protease-activated receptor-1 antagonist.

3.8.4 Glycoprotein IIb/IIIa inhibitors

The final common pathway of platelet activation and aggregation involves a conformational change of the GPIIb/IIIa receptors from a resting state to an active state. The activated

GPIIb/IIIa receptors undergo bivalent binding with soluble ligands, with fibrinogen, and, under high shear conditions, with von Willebrand factor, which leads to fibrinogen-mediated cross-linking of platelets; a key event in thrombus formation and thrombosis. GPIIb/IIIa inhibitors are potent inhibitors of platelet aggregation by all types of stimuli (for example, ADP, serotonin, collagen, and thrombin). Currently three types of GPIIb/IIIa inhibitors are used clinically: abciximab, tirofiban, and eptifibatide.

3.8.4.1 Abciximab

It is a recombinant human-murine chimeric Fab-fragment with a half-life of 10 minutes. Abciximab was initially studied in percutaneous trans-luminal coronary angioplasty (PTCA) trials, in the prestent era of the early 1990s. However, the advent of GPIIb/IIIa inhibitors revolutionized the use of catheter-based therapies in the treatment of peripheral artery disease, cerebrovascular atherosclerotic disease, and various forms of coronary artery disease, as well as stable angina, UA, NSTEMI, and STEMI. Results from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial showed that in relatively high-risk patients (those with UA, evolving MI, or complex angiographic lesion morphology) who were given abciximab, there was a 35% reduction in the primary composite end-point (death, MI, or recurrent ischemia) compared with patients who received a placebo (EPIC investigation, 1994). The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial [1997] showed a 30% relative reduction, within 30 days after PTCA, in the primary endpoint of death (any cause), myocardial infarction, or recurrent ischemia requiring urgent revascularization. Furthermore, abciximab reduced the rate of myocardial infarction before, during, and after PTCA, even in patients given nitrates and heparin. Also revealed that abciximab facilitated thrombus resolution and prevented recurrent ischemia, as measured by continuous electrocardiographic monitoring. The Global Use of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndrome (GUSTO IV-ACS) trial studied 7,800 UA/NSTEMI patients who were not scheduled to undergo early revascularization. The results of the study showed that abciximab administration provided no benefit, even in a subgroup of patients who had elevated troponin levels (Simoons et al., 2001).

3.8.4.2 Tirofiban hydrochloride

It is a low molecular weight nonpeptide derivative of tyrosine with a half-life of 1.3 hours. In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study (1998), 3,232 patients with UA were randomlyassigned to receive either heparin or tirofiban for 48 hours. Results showed a 32% reduction in the rate of death, MI, or refractory ischemia at 48 hours (3.8% with tirofiban *vs* 5.6% with heparin), but there was no significant difference in the composite endpoint at 30 days (15.9% in the tirofiban group vs 17% in the heparin group). In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial (1998) 1,915 patients with UA and non-Q-wave MI were randomly assigned to receive heparin, tirofiban, or both. Patients also received ASA in the absence of any contraindications. The tirofiban only arm was stopped prematurely because of excess death at 7 days (4.6% *vs* 1.1% in the heparin-only arm). The greatest benefit was seen in the group receiving both heparin and tirofiban, for whom the frequency of the composite endpoint (7-day death, MI, or refractory ischemia) was reduced (17.9% *vs* 12.9% in the heparin-only arm). The observed benefit was sustained at 30 days (18.5% *vs* 22%) and at 6 months (27.7% *vs* 32%).

3.8.4.3 Eptifibatide

It is a cyclic heptapeptide that selectively inhibits the arginin-glycin-aspartate (RGD) motifs sequence of the GPIIb/IIIa receptors and has a half-life of 150 minutes. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial (1998) data showed that the administration of eptifibatide resulted in a 10% reduction in the relative risk of death and MI at 30 days in patients who had NSTEMI. Boersma and colleagues (2002) clarified the importance of GPIIb/IIIa inhibitors in the management of moderate to high-risk UA/NSTEMI patients. Boersma's meta-analysis pooled 31,402 patients from six GPIIb/IIIa trials for ACS. Results showed a 10.8% event rate in the GPIIb/IIIa inhibitor group (n=18,297), versus an 11.8% event rate in the placebo group (n=13,105), and a 9% reduction in the odds ratio of death or MI. The benefit was largest in a subset of patients who had evidence of myocardial necrosis, as suggested by elevated troponin levels. The magnitude of the treatment effect also was found to be greater in patients who underwent a PCI procedure within 5 days. The Early GPIIb/IIIa Inhibition in Non-ST-Segment-Elevation Acute Coronary Syndrome (EARLY ACS) trial (Giugliano et al., 2009) studied 9,494 high-risk NSTEMI patients undergoing an invasive procedure at study centers in 29 countries were randomly assigned to receive either eptifibatide ≥12 hours before angiography (the early eptifibatide group) or a matching placebo infusion with provisional use of eptifibatide after angiography (the delayed-eptifibatide group). Results showed no statistical difference in the primary efficacy endpoint of a composite of death, MI, or recurrent ischemia requiring urgent revascularization, or in the occurrence of a thrombotic complication during PCI (9.3% in the early-eptifibatide group *vs* 10% in the delayed-eptifibatide group). However, early use of eptifibatide was associated with an increased risk of nonfatal bleeding and the need for transfusion (Giugliano et al., 2009).

3.9 Anticoagulants

Anticoagulants are effective for reducing the occurrence of major ischemic events in patients with ACS. The principal adverse effect associated with their use is bleeding. Bleeding during anticoagulant therapy is independently associated with an increased risk of MI and death, which further offsets the clinical benefit (Eikelboom et al., 2006; Rao et al., 2004). In the treatment of non-ST elevation (NSTE) ACS, enoxaparin, a low-molecular-weight heparin (LMWH), reduces the odds of death or non-fatal MI by 16% compared with unfractionated heparin (UFH) (odds ratio [OR]: 0.84; 95% C.I: 0.76-0.92) but does not reduce death and increases the odds of major bleeding by 25% (OR: 1.25; 95% CI: 1.04-1.50) (Murphy et al., 2007). In the treatment of STEMI, enoxaparin compared with UFH reduces the odds of death or non-fatal MI by 22%, but increases the risk of bleeding by 45% and is not associated with a mortality benefit. Another LMWH, reviparin, reduces both reinfarction and mortality among patients with acute STEMI compared with standard treatment, but increases the risk of life-threatening bleeding (Yusuf et al., 2005).

