CARDIOVASCULAR DRUG GUIDELINES
Second Edition, 2006

This first edition of the guidelines published in 1999 was drafted by Professor Anthony Smith of Newcastle, Australia during a month-long consultancy generously funded by the World Health Organisation and published in 1999. The guidelines hae been revised by a subcommittee of the National Drugs and Therapeutics Committee.

Subcommittee on the preparation of the second Edition of the Cardivascular Drug Guidelines.

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Preface

The publication of second edition of the Cardivasular Drug Guidelines represents the culmination of the efforts of the National Drugs and Therapeutics Committee to publish clinical drug guidelines for common diseses seen in fiji. These guidelines are targeted for health care professional working at hospitals and at the primary health care settings. It sets the gold standards for the use of cardivasular drugs in Fiji.

The guidelines have been endorsed by the Heart Health Fiji, a subcommittee of the National Noncommuniable Disese Committee.

The guidelines have taken into account the drugs available in the Fiji Essential Medicines Formulary (EMF), 2006 Edition, in recommending treatments approaches. All recommended drug therapies are either evidence-based or universally accepted standards.

It is hoped that these guidelines will be used by all health care workers in theor daily care of patients suffering from cardiovascular diseases.

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1 Drugs used in cardiovascular disease

This chapter contains brief summaries of the major drugs used in the management of cardiovascular disease and are recommended in these guidelines. The summaries do not contain comprehensive accounts of the pharmacology of these compounds. The reader is advised to consult standard textbooks and/or the industry product information for more details.

1.1 Beta-receptor blocking drugs (beta-blockers)

These compounds competitively block the adrenergic beta-receptors found at sympathetic nerve endings and in non-innervated tissue, e.g. lymphocytes, hepatic parenchymal cells. The endogenous substances that bind to these receptors are adrenaline and noradrenaline. Their actions are blocked during the time the beta-blocker occupies the receptor.

Important adverse effects of beta-blockade include precipitation of asthma, mental depression, lethargy, aggravation of Raynaud's phenomenon and intermittent claudication.

Recent evidence supports the use of beta-blockade in **small doses** in the treatment of chronic heart failure.

Abrupt withdrawal of beta-blockers may result in rebound exacerbation of angina, cardiac arrhythmias and occasionally, in a patient with pre-existing angina, myocardial infarction. **It is best to reduce doses slowly over a 7-10 day period if possible.**

The beta-blockers in the Fiji EDL are atenolol, propranolol and labetalol (which also has activity at the alpha-adrenergic receptor). Labetalol is only available as intravenous preparation in the Fiji EDL (Essential Drugs List).

1.1.1 Propranolol

Propranolol blocks both the beta-1 and beta-2 receptors. It reduces

cardiac rate, contractility and excitability. It reduces the caliber of the bronchial tree. It increases the resistance of peripheral limb arterioles and reduces the mobilisation of glucose from glycogen in response to hypoglycaemia. It lowers blood pressure by reducing cardiac output and modulating peripheral vascular resistance possibly by a central effect on sympathetic efferent pathways. Its action in angina depends on the reduction of exercise-induced increases in cardiac work. After myocardial infarction its protective effect may depend on the suppression of cardiac arrhythmias.

Propranolol is metabolised in the liver to several compounds. The principal metabolite is active as a beta-blocker. Its duration of action is less than that of atenolol and normally it will need to be given two or three times daily.

1.1.2 Atenolol

Atenolol is more selective for beta-1 receptors than propranolol. In high doses, this selectivity is lost. Atenolol and propranolol have the same action on the heart and blood pressure but it is less likely to produce adverse effects on the peripheral vasculature, the bronchi and on the recovery from hypoglycaemia.

Despite these differences in selectivity**, beta-blockers should not be used in anyone with a history of, or concurrently with asthma.**

Atenolol is largely excreted unchanged by the kidney and doses may need to be reduced in patients with renal impairment. It may be given once daily.

1.1.3 Labetalol

Labetalol has both beta- and alpha-blocking properties and produces postural hypotension and failure of ejaculation as alpha-mediated effects. **Its use is principally for urgent blood pressure reduction by the parenteral route and rarely for long-term treatment.**

1.2 Calcium channel blocking drugs (calcium blockers)

Calcium entry into cells of the cardiac conducting system, myocardial cells and the cells of vascular smooth muscle is one of the central processes leading to generation of the action potential, heart muscle contraction and constriction of vascular smooth muscle cells. Drugs that partially block this activity are termed calcium channel blockers. Two of these are in the Fiji EDL – verapamil and nifedipine.

Verapamil is a phenylalkylamine while nifedipine, which binds to a different site on the L-type calcium channel, is one of the dihydropyridines.

1.2.1 Verapamil

Verapamil has greater selectivity for cardiac than for vascular calcium channels. It has its main place in the management of cardiac arrhythmias and angina than in the treatment of hypertension. It may cause bradycardia and its negative inotropic action can be harmful in heart failure.

