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Choosing the Most Appropriate Treatment for Stable Angina

Safety Considerations

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Contents

Abstract

The goals of stable angina pectoris treatment are: (i) symptom relief and increase in angina-free walking time; and (ii) reduction of mortality and adverse outcome. Strategies used for plaque stabilisation resulting in a reduction in cardiovascular mortality and morbidity are: smoking cessation; aspirin (acetylsalicylic acid); blood pressure control; lipid lowering agents when low density lipoprotein cholesterol is elevated despite dietary therapy; coronary bypass surgery in patients with left main stem disease or triple vessel coronary disease and diminished left ventricular function; and use of estrogen in postmenopausal women.

For symptom relief and to increase angina-free walking time, long acting nitrates, β-blockers, calcium antagonists and potassium channel openers can be used. Drugs from these 3 classes are all effective when used optimally and choice of initial therapy should consider the presence of concomitant disease and under-

lying left ventricular function. However, none of the long acting nitrates provide continuous prophylaxis because nitrate tolerance develops during long term therapy.

In patients with uncomplicated stable angina, nitrates, β-blockers and calcium antagonists are all effective. Intermittent nitrate therapy is not associated with tolerance, but headache is a common adverse effect and the patient is unprotected at night and in the early hours of the morning. Concomitant treatment with a β-blocker may be beneficial if the patient experiences withdrawal or early morning angina. For patients with stable angina and hypertension, therapy with a β-blocker or a calcium antagonist rather than nitrate is indicated. β-Blockers are preferred in patients who have had a myocardial infarction, or in those with a history of supraventricular tachyarrhythmias. β-Blockers may produce excessive slowing of the heart rate, fatigue and bronchospasm in susceptible patients. Calcium antagonists are indicated as initial therapy when β-blockers are either not tolerated or contraindicated. β-Blockers and nondihydropyridine calcium antagonists should not be used in patients with sinus bradycardia and those with greater than first degree atrioventricular (AV) block because of the possibility of further slowing of heart rate and/or the development of high grade AV block.

When monotherapy with one class is ineffective or associated with adverse effects, the patient should be switched to another class rather than given an additional drug. Optimal monotherapy is often as effective as combination therapy. If maximum monotherapy is only partially effective, a combination therapy which is not additive in terms of adverse effects should be chosen. Triple therapy may be deleterious and no more effective than dual therapy.

The term stable angina pectoris refers to the predictable occurrence of pressure or a choking sensation in the chest and adjacent areas in association with physical or emotional stress caused by myocardial ischaemia, and prompt relief of these symptoms with rest or sublingual nitroglycerin (glyceryl trinitrate). The prerequisite is a haemodynamically significantly diseased coronary arterial bed that produces myocardial ischaemia and angina pectoris because of the inability of coronary blood flow to meet increased myocardial oxygen demand. In addition, more luminal narrowing at the stenotic site during stress may further compromise myocardial blood supply.[1] Plaque fissuring with superimposed platelet deposition and thrombosis in haemodynamically insignificant coronary lesions is responsible for unstable angina, myocardial infarction (MI) and sudden cardiac death, while severe atherosclerotic narrowing is responsible for stable angina pectoris (fig. 1). Patients with stable angina who, in addition to having a severe obstructive lesion, also have widespread non-obstructive coronary narrowing are prone to adverse outcomes such as unstable angina, MI or ischaemic sudden death.

The goals of treating angina pectoris are: (i) relief of symptoms and increase in angina-free walking time by increasing myocardial oxygen supply and/or decreasing myocardial oxygen consumption; (ii) reduction of cardiac mortality and incidence of MI by stabilisation of atherosclerotic plaques; and (iii) preservation or improvement of left ventricular function.

In this review, drug therapies available to achieve the above goals are discussed from the specific viewpoint of their safety profiles.

1. Pathophysiology of Stable Angina Pectoris

Angina pectoris occurs as a consequence of myocardial ischaemia produced by an imbalance between myocardial oxygen supply and demand

caused by a flow-limiting obstructive lesion of 1 or more coronary arteries. The exact mechanism which triggers anginal pain is unknown, although the underlying lesion is, invariably, a >70% narrowing of 1 or more coronary arteries. The stenotic lesion limits myocardial blood flow during periods of increased demand, e.g. during exercise or emotional stress. During certain pathological states such as thyrotoxicosis, supraventricular tachycardia, aortic stenosis, hypertension or severe anaemia, angina may occur at rest or at a lower level of physical activity, and in these patients the focus of treatment should be correction of the pathophysiological conditions in addition to anti-anginal therapy if needed.

In patients with angina pectoris, endothelial dysfunction also produces myocardial ischaemia by producing a paradoxical constriction of epicardial stenotic atherosclerotic coronary arteries during exercise or mental stress, and is a target for therapy.[1,2] Myocardial ischaemia without angina (silent ischaemia) is a far more frequent manifestation of coronary artery disease, but therapy directed at silent ischaemia is still controversial and has been reviewed by Roberts et al.[3]

In rare cases, patients with stable angina may have non-occlusive coronary artery disease. In these patients, an increased coronary arteriolar resistance, microvascular disease or decreased subendocardial perfusion secondary to raised left ventricular filling pressure may be the mechanism for myocardial ischaemia and anginal pain.[4]

2. Natural History and Prognosis

The annual death rate of patients with stable angina pectoris is 1.6 to 3.2%.[5] The principal determinants of prognosis are left ventricular systolic function, extent of coronary artery disease (CAD), exercise duration or effort tolerance and comorbid illness.[6] The ability to complete stage 2 of a standard Bruce protocol and normal left ventricular systolic function denote a relatively good prognosis. The long term mortality and incidence of MI in patients with stable angina and 1, 2 or 3 vessel CAD and normal left ventricular function are similar