3.9.1 Unfractionated heparin (UFH)

Unfractionated heparin is a glycosaminoglycan comprising multiple different polysaccharide chain lengths of varying molecular weights. It exerts its anticoagulative effect by activating and accelerating the proteolytic activity of plasma cofactor antithrombin (AT). Heparin binds to the lysine site on AT, producing a conformational change at the arginine-reactive

site that converts AT from a slow, progressive thrombin (factor IIa) inhibitor to a rapid inhibitor of thrombin and factor Xa thereby preventing thrombus propagation. Only one third of any given dose of heparin actually binds to AT and exerts its anticoagulative effect. Heparin also binds to a number of different circulating plasma proteins (acute phase reactants), blood cells, and endothelial cells, which contributes to its differing anticoagulative effects in different patients. Therefore, close and frequent monitoring of the activated partial thromboplastin time is necessary to ensure that a safe therapeutic range is maintained. In a double-blind, randomized, placebo-controlled trial involving 479 UA/NSTEMI patients, the incidence of MI was reduced from 11.9% in the placebo group to 3.3% in the ASA group, 0.8% in the heparin group, and 1.6% in the heparin plus ASA group (Theroux et al., 1988). Similarly, the incidence of refractory angina was reduced from 22.9% in the placebo group to 16.5% in the ASA group, 8.5% in the heparin group, and 10.7% in the heparin plus ASA group. *The combination of heparin plus ASA was found to be no more beneficial than heparin alone.* Meta-analysis using data from 6 randomized trials that included 1,353 patients found that patients who received a combination of UFH and ASA had a 33% risk reduction in cardiovascular death and MI ($_{95\%}$ C.I, 2%–56%) than did patients who received a placebo (Oler et al., 1996). *The ACC/AHA Guidelines state that patients with NSTEMI should receive heparin, unless contraindicated*. Most trials of UFH involving UA/NSTEMI patients recommend heparin therapy for 2 to 5 days.

3.9.2 Low-molecular-weight heparin

Low-molecular weight heparin is derived from heparin by chemical or enzymatic depolymerization, which yields fragments approximately one third the size of heparin. Most of the fragments contain fewer than 18 saccharide units and catalyze the inactivation of factor Xa more than of factor IIa (UFH inhibits factors Xa and IIa equally) (Weitz, 1997). Compared with UFH, LMWH has lower plasma-protein binding and therefore, a more predictable anticoagulative effect, has a greater bioavailability, is conveniently administered in subcutaneous doses (once/day or twice/day), and requires less frequent laboratory monitoring. Because LMWH is cleared by the kidneys, dosing should be decreased to half in patients with creatinine clearances of <30 ml/min and avoided altogether in patients with severe renal insufficiency. LMWHs; **ardeparin, dalteparin, enoxaparin, nadroparin, reviparin, and tinzaparin** are now considered the mainstay of antithrombotic agents for the prophylaxis and treatment of venous thrombo-embolism (VTE). Dalteparin, enoxaparin, and tinzaparin are all approved by the FDA and currently available in the United States. The FDA-approved indications vary among the different LMWHs. Dalteparin and enoxaparin are indicated for VTE prophylaxis and ACS treatment, while enoxaparin and tinzaparin are indicated for treatment of VTE. As enoxaparin has been available since the early 1980s, it is the LMWH most widely studied, as reflected by its extended list of FDA-approved indications. Fast Revascularization during Instability in Coronary Artery Disease (FRISC) trial found that dalteparin (120 IU/kg with a maximal dose of 10,000 IU, twice daily) was associated with a 63% relative risk reduction in death or MI (1.8% in the treatment group *vs* 4.8% in the placebo group) in the first six days (Swahn and Wallentin, 1997). At 40 days, differences in the incidence of MI and death in patients receiving dalteparin persisted, although a sub-group analysis revealed that dalteparin's effect was mostly confined to patients who were nonsmokers. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial found that the risk of death, MI, or recurrent

angina in patients with UA/NSTEMA was significantly lower in the enoxaparin (1 mg/kg twice daily) patients than in the UFH patients (16.6% vs 19.8%). Even at 30 days, the benefit remained (19.8% *vs* 23%), but at the cost of increased minor bleeding (Cohen et al., 1997). There was no significant change in the incidence of major bleeding (6.5% *vs* 7%). The Thrombolysis In Myocardial Infarction 11B (TIMI 11B) trial found that enoxaparin may be more effective than UFH for reducing death and serious cardiac ischemic events during the acute management of UA/NSTEMI patients, without causing a significant increase in the rate of major bleeding (Antman et al., 1999). A meta-analysis of the approximately 22,000 UA/NSTEMI patients enrolled in six randomized trials comparing enoxaparin and UFH showed a relative risk reduction of 9% in the combined endpoint of death or MI at 30 days for patients receiving enoxaparin (10.1% *vs* 11% with UFH). There were no significant differences in major bleeding at 7 days (Petesern et al., 2004). *Enoxaparin was consistently beneficial when an early conservative strategy was implemented.* The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial treat UA/NSTEMI patients with an early-invasive strategy taking the primary endpoint was all-cause death or nonfatal MI at 30-day follow-up (Ferguson et al., 2004). The primary endpoint occurred in 14.5% of patients receiving UFH and in 14% of patients receiving enoxaparin (a nonsignificant 3% risk reduction). Enoxaparin therapy was associated with a 20% increase in TIMI major bleeding in UA/NSTEMI patients undergoing invasive procedures, especially CABG procedures. Blazing et al., (2004) showed that the event rates in 3,987 patients receiving the GPIIb/IIIa inhibitor tirofiban were similar to those in patients receiving enoxaparin and those receiving UFH. The primary endpoint was a composite of death, new MI, or refractory ischemia within 7 days. However, the incidence of TIMI major bleeding not related to CABG revealed an event rate of 15% in the enoxaparin group compared with 4% in the UFH group. *Compared with UFH, enoxaparin appears to be superior in reducing ischemic events in UA/NSTEMI patients who are treated with early-conservative strategies.*

3.9.3 Factor X (prothrombinase enzyme) inhibitors

Fondaparinux is a synthetic sulfated pentasaccharide that binds to AT early in the coagulation cascade, thereby indirectly inhibiting factor Xa. Its specificity and selectivity, combined with its long half-life and 100% bioavailability, enables once-daily anticoagulation without the need to monitor the activated clotting time. Fondaparinux inhibits factor Xa within the clot itself without inhibiting platelet function, which prevents thrombus progression and enhances AT's effectiveness in a safe manner. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study showed that fondaparinux was statistically equivalent to enoxaparin with respect to the primary efficacy endpoint (death, MI, or refractory ischemia) at 9 days (5.8% *vs* 5.7%, respectively). The composite of death, MI, refractory ischemia, or major bleeding at 9 days occurred in 7.3% of fondaparinux patients vs 9% of enoxaparin patients. The efficacy was maintained for up to six months. Major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% *vs* 4.1%). Results from MICHEL-ANGELO OASIS-5 Steering (2005) showed that fondaparinux increased the rate of guiding-catheter thrombus formation (29 episodes (0.9%]) with fondaparinux vs 8 episodes with enoxaparin (0.3%).