In overdosage, verapamil produces bradycardia, reduction in cardiac output and occasionally electromechanical dissociation. Massive quantities of calcium salts may be required to reverse these effects. In therapeutic doses, verapamil causes constipation that can be corrected with oral or intravenous calcium. Given together with beta-blocking drugs, verapamil may produce bradycardia and rarely heart block.

1.2.2 Nifedipine

Nifedipine has greater action on vascular smooth muscle than on the heart and finds its main place in the management of hypertension and angina in which the cardiac afterload needs to be reduced. Its dilator activity on peripheral arteries and arterioles produces reflex tachycardia and increases the cardiac output. This can lead to worsening of angina or even myocardial infarction in patients with critical stenosis of the coronary vessels. For this reason, **short-**

acting preparation of nifedipine is less favourable compared to the slow-release formulation. Both the short-acting (Nifedipine 10mg) and modified-release (Nifedipine 20mg) formulations are available in the Fiji EDL; the former is mostly used by obstetricians for pregnancy-related hypertension and not advisable for other indications. Despite its indirect action to increase cardiac output, nifedipine like verapamil, is negatively inotropic. In overdosage, the direct cardiac effects predominate to produce bradycardia and reduction in cardiac output. This is treated in the same way as for verapamil. (can we indicate that 10mg is only for pregnant mothers & not for S/L use plus MR 20mg for non-pregnant individuals)

1.3 Angiotensin converting enzyme inhibitors (ACEI)

These compounds block the conversion of the 10-amino-acid peptide angiotensin I to its active 8-amino-acid derivative angiotensin II. Angiotensin II is a potent vasoconstrictor and is also one of the stimuli to the secretion of aldosterone by the adrenal cortex. It is formed in the plasma and also in the tissues – especially vascular smooth muscle where it appears to have a local regulatory role. Inhibition of the converting enzyme which catalyses the formation of angiotensin II results in a reduction of constrictor tone in the blood vessels and a fall in the secretion of aldosterone. Both of these effects are of benefit in the treatment of heart failure and hypertension. However, the enzyme inhibited also catalyses the breakdown of other peptides, notably bradykinin, and higher concentrations of these may be responsible for some of the adverse effects of the ACEI, e.g. cough.

While there are many ACEI on the international market, there is little evidence for the clinical superiority of one over the rest. Captopril was the first to be introduced but has the disadvantage of a shorter half-life and duration of action than the later ACEI. Enalapril can commonly be taken as a once daily dose and there is good evidence for the duration of its effect over 24 hours in most patients with hypertension. If this is not achieved, the drug may be given as a twice-daily dose.

Major adverse effects of ACEI are angioedema which appears to be

a class effect, cough which occurs in around six to ten percent of all patients, worsening of renal function particularly in patients with bilateral renal artery stenosis and skin rashes. Ageusia (transient loss of taste sensation) appears to have been more common in patients being treated with captopril in larger doses**.**

ACEI should not be used in pregnancy, obstructive valvular heart diseases and bilateral renal artery stenosis.

ACEI promote potassium retention and electrolytes and renal function should be monitored when introducing them.

The elderly, those dehydrated from intensive diuretic treatment or taking other hypotensive medication are at particular risk of "first dose hypotension". ACEI should be introduced at a very low dose in these patients and the dose increased gradually.

1.4 Directly-acting vasodilators

1.4.1 Hydrallazine

Hydrallazine is a directly-acting vasodilator which has a place in the management of both hypertension and heart failure. Given by the intravenous route in urgent cases – especially pregnancy – it produces reflex tachycardia, flushing and headache. These can be reduced by the use of beta-blocking drugs in combination.

Long-term use may lead to the development of a syndrome resembling lupus erythematosus. Those at risk are younger women who are slow acetylators of hydrallazine and take the drug in doses of 100 mg daily or greater for a prolonged period. It is rarely necessary to use the drug in this way and its principal place is in the urgent reduction of blood pressure especially in pregnancy.

2.2.2 Nitrates

The Fiji EDL lists two nitrate preparations. Glyceryl trinitrate is available as the sublingual tablet of 600 micrograms. Isosorbide

dinitrate is an orally available formulation that has a comparatively low and variable bioavailability (around 25 percent only). Both preparations act as precursors for nitric oxide, the endothelium's intrinsic vasodilator that is not produced as effectively in diseased arteries.

The major drawback to nitrate treatment is the emergence of tolerance. Nitrate-free periods help to reduce the development of tolerance.

Glyceryl trinitrate deteriorates in storage particularly in glass bottles and is likely to have very little effect after three months' storage in this way.

Nitrates must not be used concomitantly with sildenafil (Viagra) as it potentiates the action of nitrates and produces significant hypotension, which, on occasion, has been fatal in patients with critically narrowed cerebral or coronary arteries. Sildenafil is not available in the Fiji EDL.