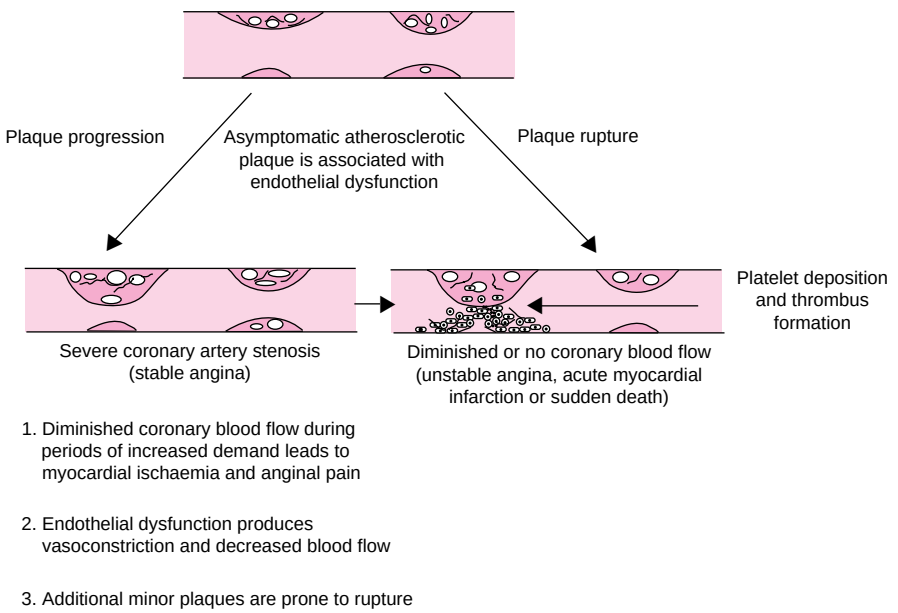

Fig. 1. Diagrammatic representation of asymptomatic coronary lesions and progression of lesions in patients with stable angina pectoris and in patients presenting with acute coronary syndromes.

following coronary artery bypass graft (CABG) surgery or drug therapy.[7-9] Whether percutaneous transluminal coronary angioplasty (PTCA) improves survival in patients with stable angina pectoris more than drug therapy remains to be studied.

3. Treating the Patient with Stable Angina

Once the diagnosis of stable angina is made, comorbid conditions which could aggravate angina must be sought and treated. In all patients, life style changes, especially smoking cessation and risk factor modification, must be stressed. The 3 options of treating patients with stable angina are drug therapy, PTCA and CABG[10] surgery.

Therapy should be individualised and consideration should be given to the risks as well as benefits of each therapeutic option with regards to symptom relief and longevity. Coronary angiography is not indicated in all patients with stable angina. It is indicated for patients who remain symptomatic despite optimal drug therapy. It may also be performed in patients with an early positive exercise test and in those with poor left ventricular function to exclude left main or triple vessel disease and to assess suitability of coronary artery anatomy for revascularisation procedures.

CABG surgery is the preferred modality of treatment in patients with left main disease or 3 vessel disease and decreased left ventricular function. In all other patients long term mortality and incidence of MI is similar during drug therapy or after CABG surgery.[7-9] Drug therapy is usually effective in decreasing anginal episodes, increasing effort tolerance and enabling patients to lead a productive and enjoyable lifestyle. Patients who either do not tolerate drug therapy or who continue to have symptoms despite optimal drug therapy should be considered for PTCA or CABG surgery.

Plaque stabilisation via risk factor modification, lipid lowering therapy, estrogen supplementation and possibly ACE inhibitor therapy should be considered in all suitable patients even when the anginal symptoms are controlled.

4. Drug Therapy for Plaque Stabilisation, Prevention of Myocardial Infarction and Mortality Reduction

4.1 Smoking Cessation Therapies

Cigarette smoking is the leading preventable cause of death among men and women in the US and each year smoking is the cause of 30% of coronary heart disease deaths.[11] A strong dose response relationship has been demonstrated between number of cigarettes smoked and fatal coronary disease.[12] Encouragingly, the percentage of smokers in the US has declined from 1965 to 1990. Stopping smoking reduces the risk of coronary heart disease by 50% in 1 year and after 5 to 10 years reduces coronary mortality risk to that of a nonsmoker.[13]

While the benefits of smoking cessation are generally well established, the safety of nicotine replacement therapy for patients with CAD has been questioned. The main concern has been worsening of coronary disease symptomatology and increased risk of MI with the use of nicotine replacement therapies, especially in patients who continue to smoke while receiving therapy. This safety issue is of particular concern since worsening angina has been reported in patients with CAD who are most likely to benefit from smoking cessation.

The Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease[14] studied the safety of transdermal nicotine in patients with CAD. Smoking cessation was achieved in 36% of treated patients compared with 22% of patients receiving placebo. Transdermal nicotine was well tolerated by patients with CAD and chronic stable angina in this 5 week trial,[14] and there was no significant difference in angina frequency or in the number of episodes of ST segment depression on 24 hour ECG monitoring between patients receiving transdermal nicotine and placebo patches. The safety of this therapy was noted even in patients who continued to smoke intermittently. Although longer duration studies are required, it appears that the benefits of nicotine

replacement therapy outweigh the risks in patients with CAD.

4.2 Aspirin (Acetylsalicylic Acid)

4.2.1 General Considerations

Aspirin (acetylsalicylic acid) reduces mortality and morbidity in patients with acute coronary syndromes. Aspirin, by irreversibly inhibiting cyclooxygenase in the platelets, halts the production of proaggregatory thromboxane A_2 and thus acts as an antithrombotic agent.[15] However, aspirin-induced vascular endothelium cyclo-oxygenase inhibition results in a decreased formation of the anti-aggregatory substance prostacyclin. The vascular endothelium can, however, resynthesise cyclo-oxygenase while the platelet cannot, thus, aspirin has a net antithrombotic effect, especially at lower doses.[16]

In the Swedish Angina Pectoris Aspirin Trial,[17] which enrolled over 2000 patients with chronic stable angina, daily use of aspirin decreased the incidence of acute MI and sudden death by 34% with an absolute reduction of 12 sudden deaths for every 1000 patients treated over a median period of 50 months.[17] In this study, low dose aspirin (80 mg/day) was given in addition to sotalol, a β-blocker, and was compared with sotalol treatment alone. In another smaller study, the risk of a first MI in men with stable angina pectoris was reduced by 8.7% when patients were treated with aspirin.[18] Studies on concomitant use of aspirin with other antianginal agents have not been performed. Recently, the US Food and Drug Administration (FDA) approved daily use of low dose aspirin for mortality and morbidity reduction in patients with stable angina.

4.2.2 Safety Concerns

Adverse Effects

The main adverse effects of aspirin therapy are gastrointestinal. Nausea, vomiting and dyspepsia occur in about 40% of patients taking aspirin 150 to 300 mg/day compared with 30% of patients receiving placebo.[15,19] These adverse effects are more pronounced at higher dosages but may occur at dosages as low as 30 mg/day. Gastrointestinal bleeding occurs in about 5% of patients.[15,19,20] Very low dosages of 30 mg/day greatly decrease the risk of bleeding.[19] The use of buffered aspirin or enteric coated aspirin decreases gastrointestinal symptoms but not the risk of bleeding. A slight increase in the risk of haemorrhagic stroke has been found in some studies[18,20] and hence the FDA has warned against self-administration.[15] In addition, low dose aspirin may aggravate gout. However, clearly the benefits of aspirin in preventing vascular events or death far outweigh the low risk of toxicity.