Bivalirudin is an FDA-approved direct thrombin inhibitor. The Bivalirudin Angioplasty Trial (BAT) compared bivalirudin to heparin and found that bivalirudin had superior

clinical outcomes in terms of reducing the rate of death, MI, and revascularization (6.2% *vs* 7.9% for bivalirudin versus heparin). Also, bivalirudin was associated with a decreased frequency of hemorrhage compared with heparin (3.5% *vs* 9.3%) (Bittl et al., 2001). In a similar study (Comparison of Abciximab Complications with Hirulog Ischemic Events Trial [CACHET]), bivalirudin plus provisional abciximab was compared with heparin plus planned abciximab (Lincoff et al., 2002). Again, bivalirudin had superior clinical outcomes regarding death, MI, revascularization, and major hemorrhage at seven days (14.1% *vs* 3.5% for heparin versus bivalirudin). Bivalirudin is addressed in the guidelines as an option for invasive management of ACS. It was studied in 6010 low- to moderate-risk patients undergoing urgent or elective PCI in the REPLACE-2 trial (Lincoff et al., 2003). In that study, the primary composite endpoint (death, MI, urgent repeat revascularization, or in-hospital major bleeding) occurred in 9.2% of patients in the bivalirudin group *vs* 10% of those in the heparin plus GP IIb/IIIa group within 30 days of randomization. There was no significant difference between bivalirudin alone compared with heparin plus a GP IIb/IIIa inhibitor for the composite ischemia endpoint. In addition, bivalirudin alone was shown to have a significantly lower rate of major bleeding and reduced rate of the net clinical outcome (Stone et al., 2006).

3.10 Thrombolytics

All available fibrin-specific thrombolytic agents have the same general mechanism of fibrinolysis. They have the property of fibrin-enhanced conversion of plasminogen to plasmin. When introduced into systemic circulation at pharmacologic concentrations, they preferentially bind to fibrin in a thrombus and catalyze cleavage of entrapped plasminogen to plasmin. This begins local fibrinolysis with limited systemic proteolysis. These agents differ from the prototype streptokinase (nonfibrin-specific) in that they enzymatically cleave plasminogen to plasmin, whereas streptokinase causes an indirect conformational change in the plasminogen molecule, which then acts as plasmin. Examples of these agents include alteplase (rt-PA), reteplase (r-PA) and tenecteplase (TNK) which are approved for treatment of acute myocardial infarction. As measured by decreases in plasminogen and fibrinogen levels, r-PA, rt-PA, and TNK have increasing fibrin specificity. TNK, is a genetically engineered variant of rt-PA. Its name refers to the sites of amino acid modification (T103N, N117Q, KHRR 296-299 AAAA). This modification is believed responsible for the increased fibrin specificity compared with r-PA and rt-PA. TNK has improved resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1) compared with rt-PA (Collen et al., 1994; Keyt et al., 1994). Plasminogen activator inhibitor-1 is an endogenous substance capable of rapidly binding and inhibiting both single-chain and two-chain endogenous tissue plasminogen activator (t-PA), and similarly inactivates r-PA and rt-PA (Nordt et al., 1998). Thrombolytic therapy reduced the mortality of patients with acute myocardial infarction. Survival benefit is documented with streptokinase, anistreplase, rt-PA, r-PA, and TNK. Thrombolysis trials showed thrombolytics to be beneficial in most patients; however, approximately 25% of patients eligible for therapy do not receive it, with those at highest risk for death least likely to be treated (Barron et al., 1998). The available data showed the efficacy fibrin-specific thrombolytic drugs in establishing the patency in an occluded coronary artery. These studies were specifically designed to measure patency rates, not mortality rates, as the primary outcome. Also r-pA-rt-PA and TNK improve the survival rate and provide similar combined mortality benefit after acute myocardial infarction. In all trials the most critical adverse event was bleeding. Intracranial hemorrhage occurred at a

rate less than 1% with r-PA, rt-PA, and TNK, with higher frequency in patients older than 75 years. Other noncerebral major bleeding complication requiring blood transfusion occurred at a similar rate with r-PA and rt-PA, and was significantly less with TNK. No other adverse events have been reported. Unlike streptokinase, rechallenge with fibrin-specific agents does not produce an antigenic response. Contraindications for r-PA, rt-PA, and TNK include active internal bleeding; intracranial or intraspinal surgery or trauma within 2 or fewer months; intracranial neoplasm, arteriovenous malformation, or aneurysm; bleeding diathesis; and severe uncontrolled hypertension. Conditions that may increase the risk of bleeding (warnings) are recent major surgery (≤ 10 days), cerebrovascular disease, recent (≥ 10 days) gastrointestinal or genitourinary bleeding, recent (≤ 10 days) trauma, hypertension (≥ 180 mm Hg systolic, ≥ 110 mm Hg diastolic), acute pericarditis, subacute bacterial endocarditis, hemostatic defects secondary to severe hepatic or renal disease, significant liver dysfunction, pregnancy, retinopathy, current therapy with oral anticoagulants (warfarin), and septic thrombophlebitis. Although advanced age (> 75 yrs) increases the risk of bleeding, these patients still experience significant benefit from therapy.

3.11 Angiotensin converting enzyme inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce the rate of mortality and to prevent cardiovascular events in patients with coronary artery disease, especially after acute myocardial infarction (The EUROPA, 2003; Pfeffer et al., 1995). The authors of the EUROPA (European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease) study showed a 14% reduction in total rate of mortality, nonfatal MI, unstable angina, and cardiac arrest. ACEIs, through the reduction of angiotensin II and increased bradykinin availability, explicate their cardioprotective proprieties on left ventricular afterload and remodeling, improving cardiac hemodynamics, and reducing ventricular mass (Okin et al., 2003). In addition to lowering blood pressure, ACEIs possess a vasculoprotective and anti-ischemic action through their antiatherosclerotic, antithrombotic, anti-inflammatory effects (Brasier et al., 2002).Long-term treatment with ACE inhibitors after myocardial infarction is associated with improved outcomes, especially in patients with left ventricular systolic ejection fraction less than 40%. Elderly ACS patients appear to derive greater benefit from ACE inhibitors than their younger counterparts. ARBs should be used as an alternative in ACE inhibitor intolerant patients. ACE inhibitors and angiotensin receptor blockers (ARBs) are not part of the initial management of ACS patients and should not be started until the patient is stabilized and is ready for hospital discharge. Renal function and electrolytes should be monitored closely, especially in elderly patients.

3.12 Lipid lowering agents; HMG-Co reductase inhibitors; Statins

Statins were initially identified as secondary metabolites of fungi. One of the first natural inhibitors of HMG-CoA reductase, ML-236B, was isolated as a metabolite from cultures of *Penicillium citrinum* and was shown to be an extremely potent competitive inhibitor of HMG-CoA reductase. Statins are either hydrophilic such as pravastatin and rosuvastatin or lipophilic statins e.g. atorvastatin and simvastatin. The beneficial effects of statins extend to patients regardless of age, sex, or baseline cholesterol levels. The pleiotropic (pleiotropy" comes from the Greek words *pleio*, which means many, and *trepein*, which means influencing) effects of statins include:

1. Improve endothelial function in patients with hypercholesterolemia and atherosclerosis *via* up-regulating eNOS.
2. Attenuate cytokine-mediated vascular smooth muscle cell (VSMC) proliferation in coronary artery smooth muscle cells and also inhibit pathological proliferation such as that observed in transplant-associated arteriopathy
3. Could inhibit cardiac hypertrophy through an antioxidant mechanism involving inhibition of Rac1 geranylgeranylation
4. Exert protective function against ischemic myocardial injury
5. Inhibit platelets aggregation
6. Modulate immune activation and to exert anti-inflammatory effects on the vascular wall by decreasing the number of inflammatory cells in atherosclerotic plaques
7. Contribute to plaque stability by reducing plaque size or by modifying the physiochemical properties of the lipid core
8. Protect the brain from Alzheimer's dementia

Statins very effective in the reduction of mortality and non-fatal cardiovascular events rates in both primary and secondary prevention of ischemic heart disease. Statins *via* their pleotropic effects inhibit the pathogenic pathways of coronary artery disease. They reduce total-and LDL-cholesterol accumulation in plaque, endothelial dysfunction, activation of inflammation and thrombus formation. An increasing number of observations demonstrate that statins may play a beneficial role not only in early secondary prevention but also directly in the therapy of ACS i.e. when statin treatment is started as first-line care in clinically unstable patient. The study of Ostadal et al., (2010) failed to demonstrate the beneficial effect of fluvastatin as first line therapy in acute coronary syndrome on the serum markers of inflammation and plaque instability; C-reactive protein, interleukin 6, pregnancy-associated plasma protein A (PAPP-A/proMBP). Statins is the most efficacious therapies for patients with established coronary disease, and evidences suggest that these agents are beneficial in the setting of ACS. Intensive lipid-lowering therapy reduces adverse clinical events, including death and MI, compared with moderate-dose therapy in patients with acute coronary syndrome (de Lemos et al., 2004). The best recognized and most commonly reported adverse effects of statins are muscle adverse effects and include muscle pain, fatigue and weakness as well as rhabdomyolysis. Fibrates, particularly gemfibrozil, amplify the risk of rhabdomyolysis on statins (most powerfully for cerivastatin), due to their effect of impeding statin metabolism and perhaps their additional lipid-modifying effects. Concurrent administration of statins with CYP3A4 inhibitors (e.g. cyclosporine, erythromycin, azole antifungal and antiretrovirals such as ritonavir.) may raise statin concentrations and risk of toxicity, including rhabdomyolysis. Grapefruit juice and perhaps pomegranate juice inhibit CYP3A4 and have been presumptively linked to statin rhabdomyolysis. Non muscle statin adverse effects include cognitive problems, gastrointestinal and neurological symptoms, psychiatric symptoms, sleep problems, glucose elevations.

4. Miscellaneous

Perhexiline has been used as an antianginal drug since the early 1970s (Armstrong et al., 1974) when its mode of action was thought to be *via* coronary artery vasodilatation mediated by calcium channel antagonism (Opie, 1980). Perhexiline is now thought to exert its anti-anginal action primarily by inhibiting the enzyme carnitine palmitoyltransferase (Kennedy

et al., 1996). This inhibition reduces fatty acid metabolism in favour of carbohydrate metabolism which increases available energy for the same amount of oxygen. Perhexiline is relatively free of negative inotropic effects and does not increase airways resistance and is therefore not contraindicated in such situations. Perhexiline has been shown to be superior to β-adrenoceptor blockers in its ability to reduce the frequency of anginal attacks and in addition, because it has a different mode of action, it provides additional antianginal benefit when added to existing agents (Stewart et al., 1996). Its use declined in the mid 1970s (Horowitz, 1995) because of the occurrence of severe adverse effects during long-term therapy including neuropathy and hepatotoxicity (Cooper et al., 1985). The incidence of these adverse effects was noted to be related to plasma perhexiline concentration and it was observed that adverse effects could be prevented if plasma concentrations were kept below defined values (Pilcher et al., 1985; Horowitz., 1986).

_l_-carnitine

L-carnitine is a naturally occurring amino acid essential for the transport of fatty acids into the mitochondria. It involved in oxidation of long-chain fatty acids and stabilization of cellular membranes and is also a free-radical scavenger. Skeletal and cardiac muscle use fatty acids as main source of energy, therefore, carnitine deficiency mainly manifests as dysfunction of the above tissues. Carnitine depletion can also cause hypoglycemia, hyperammonemia, hypoketonemia, coma, seizures, and developmental disorders. Cardiac muscle contains very high levels of carnitine compared with other tissues. Myocardial ischemia has been shown to deplete carnitine levels in the myocardium. When combined with elevated levels of fatty acids during ischemia, this leads to elevation of toxic metabolites of fatty acid esterification. It has been suggested that depletion of free L-carnitine in the ischemic myocardium can impair the electrical and contractile activities of the heart. Carnitine may make cardiomyocytes more resistant to free radicals. Another proposed mechanism is through shifting the metabolism from fatty acid oxidation to glucose oxidation. Propionyl L-carnitine (PLC) is a carnitine derivative that may have enhanced beneficial effects compared with carnitine. Carnitine significantly reduced left ventricular end-diastolic, end-systolic pressures, and infarct size in patients presenting with acute myocardial infarction and reduced the mortality rate from heart failure (Iliceto et al., 1995; Singh et al., 1996). In patients with chronic stable angina, carnitine improved exercise tolerance; significant improvements in exercise duration and time needed for ST-segment changes to return to baseline (Iyer et al., 2000).