Drug Interactions

The risk of bleeding is increased with concurrent administration of warfarin, corticosteroids, other nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol (ethanol). In patients taking warfarin with an international normalised ratio (INR) between 1.8 to 2.5 the addition of aspirin appears to be as well tolerated as aspirin therapy alone (as seen in the ongoing Veterans Affairs Cooperative Study #387: Warfarin and Aspirin in Secondary Prevention Study), but the clinical benefit of this combination remains unknown.

Aspirin decreases the efficacy of uricosuric drugs. In survivors of acute MI, ACE inhibitors improve outcome when given concomitantly with aspirin. However, there is some concern that aspirin may offset the protective effect of ACE inhibitors in patients with congestive heart failure.[21] In the Studies of Left Ventricular Dysfunction (SOLVD),[22] retrospective analysis revealed that enalapril did not improve the outcome of patients with heart failure who were also taking aspirin. The significance of this finding is not completely clear, but hopefully the Warfarin Aspirin Heart Failure trial will help to clarify this controversial issue.[23]

4.3 Ticlopidine

There are no outcome studies with ticlopidine in patients with stable angina pectoris. Ticlopidine inhibits the activation of the glycoprotein IIb/IIIa receptor. It has been used as an alternative to aspirin in patients intolerant of or allergic to aspirin.

However, in the absence of outcome data its routine use in patients with stable angina cannot be justified. The main safety considerations with ticlopidine are neutropenia (2.4%), which can be fatal, and minor bleeding, skin rash, liver toxicity and diarrhoea.[20] The neutropenia is, however, reversible if recognised early and occurs in the first 3 months of therapy.[24] Clopidogrel, which has properties similar to ticlopidine, but does not cause leucopenia, has recently been approved by the US FDA and may be a suitable alternative in patients intolerant to aspirin.[20]

4.4 Lipid Lowering Therapy

The atherogenic effects of serum lipids have long been known.[25] A recent surge in the interest in lipid lowering therapy has occurred for the following reasons:

- There is a better understanding of the role of the vascular endothelium in the production of myocardial ischaemia.
- Atheroma regression trials have shown clinical benefits.[26]
- The results of the Scandinavian Simvastatin Survival Study (4S)[27] showed a significant decrease in both cardiovascular mortality and morbidity and all cause mortality with effective lipid lowering therapy.
- Many of the safety concerns raised from prior studies have now been accepted as largely unfounded.[28]

Effective lipid lowering results in plaque stabilisation, regression of coronary lesions and, in some studies, reduction in total and cardiovascular mortality, in the need for revascularisation and in episodes of ambulatory ischaemia in patients with CAD.[27-34] In the 4S study 4444 patients with known coronary heart disease (angina or MI) were randomised to receive simvastatin or placebo.[27] During the 5.4 years median follow up period, simvastatin therapy produced a 38% reduction in low density lipoprotein (LDL) cholesterol and a 30% reduction in all cause mortality, a 42% decrease in fatal coronary events, and a 37% reduction in need for revascularisation compared with placebo treatment.

4.4.1 Bile Acid Sequestrants

Both cholestyramine and colestipol have an excellent safety profile and have been shown to decrease cardiac mortality, but not overall mortality.[30] The major adverse effects of these agents are constipation and flatulence and, at high doses, steatorrhoea.[20,35] These agents can interfere with the absorption of several drugs including digoxin, warfarin, thiazides and phytomenadione (vitamin K).[20,35] These drugs need to be taken 1 hour before or 4 hours after the sequestrant.[35] The increase in triglyceride levels seen with these agents may be a problem in patients with diabetes.

4.4.2 Nicotinic Acid (Niacin)

Nicotinic acid (niacin) is the cheapest compound available for lipid lowering and it is an effective lipid lowering drug. It was the first drug to show a decrease in 1 year mortality in patients with CAD.[31] The primary problem with this drug is the numerous subjective adverse effects associated with its use; these include flushing, dizziness and palpitations.[20] Treatment with aspirin 325mg 30 minutes before taking nicotinic acid or taking the agent with meals may decrease these symptoms. Long acting preparations reduce subjective symptoms but may be linked to hepatotoxicity. Diabetes, pregnancy, gout and peptic ulcer disease are known contraindications to this drug.[20]

4.4.3 HMG CoA Reductase Inhibitors

HMG CoA reductase inhibitors ('statins') are highly effective in reducing total and LDL cholesterol levels. Their long term safety and efficacy in several thousand patients for up to 5 years of treatment is well established.[36-40] Despite a minor decrease of 2% in angiographic narrowing of severe stenotic lesions and the progression of CAD in angiographic studies with statins, these drugs reduce mortality and morbidity by 30 to 50%. This is believed to be caused by stabilisation of plaques laden with large lipid stores.

Class adverse effects are few and include dose dependent liver damage that occurs with an inci-

dence of 0.1 to 1.5%.[20,35] There is little difference in the adverse effect profile between drugs of this class. Myopathy is rare and occurs especially during concomitant therapy with fibrates, nicotinic acid, azole antifungals or during cyclosporin therapy in transplant patients.[40] Fluvastatin has the least association with myopathy and this drug can be coprescribed with nicotinic acid.[20] Rhabdomyolysis can occur with concomitant use of simvastatin or lovastatin and mibefradil, and concomitant use of these agents is therefore contraindicated.[20]

Mild gastrointestinal problems occur with all these agents and at times are severe enough to necessitate discontinuation of the drug.[35,39] Pregnancy is a contraindication to therapy with these agents. Headache appears to be more common with pravastatin and paraesthesia may be related to simvastatin use.[41] Alopecia areata has been reported with pravastatin treatment (unpublished observation).

4.4.4 Fibrates

Fibrates are not as effective in lowering cholesterol when compared with the statins or nicotinic acid. They are especially effective in patients with elevated triglyceride levels and in patients with type 3 hyperlipidaemia. In the Helsinki Heart study, gemfibrozil was found to decrease coronary events, but not to reduce the all cause mortality rate as there was an increase in intracranial haemorrhage and violent deaths associated with use of the agent.[42]

Few adverse effects are associated with fibrates; however, the agents are associated with a slight increase in the need for cataract surgery.[42] There is also a theoretical risk of increased gall stone formation. Significant drug interactions include potentiation of warfarin effect and the risk of myopathy and rhabdomyolysis when used with simvastatin.[20,39]

4.4.5 Probucol

Probucol decreases both LDL and high density lipoprotein (HDL) cholesterol levels. Despite its adverse effect on HDL levels there is renewed interest in this drug because it has prominent antioxidant effects.[43] However, the most serious adverse effect is QT prolongation with a threat of torsade de pointes and sudden death. In addition, pregnancy is contraindicated for up to 6 months after discontinuation of the drug.