Ribose

Ribose is a pentose sugar that has been shown in numerous animal experiments to enhance ATP production and improve cardiac function. Ribose can enhance metabolism by entering the pentose phosphate pathway and bypassing the rate limiting enzymes of glucose-6-phosphate dehydrogenase and 6-phosphogluconate-dehydrogenase. It improves the time to ST-segment depression and time to moderate angina, and diastolic relaxation by restoring ATP levels (Pliml et al., 1992). Ribose supplementation improves diastolic heart function, increases exercise tolerance and enhances patient quality of life. These benefits are provided by the role ribose plays in increasing cardiac energy reserves that become depressed during ischemia or hypoxia associated with coronary artery disease or congestive heart failure.

Dichloracetate (DCA)

Dichloroacetate (DCA) can overcome fatty acid inhibition of glucose oxidation by stimulating the pyruvate dehydrogenase complex, the rate-limiting enzyme for glucose oxidation (Stacpoole et al., 1998). By this effect, DCA enhances contractile function during reperfusion and significantly improves cardiac efficiency. The beneficial effect of DCA in ischemia-reperfusion injury may be attributed to:

1. DCA reduces the proton production from glucose metabolism. This was associated with an increase in the rate of intracellular pH recovery as well as in improvement in cardiac efficiency (Liu et al., 1999).
2. DCA may exert its beneficial effects by influencing mitochondrial proton leak. Proton leak occurs when proton motive force is consumed without ATP synthesis (Brand et al., 1994).

In clinical studies, DCA has been shown to increase left ventricular stroke volume in patients with coronary artery disease and dramatically improve recovery of cardiac work following ischemia. DCA improves acidosis in critically ill patients and, likewise, improves myocardial hemodynamics in those with chronic coronary artery disease and congestive heart failure; however, its metabolism is variable and clinical data on its use in chronic ischemic heart disease are limited (Schofield and Hill, 2001). The use of DCA is limited by its low potency (blood levels need to approach millimolar levels) and short half-life.

Glucose Insulin Potassium (GIK)

Glucose-insulin-potassium (GIK) therapy is one of the most widely investigated approaches used in a clinical setting; it was first reported in 1962 with results from new trials continuing to be published. In the 1960's Sodi-Pallares refined the treatment by adding insulin and potassium to the infusion, and demonstrated that the treatment was effective for the arrhythmias and angina (Sodi-Pallares et al., 1962; 1963).

The beneficial effects of hyperglycemia and hyperinsulinemia could be due to:

1. An increase glycolytically derived ATP
2. An increase in pyruvate dehydrogenase enzyme activity due to decreased plasma FFA concentration and elevated insulin levels, resulting in less lactate and H^+ accumulation
3. Less accumulation of noxious fatty-acyl CoAs due to lower FFA levels.

Glucose and insulin infusion was also decrease infarct size and prevent the fall in creatine phosphate, ATP and pH in animal models of ischemia/reperfusion injury (Maroko et al., 1972; Opie and Owen, 1976). Clinical trials with glucose and insulin infusion following myocardial infarction) or coronary artery by-pass surgery (Gradinak et al., 1989) have generally been favorable. Although in general GIK therapy is found to improve outcome after acute myocardial infarction, this is not a uniform observation (Pache et al., 2004). The most frequently mechanism underlying the protection associated with increased myocardial glucose use are that it improves efficiency by decreasing oxygen consumption and improves the coupling between glucose oxidation and glycolysis, thereby reducing intracellular acidosis (Liu et al., 2002). Glucose and insulin infusions have been used to raise glycogen

levels prior to cardiac surgery. In general, an infusion of glucose and insulin results in hyperglycemia (>10 mM), hyperinsulinemia (>80 μU/ml), and low plasma FFA levels (<0.3 mM) (Wisneski et al., 1990). Hyperglycemia and hyperinsulinemia result in an increase in glycogen synthesis. Studies in patients have shown that infusing glucose and insulin overnight prior to cardiac surgery results in a 50–70% increase in cardiac glycogen concentration and improved clinical outcome from cardiac surgery (Berggren et al., 1982). Coronary-artery-bypass graft patients with elevated preoperative myocardial glycogen levels had reduced serum levels of myocardial enzymes during the post-operative period and a lower incidence of arrhythmias.

Etomoxir

Etomoxir (ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate) is an inhibitor of carnitine palmitoyltransferase I enzyme (CPT I). It is of potential interest in the treatment of diabetes since inhibition of fatty acid oxidation should increase glucose utilization and decrease gluconeogenesis. By inhibiting fatty acid oxidation, fatty acid-induced inhibition of glycolysis may be overcome, thereby increasing glucose utilization. As a result of inhibition the CPT I the myocardial fatty acid oxidation is reduced and thereby relieves fatty acid inhibition of pyruvate dehydrogenase enzyme activity, and increases the oxidation of glucose and lactate. This has anti-ischaemic efficacy and improves cardiac function during the recovery from ischaemia. However, long-term administration of such agent has been found to be associated with toxicity problems, and in particular their causing cardiac hypertrophy (Rupp et al., 1995). In experimental animal model, etomoxir does not affect ventricular mass in rats with left ventricular hypertrophy following aortic banding, and actually prevents the impairment in contractile function in this model.

Diazeniumdiolates (NONOates)

The first of this class was diethylamine NONOate; DEA/NO synthesized in 1960. However, Diazeniumdiolates only became the focus of attention in the NO world in the 1990s when their NO donor properties were considered in biological settings (Maragos et al., 1991). An attractive feature of this class of compounds is that their decomposition is not catalysed by thiols or biological tissue, unless specifically designed to (see below) and, because NO release follows simple first-order kinetics, the rate of NO release can be accurately predicted. Subsequently, biological activity such as vasodilatation, inhibition of platelet aggregation, inhibition of blood coagulation and inhibition of VSMC proliferation closely correlate with the amount of NO generated *in vitro*. At present, NONOates not used clinically, although they have been tested frequently in experimental models of cardiovascular disease. The primary cardiovascular focus for NONOates has been in the prevention of thrombosis and neointimal formation following vascular injury, an inevitable result of interventional cardiology techniques, such as balloon angioplasty, bypass grafting or placement of stents.

S-Nitrosothiols

The *S*-nitrosothiol class of NO donors covers a vast array of different compounds which contain a single chemical bond between a thiol (sulphydryl) group (R-SH) and the NO moiety. Biological activity of *S*-nitrosothiols is highly influenced by the molecular environment of the parent thiol**.** It is important to acknowledge that a vast number of factors are capable of releasing NO from *S*-nitrosothiols, including light, heat, transition metals,

thiols, superoxide and enzymes such as xanthine oxidase, superoxide dismutase, protein disulphide isomerase and various dehydrogenases. *S*-nitrosothiols have advantages over other classes of NO donors, such as the nitrates, as they have far less stringent metabolic requirements and this may be the reason that they do not induce tolerance with long-term use (Hanspal *et al.,* 2002). *S*-Nitrosothiols are not used clinically at present, but there are a large number of animal and clinical studies demonstrating their advantageous features, especially in the cardiovascular system.

Plants, herbs, and other natural resources

Several studies reported that some herbal medicines exert an effect on hemodynamic function in human. The effect of these natural plants and herbs are either directly or indirectly *via* their antioxidant properties. The use of such remedies is not free from serious adverse effect as well as adverse interactions with other drugs prescribed in acute coronary syndrome. The followings are the most common natural substances that exert certain pharmacological actions on the cardiovascular system.

Hawthorn

It also known as Crataegus laevigata or Crataegus monogyna, is an herb commonly found in Europe, western Asia, North America and North Africa. Modern medicinal extracts usually incorporate the leaves and flowers of the hawthorn tree, whereas traditional preparations use the fruit. Parts of the hawthorn tree contain flavonoids, which decrease the likelihood of blood vessel damage. Consuming hawthorn extract may improve angina patients' heart function and ability to exercise. It has been used for cardiac and circulatory disorders since the first century AD (Weihmayr and Ernst, 1996). Hawthorn berries, flowers and leaves of *Crataegus laevigata* (Poiret) have been used traditionally throughout Europe to treat cardiovascular diseases including hypertension, myocardial dysfunction, angina and tachycardia (Mills and Bone, 2000). In France, it is also used for insomnia and anxiety (British Herbal Medicine Association, 2003). Twentieth century German research revealed the efficacy of hawthorn for the treatment of cardiac failure (Pittler et al., 2003), and it is for this use that hawthorn is best known. The ethanolic extract of *Crataegus oxycantha* (COC) is traditionally used as a cardiotonic in China, India, and many European countries. COC contains oligomeric proanthocyanidins, flavonoids, and polyphenols which are well-known for their antioxidant properties (Svedstrom et al., 2002). Human subjects treated with COC extract after myocardial infarction have shown improvements in heart rate, reduction in blood pressure, and an increase in the left-ventricular ejection volume (Degenring et al., 2003; Walker et al., 2002). It has also been shown that an alcoholic extract of COC promoted improvement in tricarboxylic acid (TCA) cycle enzyme activity and protected the mitochondria against isoproteronol-induced cardiac injury (Jayalakshmi and Devaraj, 2004; Jayalakshmi et al., 2006). Recently COC extract may reduce the oxidative stress in the reperfused myocardium of isolated rat heart preparation, and play a significant role in the inhibition of apoptotic pathways (*via* upregulating the antiapoptotic proteins and downregulationg the proapoptotic proteins) to cardioprotection (Swaminathan et al.,2010). Hawthorn demonstrated numerous properties that may be beneficial in heart failure including anti-arrhythmic activities (Garjani et al., 2000; Chatterjee et al., 1997), and the ability to increase coronary blood flow (Occhiuto et al., 1986 (a,b), and cardiac output (Brixius et al., 1998). These effects may be mediated by inhibition of phosphodiesterase types

III and IV (Schussler et al., 1995), antioxidant activities (Bahorun et al., 2003) and anti-inflammatory effects (Chatterjee et al., 1997). A meta-analyses of clinical trials concluded that hawthorn may be a safe and effective treatment for chronic heart failure (Pittler et al., 2003). Crataegus extract (hawthorn), raises intracellular calcium, prolongs the action potential, and may improve exercise capacity in mild heart failure. It is widely used in Europe by heart failure patients as a "natural" remedy. Hawthorn contains no cardioactive glycosides. The principle active components are flavonoids: non-toxic phytochemicals that are widespread in fruit and vegetables and that have health benefits. It showed low toxicity in animal studies and minimal side effects in clinical trials (Mills and Bone, 2005). No drug–herb interaction has been reported in animal trials, and in a human study no interaction was observed between hawthorn and digoxin (Tankanow et al., 2003). Herbal practitioners use hawthorn for cardiovascular dysfunction, including mild manifestations in otherwise healthy people, without restriction on long-term use.

Cactus

Cactus (*Opuntia*) has been used for many years as a common vegetable and as medicine by the Native Americans and Mexicans (Cornett, 2000; Kay, 1996; Knishinsky, 1971; Tesoriere et al., 2004). Cactus contains a fruit known as cactus pear (*Opuntia ficus-indica*) and the plant is referred to as nopale (pad). Cactus pear contains pectin, carotenes, betalains, ascorbic acid, quercetina and quercetin derivatives all of which have antioxidant activity (Wang, 1988). In Chinese medicine, cactus fruit is considered a weak poison and used as medicine for treatment of inflammation and pain. It has also been used as a detoxification agent for snake bite**.** Opuntia ficus indica supplementation induced changes in heart rate variability in athletes in terms of increasing high and low frequency activities and reducing the heart rate (Schmitt et al., 2008). Cactus, also known as *Selenicereus grandiflorus*, may be effective for treating angina. Cactus can be used as a diuretic, cardiac stimulant and spinal and motor nerve stimulant. The principle action of cactus is upon the circular muscle fibers of the heart and arterioles, or tiny arteries, and that cactus is beneficial for cardiac incompetence, congestive heart failure, cardiac weakness, mitral insufficiency and angina. The succulent stem is the part of the cactus used for treating heart-related conditions. Overdose may cause arrhythmias, chest pain, pericarditis, confusion, headaches, vertigo and gastrointestinal symptoms.

***Ammi visnaga* (Khella, Khillah)**

Khella, also known as *Ammi visnaga*, may help treat angina. Khella is an African plant that contains spasm-relieving compounds, including khellin. In early studies, purified khellin demonstrated an ability to relieve angina-related symptoms, although it is unknown whether the whole herb would have similar effects. Khella improves blood supply to the myocardium, and increases efficiency of myocardial metabolism--two factors that could decrease angina-related pain or discomfort. Khella is often used to treat mild forms of angina, mild obstructive pulmonary disease and various problems of the urinary tract. As early as 1945 Anrep et al., demonstrated in physiological experiments that khellin is an effective coronary vasodilator in doses insufficient to cause any general fall in blood pressure. And in the preliminary clinical trial khellin has advantages over the nitrites and other reputed vasodilators in that it has a selective action on the coronary vessels, and effective doses need not, therefore, lower systemic blood pressure. Its action is slower but

more prolonged than that of the nitrites. It may be given in the form of continuous treatment to abolish or reduce the frequency and severity of anginal attacks, or to relieve individual severe attacks of pain.