4.4.6 Long Term Safety Considerations

Recent major trials with the statin group of drugs have clearly shown the safety of lipid lowering.[38] Earlier studies[42] showed a possible relationship between lipid lowering and increased cancer risk and increased rate of violent deaths as well as lenticular opacification. No such relationships have been found in recent large studies with statins.[38] Previously observed adverse effects were probably related to the particular agent, gemfibrozil, used in those studies.

In summary, lipid lowering therapy, especially with statins, is well tolerated and plays a pivotal role in the management of patients with angina pectoris.

4.5 Estrogen Supplementation

4.5.1 General Considerations

The incidence of CAD in women substantially increases after menopause, suggesting the loss of a protective effect of estrogen. Women with premature menopause who do not take estrogen supplementation are twice as likely to have CAD compared with premenopausal women of the same age.[44] There is compelling evidence that estrogen supplementation reduces both the risk of CAD[45] and mortality in postmenopausal women.[46]

Estrogen affects CAD via its beneficial effects on the lipid profile and endothelial dysfunction.[47,48] Estrogens reduce LDL levels and increase HDL levels by 15%, and produce greater reductions of intracellular LDL cholesterol levels.[49] An inhibition of LDL oxidation and a reversal of endothelial mediated arteriolar vasoconstriction has been reported. In a study evaluating 90 postmenopausal women with chest pain, women who were receiving estrogen supplementation had higher HDL levels and an 87% reduction in the prevalence of coronary disease at angiography.[50] In this study, the lack of estrogen supplementation

was the strongest predictor of CAD by multiple regression analysis. In the Nurses' Health Study[51] involving 48 470 postmenopausal women, there was a significant decrease in both cardiovascular as well as all cause mortality in women who were current or former users of estrogen supplementation, when other risk factors were adjusted for. A review of 32 epidemiological studies showed a 44% reduction in the risk of CAD in postmenopausal women receiving estrogen replacement therapy.[52] Several other cross-sectional studies have used coronary angiography to confirm the beneficial role of estrogen supplementation on endothelial function.[53-55] This benefit of estrogen supplementation on decreasing coronary disease is in addition to its effect on reducing osteoporosis and menopausal symptoms.

4.5.2 Safety Considerations

The overall health benefit of estrogen replacement therapy, however, is unclear. The main safety concerns include endometrial cancer and the possible influence of estrogen on the development of breast cancer. The effect of estrogen plus progesterone on the risk of breast cancer was evaluated in the Nurses' Health Study cohort.[56] The relative risk of breast cancer was 1.3 for postmenopausal women taking estrogen and 1.4 for postmenopausal women taking estrogen and progesterone, compared with postmenopausal women not taking hormone replacement therapy. In older women who had taken hormone replacement therapy for more than 5 years, the relative risk was 1.7. In the Postmenopausal Estrogen/Progesterone Interventions (PEPI) trial[56] unopposed estrogen was best at raising HDL cholesterol levels, but was associated with a high rate of endometrial hyperplasia.

Gall bladder disease and prothrombotic risk are other important safety concerns with long term estrogen use. There is a clear synergy between high dose contraceptives and cigarette smoking in causing MI.[57-59] However, it is felt that the lower doses used in supplementation will not show such adverse effects.[20,58]

If estrogen does, in fact, reduce the risk of CAD by 50% then it is unlikely that this benefit would be significantly affected by the known risks. Unfortunately, the large majority of published data suggesting such benefits are observational studies with the numerous biases inherent in observational studies of medication. The fact that women taking estrogen in these studies are more likely to be of lower cardiac risk profile may significantly overestimate the benefit.[51,60-64] Only prospective, double-blind, randomised trials can answer the question of true benefits versus risks. Two such trials under way are the Heart Estrogen/Progestin Replacement Study (HERS) which is investigating the efficacy of supplementation in women with known CAD, and a larger study designed to test primary prevention under the auspices of the Women's Health Initiative. Presently, risk-benefit analysis is left up to the individual physician to judge on a case by case basis.[50,65,66]

4.6 ACE Inhibitors

4.6.1 General Considerations

Although initially introduced as therapy for hypertension, ACE inhibitors have many important effects in other areas of cardiovascular medicine. The role of these agents in congestive heart failure is well established. An unexplained observation from the major trials involving ACE inhibitors [Survival and Ventricular Enlargement (SAVE) trial[67] and SOLVD[22]] was the decrease in CAD-related outcomes with their long term use. These observations have generated intense research activity into the role of ACE inhibitors in CAD, including stable angina pectoris.[68,69]

There is an increasing awareness of the central role of the vascular endothelium in various cardiovascular disorders. ACE is a key element of the renin-angiotensin system and is mainly found in the vascular endothelium. By targeting this site, ACE inhibitors can inhibit both the endocrine and paracrine actions of angiotensin II.

The deleterious effects of angiotensin II include a direct positive inotropy and chronotropy on the heart, and it is also a growth factor implicated in the pathogenesis of ventricular hypertrophy and atherogenesis.[70,71] Of interest is the reported as-

sociation between a deletion polymorphism in the gene encoding for ACE and enhanced atherogenesis.

Currently available ACE inhibitors are classed according to their pharmacokinetics. Class 1 is represented by captopril which, by itself, is active and also has active metabolites. Class 2 agents consist of prodrugs that are active only after hepatic metabolism. Included in this class are enalapril, fosinopril, ramipril, benazepril and quinapril. The only class 3 agent is lisinopril, which is not metabolised and is excreted unchanged in the urine.

Several other studies[68] are looking at surrogate outcome measures such as carotid atherosclerosis or endothelial function in response to ACE inhibitor therapy in patients with CAD and preserved left ventricular function. In the Trial on Reversing Endothelial Dysfunction (TREND), quinapril is being evaluated in terms of its ability to decrease endothelial dependent vasoconstriction. In the Prevention of Atherosclerotic Risk and Thrombosis (PART 2) trial, the effect of ramipril on B mode ultrasound measures of carotid atherosclerosis in patients with prior atherothrombotic disease is being evaluated.

4.6.2 Safety Considerations

Adverse effects

Adverse effects common to all ACE inhibitors include cough, hypotension, renal effects, angioedema and hyperkalaemia.

Cough is one of the most common and troublesome problems with ACE inhibitors. It is probably caused by an increased sensitivity to the cough reflex, and prostaglandins and bradykinin are thought to be involved. Decreasing the dose of the ACE inhibitor and adding both nifedipine and clonidine have been suggested as methods of decreasing the severity of cough while continuing the agent.[20] However, changing treatment to an angiotensin II receptor blocker has the theoretical advantage of similar benefit without the risk of cough.

Patients most at risk for hypotension (those patients with poor ventricular function, low serum sodium levels, patients taking diuretics, etc.) are often also those who could benefit the most from ACE inhibitor treatment. It should be noted that there is no absolute blood pressure value at which therapy needs be modified. It is orthostatic symptoms that guide safe and effective therapy.