***Vaccinium myrtillus* (Bilberry)**

It is a member of the Ericaceous family found in the mountains and forests of Europe and North America. *Vaccinium myrtillus* extracts (VME) contained 15 different anthocyanins which possess potent antioxidant properties, stabilize collagen fibers, promote collagen biosynthesis and inhibit platelet aggregation. In experimental animal studies VME have demonstrated to be of benefit in improving vascular tone, blood flow and vasoprotection (Lietti et al., 1976; Colantuoni et al., 1991). In isolated rat heart preparation bilberry extract increases the coronary flow, decreases the lactic dehydrogenase enzyme release during reperfusion and shorten the duration of arrhythmias (Žiberna et al., 2009).

Co-Enzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}) is the predominant human form of endogenous ubiquinone. It synthesized in the mitochondrial inner membrane. CoQ_{10} and comprised of a ubiquinone head group attached to a tail of 10 five-carbon isoprenoid units that anchors the molecule to the mitochondrial membranes. It acts in the in the mitochondrial respiratory chain as electrons carrier from complex I and II to complex III. It is antioxidant and plays a role in the regulation of membranes physiochemical properties and modulates the endothelial function. Supplemental CoQ_{10} is known to reduce lipid peroxidation (Sugiyama et al., 1980). Good evidence supports its use in congestive heart failure, type 2 diabetes, atherosclerosis, migraine, and Parkinson disease (Bonakdar and Guarnieri, 2005). Coenzyme Q10 levels are reduced by statin therapy because it shares the hepatic mevalonate synthetic pathway with cholesterol (Jula et al., 2002). Patients with hypertension have reduced serum levels of CoQ_{10} (Yamagami and Shibata, 1975). A meta-analysis of 12 clinical trials of 352 patients concluded that CoQ_{10} lowers blood pressure therefore it would seem acceptable to add CoQ_{10} to conventional anti-hypertensive therapy (Rosenfeldt et al., 2007). CoQ10 supports the production of energy in the heart and supports the health of the cardiac muscle.

***Zingiber officinale* (Ginger)** also strong antioxidants that support the health of the blood vessel and help protect the heart and vessels from the damage of free radicals. It reduces the levels of triglycerides and low-density lipoprotein-cholesterol, and inhibits the blood platelet aggregation. The pharmacologic cardiac effects of ginger are based on its activity as hypolipemic agent, anticoagulant and hypotensive.

***Allium sativum* (Garlic)**

The health benefits of garlic have been known since at least 1500 B.C. when ancient Chinese and Indians used it as a blood-thinning agent. Hippocrates, the father of modern medicine, used garlic to treat cervical cancer. Subsequent studies found efficacy of garlic as a cardioprotective. Numerous studies documented the hypoglycemic, antiatherogenic and antiatherosclerotic properties of garlic (Elkayam et al., 2003; Agarwal, 1996; Banerjee and Maulik, 2002). Garlic was also found to be beneficial against ischemic heart disease (Tyrrell. 1979). A significant number of clinical trials found garlic to lower total as well as LDL cholesterol (Kwon et al., 2003) and recently it is useful for lowering high blood pressure (McMahon and Vargas, 1993). Many of the physiological effects of garlic are attributed to

the volatile sulfur compounds like thiosulfinates, which are also responsible for its pungent aroma. Recently, the cardioprotective ability of garlic was attributed to s-allylcysteine (Perez-Severiano et al., 2004). Blood pressure reducing properties of garlic have been linked to its hydrogen sulphide production and allicin content – liberated from alliin and the enzyme alliinase which has angiotensin II inhibiting and vasodilating effects, as shown in animal and human cell studies. Bhatti et al (2008) demonstrated that garlic extract exaggerated the cardio protection offered by ischemic preconditioning and *per se* treatment with garlic extract also protects the myocardium against ischemia reperfusion induced cardiac injury. This effect is probably attributed to the inhibition of platelet aggregation, oxidative stress or to fibrinolytic properties.

Arjun (*Terminalia arjuna*) has demonstrated great promise for improving heart function and reducing angina. Arjun (*Terminalia arjuna*) is a tree common in Central and South India. Its bark has a long history of use in Ayurvedic medicine (the traditional medicine of India) for the treatment of heart problems, such as angina. Research demonstrates that arjun may in fact be very effective in reducing angina and improving heart function. A one-week, double-blind, placebo-controlled crossover trial of 58 people evaluated the effectiveness of arjun for angina by comparing it against placebo, isosorbide mononitrate (Bharani et al., 2002). The results indicated that the herb reduced anginal episodes and increased exercise capacity. A subsequent 3-month study compared the effectiveness of arjun against placebo in 40 people with a recent heart attack (Dwivedi et al., 2005). All participants in this study suffered from ischemic mitral regurgitation. The results showed that use of the herb improved heart function and reduced angina symptoms. Another study found benefits with an Ayurvedic herbal combination containing arjun (Antani et al., 1990).

Coleus forskohlii

Coleus forskohlii (CF) is a plant native to India. Since ancient times, plants of the *Coleus* species have been used as an herbal medicine to treat various disorders of the cardiovascular, respiratory, gastrointestinal, and central nervous systems. Forskolin has been isolated from the roots of the India-based *Coleus Forskohlii*. Forskolin is a diterpene that acts directly on adenylate cyclase leading to generate cAMP from ATP in the cell. cAMP regulates the body's thermogenic response to food, increases the body's basal metabolic rate, and increases utilization of body fat and stimulates lipolysis. cAMP stimulates the cardiac muscle and dilates the large blood vessels.

Vitamins

Ascorbic acid

It has a favorable redox couple that protects vitamin E and glutathione from oxidation. In clinical studies, ascorbic acid supplementation improves nitric oxide-dependent vasodilation in human subjects with coronary artery disease, hypertension, hypercholesterolemia, and diabetes mellitus (Taddei et al., 1998).