In addition to hypotension affecting renal function, bilateral renal artery stenosis is a contraindication to ACE inhibitor therapy. Of note is the fact that mild elevation in serum creatinine levels is to be expected at initiation of therapy and its occurrence should not be a reason to discontinue therapy.

The incidence of angioedema, a potentially life threatening complication, is about 0.1%.[20] This adverse effect can be treated with subcutaneous epinephrine (adrenaline). Potassium sparing diuretics and potassium supplements should be discontinued at initiation of ACE therapy because dangerous hyperkalaemia may ensue.[20]

Finally, ACE inhibitors are absolutely contraindicated in pregnancy since the agents have teratogenic effects that occur mainly in the second and third trimesters.[20]

Drug Interactions

In general, adverse drug interactions with the ACE inhibitors are uncommon and are usually the result of additive physiological effects.

In addition to the risk of hyperkalaemia with potassium sparing diuretics there are several beneficial interactions with diuretics. Even small doses of ACE inhibitors can significantly potentiate furosemide (frusemide) diuresis. ACE inhibitors oppose vasoconstriction associated with renin release from diuresis.

Serious hypotension can occur from the additive hypotensive effects of ACE inhibitors with other vasodilators. In addition, there may be an added risk of immune dysfunction when captopril is combined with hydralazine.

NSAIDs, especially indomethacin and high dose aspirin, may lessen ACE inhibitor effectiveness. This effect may be related to the role of bradykinin and prostaglandins in vasodilation.[69,70]

In summary, the potential benefits from ACE inhibition in CAD are both tantalising and promising. However, the safety concerns with ACE inhi-

bition in this setting are no different from those experienced with their use in other conditions. Care is needed to avoid adverse additive effects on haemodynamics in patients with angina who are receiving nitrates or calcium antagonists. As more and more therapies that reduce cardiovascular risk are uncovered, the incremental gain with ACE inhibition in addition to other life saving and symptom decreasing modalities in comparison to the incremental risk needs clarification.

4.7 Antioxidants

Increased intake of dietary antioxidants may protect against CAD hypothetically by preventing the oxidation of LDL cholesterol. Two large studies support the protective role of tocopherol (vitamin E).[72,73] The protective role of betacarotene may be significant in smokers.[72,74] The Cambridge Heart Anti-Oxidant Study (CHAOS)[75] confirmed the effectiveness of high dose tocopherol in CAD. This trial was a secondary prevention trial in 2200 patients with angiographically documented CAD. High dose tocopherol (800IU), but not low dose tocopherol (400IU), reduced nonfatal MI by 77% with a median duration of follow up of 510 days. The Alpha Tocopherol Beta Carotene (ATBC) trial,[76] however, did not support the CHAOS results.

The long term safety issues are poorly characterised. There was an increased risk of lung cancer noted in the Beta-Carotene and Retinol Efficacy Trial (CARET).[77] However, other studies have shown possible benefit in cancer reduction.[77,78]

5. Drugs Primarily Directed at Symptoms

5.1 Nitrates

Organic nitrates have a well established role in the drug therapy of angina pectoris. Several well designed trials have shown symptom improvement during exercise testing in patients with angina pectoris.[79-82] There is an increase in time to onset of chest pain and exercise duration and a decrease in ischaemic ST depression with nitrate use. These beneficial effects have been demonstrated using several nitrate formulations and administration protocols. Nitroglycerin remains the mainstay for treating acute attacks of angina pectoris. There is a reproducible alleviation of chest pain 2 to 6 minutes after administration of sublingual nitroglycerin. Nitrates can produce their vasodilatory effects in the absence of endothelium.[83] Nitrates are metabolised to nitric oxide, which in turn stimulates production of cyclic guanosine monophosphates. This inhibits calcium influx and enhances calcium effluxes from the contractile cells, thus causing vascular smooth muscle relaxation and vasodilation. Nitric oxide has important antiplatelet and perhaps important antioxidant properties as well.[84,85]

5.1.1 Mechanism of Action

Nitrates are coronary vasodilators, although their anti-ischaemic (antianginal) effects are more far reaching. Nitrates produce peripheral venodilation, thereby reducing preload, and at higher doses nitrates also reduce afterload by arterial vasodilation.[86-88] The clinically important effect is the reduction in preload secondary to reduced venous return and thus a reduction in ventricular volume and intracavitary pressure and ventricular wall stress. Nitrates can produce dilation at the site of stenotic coronary lesion and improve perfusion of ischaemic myocardium by increasing collateral flow.

Nitrates are inexpensive, well tolerated and effective,[89-92] and are thus often first line therapy for angina pectoris. The main problems with their use are: (i) some patients will not take nitrates, irrespective of their effectiveness for angina relief, because of adverse effects such as headache and flushing; (ii) patient education is important because sublingual nitroglycerin tablets lose their potency over time and need to be replaced every 2 months; and (iii) the effective long term use of nitrates is hampered by the development of tolerance to these agents.[83]

5.1.2 Nitrate Tolerance

Longer acting nitrate preparations provide sustained blood concentration, but paradoxically lose their effectiveness with time. The mechanism for this tolerance is unclear. Depletion of sulfhydryl groups, neurohumoral counter-regulation,[93] shift

of fluid from extravascular to intravascular compartments and oxygen free radical generation with inactivation of nitric oxide have all been proposed as mechanisms responsible for nitrate tolerance.[83] Another hypothesis is the down regulation of high affinity receptors while low affinity receptors, which are also responsible for vasodilation, remain unaffected with rising plasma nitrate concentrations and are activated.

Interval administration using eccentric regimens (table I) is a simple and proven method to prevent tolerance.[94-96] Rapid release formulations of isosorbide mononitrate administered 7 hours apart, or once daily administration of extended release isosorbide mononitrate, successfully prevents tolerance. However, these regimens leave patients unprotected in the late night or early morning.[97-100] The use of phasic delivery systems or the addition of hydralazine (to improve renal perfusion), captopril (with a sulfhydryl group to prevent reflex vasoconstriction) and sulfhydryl donors have been proposed to avoid nitrate tolerance, but definitive studies are lacking.[96]

5.1.3 Safety Considerations

Adverse Effects

The most common adverse effect associated with nitrate use is headache. This may go away with continued use of nitrate. However, in about 10% of patients, headaches preclude the use of nitrates or causes poor compliance. With current preparations and administration regimens, nitrate-induced mild to moderately severe headaches have been reported in 36 to 52% of patients.[20,89,95,97-99] Concomitant use of aspirin may prevent headache and coronary events.

The most serious adverse effect of nitrates is hypotension and in some patients nitrates can cause syncope. This can be troublesome in the setting of acute MI. Syncope is usually associated with bradycardia rather than expected tachycardia and usually responds to volume expansion. Patients should be warned about this adverse effect and instructed to lie down and raise their legs if they experience dizziness after taking nitrates. Also, prolonged high dose therapy can occasionally result in methaemoglobinaemia.

Drug Interactions

There is a predictable added physiological effect when nitrates are combined with other drugs that decrease preload or afterload resulting in severe hypotension.

Effect of Concomitant Illness

Nitrates may exaggerate the outflow obstruction in hypertrophic obstructive cardiomyopathy and are contraindicated in this condition. In acute inferior MI with right ventricular involvement, nitrates can reduce the right ventricular filling pressure and may lead to haemodynamic deterioration. In patients known to have significant aortic stenosis and angina, use of nitrates can lead to syncope. Nitroglycerin should be used with caution in patients with chronic obstructive pulmonary disease because oxygen desaturation may occur.

Use in the Elderly

Nitrate plasma half-life is longer and its volume of distribution is larger in older patients. This leads to greater vascular effects and results in more hypotension especially in the setting of an MI. Bradycardia is also more likely in the elderly.[101]

Other Issues

Rebound or withdrawal has been reported with intermittent nitrate transcutaneous patch therapy and may rarely occur with abrupt discontinuation of oral nitrates, especially in the absence of β-

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blocker use.[89,95,100] Newer agents related to the nitrates include molsidomine and pirisodimine which act by release of vasodilatory compounds during first pass metabolism through the liver.[83] These agents appear not to be prone to tolerance, but are not commercially available for clinical use.

5.2 β-Blockers

5.2.1 General Considerations

β-Blockers are effective in the management of stable angina pectoris. These agents decrease myocardial work and improve exercise tolerance.[102-104] The primary mechanism of this benefit is via β_1-adrenergic receptor blockade producing a reduction in heart rate and contractility and therefore reducing myocardial oxygen demand. In addition, β-blockers decrease exercise-induced vasoconstriction and blunt the rise in systolic blood pressure during exercise. β-Blockers also increase coronary perfusion by prolonging diastolic perfusion time.

Numerous β-blockers are available for clinical use. These agents have the common property of blocking β_1-receptors. Nonselective agents block β_1- and β_2-receptors. Some agents additionally block α_1-receptors and/or directly dilate blood vessels; these agents, along with those that possess intrinsic sympathomimetic activity (partial agonists), are referred to as vasodilator β-blockers. An ancillary property unrelated to antianginal effect is a quinidine-like membrane stabilising effect. Irrespective of these individual differences all β-blockers are equally effective in patients with stable angina pectoris.[102] Selection of an individual agent is based on duration of action, the presence of concomitant disease state and cost considerations.

β-Receptor blockade is the most effective means of reducing myocardial ischaemia, both during exercise and at rest at night. β-Blockers may be combined advantageously with other antianginal agents like nitrates and dihydropyridine calcium antagonists such as nifedipine which, by a vasodilating effect, produce reflex tachycardia.[102]

β-Blockers are the only antianginal agents which have been shown to reduce mortality when used after an acute MI:[97-105] 26 deaths were found to prevented when 1000 patients were treated with propranolol for 3 years.[105] This benefit occurs both when the agents are used immediately or a few weeks after the MI. However, the effect of these agents on survival in patients with stable angina has not been studied.

5.2.2 Safety Considerations

Adverse Effects

Common adverse effects directly related to β-blockade include bradycardia, hypotension, reduction in left ventricular contractility, bronchospasm and an inhibited response to hypoglycaemia.[20] Adverse effects unrelated to β-blockade include lethargy, depression, vivid dreams, constipation and impotence.[102] With regard to ventricular dysfunction, although β-blockers should be used with caution in patients with poor systolic function, these agents may be beneficial in improving systolic function in selected patients when used in the nonacute compensated state.[102-105] Lethargy and depression are direct effects of the drugs on the CNS and β-blockers with low lipid solubility may have a lower incidence of CNS adverse effects.[20,102]

Drug Interactions

In general, there are relatively few drug interactions with β-blockers. Predictable additive sinoatrial (SA) and atrioventricular (AV) node blockade as well as myocardial depression occurs with other cardiac drugs of similar action, e.g. verapamil. Pharmacokinetic interactions mainly occur in the liver. Cimetidine increases the blood concentrations of β-blockers that are metabolised by the liver, e.g. metoprolol and propranolol. Verapamil reduces hepatic blood flow and increases the blood concentration of β-blockers that are metabolised in the liver. β-Blockers decrease hepatic blood flow, thus increasing lidocaine (lignocaine) concentrations and the risk of lidocaine toxicity. Intravenous phenytoin should be used with great caution be-

cause of the additive cardiac depressant action with β-blockers.

5.2.3 Effect of Concomitant Illness

Generally, β-blockers are contraindicated in patients with bronchospastic disorders. However, cardioselective β_1-blockers may be used in low doses. Agents with intrinsic sympathomimetic activity or added α-blockade may also be used with caution.

In patients with diabetes mellitus the symptoms of hypoglycaemia may be masked by β-blocker use. There is a lesser risk of this effect with cardioselective agents. Glucose intolerance of a mild level may occur with any β-blocker especially if used in conjunction with a diuretic. However, β-blockers have been used safely and effectively in patients with type 2 (non–insulin-dependent) diabetes mellitus and stable angina pectoris.[102]

β-Blockade is dangerous in patients with conduction system abnormalities, especially sick sinus syndrome. Agents with intrinsic sympathomimetic activity may be tried with caution. Although Raynaud's phenomenon and peripheral vascular disease with resting leg pain are considered relative contraindications to β-blockade, there is evidence suggesting that they can be used safely in patients with intermittent claudication.[106]

Dose alteration in renal failure may be required, especially for water soluble agents excreted by the kidneys (e.g. atenolol, acebutalol, nadolol and sotalol).

5.2.4 Use in the Elderly

Elderly patients are particularly prone to adverse effects of drugs that decrease cardiac output, such as β-blockers.[107] Both β-adrenergic stimulation and blockade may be altered in the elderly, giving rise to less predictable effects of β-blockade. Lipid soluble β-blocker concentrations may be increased in the elderly because of the decreased hepatic blood flow, but this may be offset by an increased volume of distribution. Water soluble β-blockers may have a reduced volume of distribution. Elderly patients are particularly prone to the interactions resulting in increased lidocaine concentrations. Elderly patients, particularly those with ischaemic heart disease, have an increased α_1 acid glycoprotein level which binds several cardiac drugs including propranolol.