Vitamin E (alpha-tocopherol)

Vitamin E is a lipid soluble, chain-breaking radical scavenger family of eight related tocopherols and tocotrienols, and is considered the most important antioxidant in cell membranes (Herrera and Barbas, 2001). Of the various forms, alpha-tocopherol has the

highest bioavailability and protects cell membranes against oxidation by reacting with lipid radicals produced during lipid peroxidation chain reactions (Herrera and Barbas, 2001). Despite an initial small study demonstrating a therapeutic benefit of vitamin E on reducing non-fatal myocardial infarction, more recent, placebo-controlled, large-scale trials of antioxidants have been disappointing and have found no clinically benefical effects of long term vitamin E supplementation (Brown et al., 2001; Lonn et al., 2005).

Vitamin D

Recently data demonstrated that vitamin D insufficiency/deficiency is significantly associated with all-cause mortality, at least in the American population. The NHANES III database clearly shows: 1) an increase in adjusted all-cause mortality as the serum 25-hydroxy calciferol (OHD) level falls to less than 30 ng/ml, especially in women; and 2) peak protection from death with a 25OHD level in the 35–40 ng/ml range. In fact, most of the increase in all-cause mortality can be attributed to cardiovascular disease deaths in this population. The prevalence of coronary artery disease, heart failure, and peripheral artery disease is significantly increased in a stepwise fashion as the serum 25OHD level drops to less than 30 and then 20 ng/ml (Kim et al., 2008).

Omega-3 polyunsaturated fatty acids

As early as 1944, Sinclair described the rarity of CHD in Greenland Eskimos despite their consumption of diet high in fat and cholesterol (Sinclair, 1953). Sinclair observed that the Eskimos had a tendency to bruise and to bleed easily, and subsequently Bang and Dyerberg demonstrated that the Eskimos had reduced platelet counts (50 000–80 000/mm^3 lower) and decreased platelet aggregation, resulting in prolonged bleeding times. Bang and Dyerberg (1972;1980) and Dyerberg et al.,(1975) in their study comparing Greenland Eskimos and Danish controls, found, as expected, that the Eskimos, who eat about 500 g of fish per person per day (compared with 10–20 g/d in Westernized societies), had considerably higher levels of omega-3 fatty acids and lower levels of arachidonic acid in plasma, platelets, and red blood cell membranes. Interestingly, in addition to reduced rates of coronary heart disease, the Greenland Eskimos also had a more favorable lipid profile and low levels of blood pressure. Coronary heart disease is also less prevalent in Japan, despite higher prevalence of hypertension and smoking, which may be partly due to the Japanese population's traditionally high consumption of fish compared to populations in the Western world. Even within Japan, the Japanese islanders, who eat three times more fish compared to the mainland population, have lower rates of hypertension, coronary heart disease, and all-cause mortality (Lavie et al., 1987; Lavie and Milani, 1996). The mechanism of actions of Omega-3 PUFA includes:

1. Significant reduction of triglycerides.
2. Antiarrhythmic effect. The level of long-chain n-3 fatty acids was significantly and inversely related to the risk of sudden coronary death
3. Significant reduction in mean blood pressure, systemic vascular resistance,
4. Omega-3 fatty acids may confer cardioprotection in part by improving autonomic sympathovagal balance.

5. Very high doses of omega-3 fatty acids (i.e. 8 g/d) provide anti-inflammatory effects. The anti-inflammatory properties may also play an important role in stabilization of unstable plaque in patients with ACS (Lee et al., 2008; Alaswad et al., 2002). Eicosapentaenoic acid competes with arachidonic acid for the cyclooxygenase, leading to decrease the synthesis of thromboxane A_2, which is a strong platelet agonist, and increases the synthesis of thromboxane A_3, which is relatively inactive, so the net effect of high doses of omega-3 fatty acids is platelet inhibition.

Observational studies have also reported inverse associations of cardiovascular disease with dietary intake or plasma concentrations of omega 3 fatty acids (mainly eicosapentanoic acid and docosahexaenoic acid), suggesting that supplementation with omega 3 fatty acids might exert protective effects on cardiovascular disease (Bucher et al., 2002; Kromhout, 1985). These fatty acids have been shown to have beneficial effects on several cardiovascular risk factors—including blood pressure, plasma triglyceride concentration, and markers of thrombosis and inflammation—and may also have antiarrhythmic effects (Wang et al., 2006). Although some trials involving patients with a history of cardiovascular diseases or with high levels of cardiovascular risk factors have reported positive effects of omega 3 fatty acids on cardiovascular events, other trials have reported no effects on arrhythmia or mortality (Brouwer et al., 2009; Burr et al., 2003).

5. Cardiovascular adverse effects of herbal remedies

Several natural remedies interact with known pharmacological agents that indicated in acute coronary syndrome. Among these:

Aloe vera may cause hypokalemia and inducing digitalis toxicity and cardiac arrhythmias in patients with heart failure

Butcher's broom is mainly indicated for circulatory disorder and it reduced the effect of α-adrenoceptor effects in patients with hypertension and heart failure

Capsicum which is indicated for shingles, trigeminal and diabetic neuralgia may elevate the blood pressure in patients treated with monoamine oxidase inhibitors

Fumitory used as hypotensive agent and enhances the effects of β-adrenoceptors, calcium entry blockers and glycosides.

Ginseng causes high blood pressure

Gossypol, a male contraceptive increases the effect of diuretics and causes hypokalemia

Grape fruit juice augments the cardiac effects of calcium entry blockers

Hawthorn potentiates the actions of glycosides and nitrite

Irish moss potentiates the antihypertensives effects

Kelp increases the effects of antihypertensives

Khella increases the cardiac actions of calcium entry blockers

Licorice increases the blood pressure and causes hypokelemia which potentiates the

Lily of the valley increases effects of β-aderenoceptor, calcium entry blockers, digitalis and quinidine

Ma-huang (ephedra) increases heart rate and blood pressure

Oleander increases the effect of angiotensin converting enzyme inhibitors, antiarrhythmics, β-adrenoceptor blockers, calcium entry blockers and cardiac glycosides.

St. John's wort induces arrhythmias, heart block, hyperkalemia and death

Strophanthus increases heart rate and blood pressure in patients treated ith monoamine oxidase inhibitors

Yohimbine increases heart rate and induces changes in blood pressure

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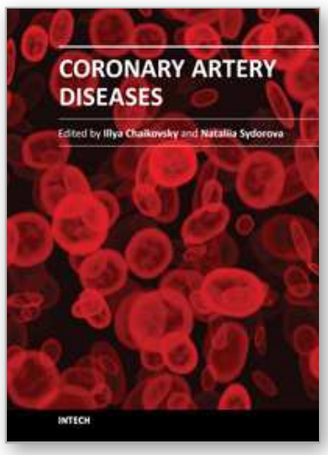

Coronary Artery Diseases
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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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