5.2.5 Long Term Considerations

β-Blockers are proven to decrease mortality in CAD patients especially after an MI. This beneficial effect occurs despite the fact that long term use is associated with a slight adverse effect on the lipid profile.[102] This effect is more pronounced with nonselective β-blockers and least with agents with partial agonism or added α-antagonism. Impotence is a frequent complaint that may limit long term use.[20] Although package inserts for β-blockers give a rate of impotence of 1% for most agents, failure of erection occurs in about 11% compared with 3% with placebo and 26% with a diuretic.[108] Reassurance, change to a vasodilatory β-blocker or decreasing the dose with combination therapy may be helpful. β-Blocker dosage should be optimised according to exercise-induced heart rate change and not to resting heart rate.[109]

5.2.6 Other Issues

Following an overdose of a β-blockers severe bradycardia may be treated with atropine or transvenous pacing. Glucagon is useful for treating both bradycardia and hypotension because it bypasses the β-receptor in stimulating cyclic adenosine monophosphate.

Newer β-Blockers

Carvedilol is a long acting agent with α-mediated vasodilatory capacity. It has mainly been studied in congestive heart failure but has remarkable antioxidant properties that may be exploited in CAD. Celiprolol is highly cardioselective and produces β_2-mediated vasodilation. This agent may have fewer adverse effects on blood lipids. Bisoprolol is considered more β_1-selective than atenolol.

5.3 Calcium Antagonists

5.3.1 General Considerations

Calcium antagonists are the most commonly used agents for angina and hypertension. They act mainly by vasodilation and reduction of peripheral

vascular resistance. They can be classified as dihydropyridines and nondihydropyridines. Selective T channel blockers related to nifedipine are examples of dihydropyridines and these agents have greater vascular selectivity than nondihydropyridines (e.g. verapamil and diltiazem), which are more myocardial selective agents. Clinically evident inhibitory effects on AV and SA nodes are features of nondihydropyridines and mibefradil, and their therapeutic spectrum closely resembles that of β-blockers. Mifebradil has T channel blocking properties, in addition to the above features. Bepridil is a nonselective calcium antagonist.

The calcium antagonists block the entry of calcium through the calcium channels in both smooth muscle and myocardium so that less calcium is available to the contractile apparatus. The net result is vasodilation and decreased myocardial contractility. The latter is usually modest because of the unloading effect of peripheral vasodilation. The nondihydropyridines and T channel blockers act on nodal tissue. Diltiazem and verapamil are effective in supraventricular tachycardia and decrease the sinus rate. These properties and the peripheral vasodilation leads to substantial reduction in myocardial oxygen demand.[110-113]

5.3.2 Use in Angina Pectoris

All calcium antagonists inhibit the L type calcium current in arterial smooth muscle at low concentrations and therefore dilate coronary arteries. Coronary vasodilation and prevention of exercise induced coronary vasoconstriction is a major antianginal effect. After load reduction and, in the case of nondihydropyridine and T channel blocking agents, suppressant effects on the sinus node and myocardium also contribute toward antianginal efficacy.

Multiple double-blind, placebo-controlled studies have demonstrated substantial decreases in anginal frequency (up to 60%) and increases in exercise time (up to 39%).[113] In comparison with long acting nitrates, calcium antagonists were equally effective with fewer adverse effects. Although similar antianginal efficacy to β-blockers is present, only β-blockers are known to decrease mortality in the postinfarction setting.

Mibefradil,[1] the first of a new class of calcium antagonist, is a tetralol derivative and it was recently approved for clinical use in many countries including the US. It is characterised by its selective blockade of T type calcium channels. In animals, blockade of T channels does not depress left ventricular function but slows sinus rate.[114] Dosages of 50 and 100 mg/day improve angina-free walking time and time to ischaemia and blunt the rise in rate pressure product during exercise.[115] In one study the drug was shown to be superior to amlodipine.[116]

5.3.3 Safety Considerations

Adverse Effects

In general, calcium antagonists are well tolerated and most adverse effects are dose related. Vasodilatory adverse effects include flushing, dizziness, headache and palpitations; they may be seen with any calcium antagonist but are most common with nifedipine.[113,117] Peripheral oedema is more commonly reported with dihydropyridine agents, probably resulting from arteriolar vasodilation.[113,117] Severe depression of myocardial function and symptomatic bradyarrhythmias occur rarely, but more so with verapamil.[113,118,119] These effects are more common in patients with baseline cardiac dysfunction or concomitant β-blocker therapy. Gastrointestinal effects, especially constipation and nausea, occur more frequently with verapamil.[113,117] Some of the adverse effects of verapamil, diltiazem, nifedipine, amlodipine, felodipine and mibefradil are listed in table II.

Drug Interactions

Intravenous verapamil is contraindicated in patients taking β-blockers. In addition to additive negative cardiac effects, a hepatic pharmacokinetic interaction may increase the blood concentrations of both agents. Thus, hydrophilic β-blockers, such

1 Mibefradil has recently been voluntarily withdrawn from the market in the US by Roche because of the potential for drug interactions, some of them serious, which may occur when the agent is administered with some other medications.

as atenolol, would be preferred when combining a β-blocker with verapamil. In the setting of digitalis toxicity, intravenous verapamil may cause fatal AV block and is contraindicated. Verapamil increases digoxin concentrations, necessitating more care in monitoring.

Hypotension when verapamil is given with quinidine occurs either via increases in quinidine concentrations or a combined effect on peripheral α-receptors. Disopyramide and verapamil potentiate the negative inotropic potential of each other. Inducers of the cytochrome P450 enzyme system, like rifampicin (rifampin) and certain anticonvulsants, decrease verapamil concentrations and verapamil increases the risk of carbamazepine toxicity

Diltiazem does interact with digoxin. The combination of diltiazem and β-blockers increases the risk of bradycardia and hypotension with little additive effect for angina. The combination of diltiazem and nitrates may lead to significant hypotension. Although diltiazem increases cyclosporin concentrations, this interaction has not been widely used to decrease cyclosporin dosage requirements as the interaction is quantitatively variable.

Mibefradil and its metabolites inhibit the activity of cytochrome P450 (CYP) 3A4, an enzyme responsible for the metabolism of many drugs, including quinidine, short acting benzodiazepines, most calcium antagonists, terfenadine, astemizole and cisapride.[20] Thus, mibefradil may increase the plasma concentration of coadministered drugs that are primarily metabolised by the CYP3A4 enzyme system, and may consequently increase or prolong their therapeutic and adverse effects. For drugs that can cause serious adverse effects if their concentration is increased, concomitant use with mibefradil should be avoided.[20]

Mibefradil can slow sinus rate and is contraindicated in patients with sick sinus syndrome.[20] Also, when given with β-blockers in patients with sinus rate less than 55 beats/min, excessive slowing of sinus node or even sinus pauses may occur.[20]

The FDA recently issued a warning regarding concomitant use of mibefradil and lovastatin or simvastatin, as the combination therapy increased plasma concentration of these statins 6- to 8-fold and resulted in rhabdomyolysis in some patients.[20] A combination of mibefradil and pravastatin or fluvastatin seems to be well tolerated.[20] Use of atorvastatin and cerivastatin with mibefradil should be avoided, until further information is available.

Mibefradil modifies T waves of the ECG without prolonging the QT interval, but appearance of U waves may make interpretation of QT interval difficult. Mibefradil should not be used concomi-

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tantly with class I or III antiarrhythmic agents which require QT monitoring during therapy.

Amlodipine concentrations are increased by liver failure and by concomitant cimetidine use. In general, dihydropyridine agents have minimal interaction with cyclosporin; however, amlodipine may be the preferred agent in view of the problem of pedal oedema with other dihydropyridine in these patients with other reasons for peripheral oedema.

5.3.4 Effect of Concomitant Illness

In general, calcium antagonists are well tolerated in many conditions where β-blockers are to be used with caution, as in patients with bronchospasm, peripheral vascular disease and depression. Dihydropyridine agents are relatively contraindicated in aortic stenosis. Amlodipine has been shown not to worsen heart failure in patients in New York Heart Association (NYHA) class II to III congestive heart failure. Whether mibefradil is also well tolerated in patients with congestive heart failure remains to be proven.

5.3.5 Use in the Elderly

Calcium antagonists are particularly useful in the elderly and may produce less orthostatic hypotension. These agents are more effective in lowering blood pressure than β-blockers in this age group. Since the elderly show a reduced response to elevated sympathetic tone and the plasma response relationship for calcium antagonists varies with sympathetic tone, a wide variation in dose response relationship can occur in this age group.

5.3.6 Long Term Considerations

The most controversial issue in the long term use of calcium antagonists relates to reports of potentially detrimental effects of calcium antagonists in hypertension and ischaemic heart disease.[120] With regard to therapy for chronic stable angina, the most worrisome reports have been those demonstrating potentially adverse proischaemic effects of short acting dihydropyridines.[120] It should be noted that there is no clear evidence questioning the safety of nondihydropyridine agents or of long acting dihydropyridine agents. Until further data are available, long acting calcium antagonists should continue to be employed in the setting of stable angina pectoris.

5.3.7 Second Generation Dihydropyridine Calcium Antagonists

The major advantage of amlodipine compared with nifedipine is its slower onset of action and longer duration of activity. Amlodipine was more effective than placebo and at least as effective as nadolol in angina pectoris.[121] Amlodipine has been shown to not worsen congestive heart failure.

Other second generation dihydropyridine calcium antagonists licensed for use in angina pectoris include nicardipine, which may have less negative inotropy than first generation dihydropyridines,[113] and is available in an intravenous form. Isradipine, with a medium duration half-life, may have antiatherogenic effects[122] and is effective in effort angina. Ankle oedema may be less than expected with isradipine.[113]

Bepridil is a nonspecific calcium antagonist with added sodium channel inhibition, class 1 antiarrhythmic effects and inhibition of repolarising potassium currents. This drug may be useful in patients with angina, refractory to diltiazem and other antianginal agents.[123] The major safety concern with this agent is torsade de pointes from QT prolongation.[123]

Nicorandil is a nitrovasodilator and a potassium channel activator and is approved for treatment of stable angina pectoris in many countries but not in the US. Comparative studies without a placebo group suggest that nicorandil is equivalent in efficacy to isosorbide dinitrate, propranolol, atenolol, nifedipine or diltiazem in the treatment of stable angina pectoris.[124] However, a recent multicentre study[125] did not confirm a previous report of superiority of nicorandil over placebo in patients with stable angina.[126]

Headache is the most commonly reported adverse effect, occurring in one-third of patients receiving the recommended therapeutic regimen of nicorandil 10 to 20mg twice daily.[113] In European trials, 5% of patients had to withdraw from treatment because of headache.[124] Postural hypoten-

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sion may also occur and should be watched for when nicorandil is prescribed with other vasodilators.

Ranolozine probably works by modulating the metabolism of the ischaemic cell.[127] In early clinical studies, ranolozine was found to prolong exercise time in patients with stable coronary disease[128] and in patients with angina.[129,130] In another study, when ranolozine was coadministered with a β-blocker or a calcium antagonist, ranolozine exerted a significant antianginal effect.[131] However, using doses similar to those used in the above studies, a recent study failed to show superiority of ranolozine over placebo in chronic stable angina.[132] The drug is not available for clinical use in the US. The reported adverse effects include headache, dizziness and asthenia.

6. Combination Therapy

With increasing numbers of effective therapeutic modalities, both for symptomatic therapy and secondary prevention of coronary events in patients with chronic stable angina, becoming available, 2 questions need be asked. First, what is the incremental benefit, both with regard to symptoms as well as risk reduction in adding one therapy to another, and secondly, what are the additional safety concerns in combining these various therapeutic modalities? Literature addressing these issues is scant.[133-135] Optimal antianginal monotherapy is often as effective as combination therapy with 2 or 3 agents.[124-141] Tolins et al.[139] and Akhras and Jackson[140] have shown that maximising medical therapy with these agents is not necessarily equivalent to optimising medical therapy for chronic stable angina.

7. Guidelines for Choosing Appropriate Drug or Combination Therapy for Stable Angina

Taking safety into consideration, we suggest the following guidelines for choosing the appropriate drug or combination of drug therapy for chronic stable angina.[142]

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1. Start with a single drug for symptom management (see table III) and maximise the dose for therapeutic effect.

2. If the desired effect is not achieved or adverse effects occur then change to a second drug from another class of agents before combining therapy.

3. Choose the initial agent based on patient profile and concomitant illness (see table IV).

4. If maximum monotherapy is only partially effective, choose a combination therapy that is not additive in terms of adverse effects, e.g. β-blockers and verapamil. Suggested combinations are: (i) a long acting nitrate plus a β-blocker; (ii) a β-blocker and a long acting dihydropyridine calcium antagonist; (iii) with care, a β-blocker and diltiazem; or (iv) a long acting nitrate plus diltiazem or verapamil or mibefradil.

5. Choose triple drug therapy with close supervision.

6. Consider adding bepridil in patients not suitable for revascularisation and refractory to conventional antianginal drugs.

7. Use simultaneous therapy aimed at plaque stabilisation and prevention of coronary events: (i) aspirin (80 to 320 mg/day) in all patients unless contraindicated; (ii) statins in patients with raised LDL levels; and (iii) estrogens in postmenopausal women and ACE inhibitors in patients with reduced left ventricular function (ejection fraction <40).

A proposed treatment outline for patients with stable angina pectoris is given in table V. Such a strategy should permit evidence based therapy and improve patient outcome.

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