1.5 Centrally-acting hypotensive drugs

Alpha-methyldopa is the only drug in this category in the Fiji EDL. It is effective orally and is converted to alpha-methyl-noradrenaline in the body that acts at the level of the brainstem vasomotor centre as an alpha-2 receptor agonist. This reduces efferent sympathetic traffic and hence reduces peripheral resistance and blunts cardiac sympathetic response.

Alpha-methyldopa is an old drug whose major place is in the management of pregnancy-related hypertension where its efficacy and safety have not been matched by other drugs. However, for the non-pregnant patient, it must be regarded as a second or third-line drug.

Adverse effects include mental depression, impotence, and rarely, autoimmune haemolytic anaemia and hepatotoxicity.

1.6 Diuretics

1.6.1 Frusemide

Frusemide is a diuretic acting on the loop of Henle, a major site of ion and water reabsorption in the nephron. It is therefore one of the "loop" diuretics which are very potent and of particular value in the treatment of heart failure. Its duration of action is from 3-4 hours and may be given orally or, for a quick response, intravenously.

2.2.2 Hydrochlorothiazide

Hydrochlorothiazide has a long duration of action and is given once daily preferably in the morning. All thiazides act at the distal renal tubule to inhibit the reabsorption of sodium and water. A relatively small percentage of overall reabsorption occurs at this site and therefore the diuresis produced by thiazides will be less than that with loop diuretics.

Because loop and thiazide diuretics act at different sites in the nephron they may be given together in the expectation of enhanced diuresis.

Adverse effects to both frusemide and hydrochlorothiazide include hypokalaemia, elevation of serum uric acid sometimes presenting as gout, impairment of glucose tolerance, and rarely, ototoxicity. Thiazides may increase serum calcium.

In renal and congestive heart failure, the access of diuretics to the site of action may be poor. Diuretics are absorbed poorly from an oedematous gut and gain access to failing kidneys (and a smaller population of nephrons) by way of a reduced renal blood flow. In both situations, there is a case for using either parenteral diuretics (in heart failure) or high dose oral preparations such as frusemide 500 mg daily or twice a day (in renal failure).

2.2.3 Spironolactone

Spironolactone is a competitive inhibitor of aldosterone at the distal renal tubule. It promotes sodium loss and potassium retention. Used with thiazide or loop diuretics, it enhances sodium loss and helps prevent hypokalaemia. Recent evidence suggests that in low doses (25 mg daily) it may be of value when added to conventional treatment in congestive heart failure.

It causes hyperkalaemia particularly in patients with renal impairment. Other significant adverse responses relate to its anti-androgen activity that can cause painful gynaecomastia in men and irregular or postmenopausal vaginal bleeding in women.

1.7 Anticoagulants, antiplatelet drugs and thrombolytics

1.7.1 Heparin

Heparin is only available in the unfractionated form (UFH) in the Fiji EDL. UFH is a mixture of high molecular weight compounds only a portion of which has anticoagulant activity. UFH acts by binding to antithrombin. This inactivates thrombin and activated factor X (Xa) that diminishes their procoagulant effect and tips the balance of the clotting cascade towards anticoagulation. .

The action of UFH is dose-dependent and is measured by the activated partial thromboplastin time (APTT). The unmodified APTT is less than 50 seconds and the therapeutic range lies between 60 and 85 seconds. Values over 100 seconds represent overanticoagulation and heparin should be stopped temporarily. UFH has a short plasma half-life of about 1.5 hours and effects are readily reversed. In emergency situations, its action can be terminated by the intravenous use of protamine sulphate.

Heparin may be administered by the intravenous or subcutaneous routes.

A major but rare adverse effect is heparin-induced thrombocytopaenia

and thrombosis syndrome (HITTS). This is an autoimmune process that results in low platelet counts, paradoxical thrombosis from platelet deposition and a tendency to bleed.

2.2.2 Warfarin

Warfarin is an oral anticoagulant that acts by antagonising the Vitamin K-mediated final steps in the synthesis of clotting factors II, VII, IX and X in the liver. It inhibits the synthesis of proteins C and S that normally maintain an anticoagulant effect. As protein C has a short half-life in the plasma it falls early after starting warfarin and this may lead to a hypercoagulable state in the first 24-48 hours. It is recommended therefore to maintain heparin treatment for the first 48 hours after introducing warfarin until the inhibition of the procoagulant factors outweighs the effects on protein C.

Warfarin therapy is monitored by the international normalised ratio (INR).

Warfarin is virtually completely bioavailable, is over 90 percent protein bound in the plasma and metabolised in the liver to inactive metabolites that are excreted in the urine.

The major adverse effects of warfarin are related to over- or underactivity of the drug. Bleeding is the major risk from overdosage. The major risk for ineffective dose is the failure to treat the thrombotic disease adequately.

There is a big potential for other drugs to interact with warfarin especially with its metabolism.

Drugs that may enhance the anticoagulant effect of warfarin include:

- amiodarone
- chloramphenicol
- ciprofloxacin
- cotrimoxazole
- doxycycline

- erythromycin
- ketoconazole
- metronidazole
- miconazole
- simvastatin
- tetracycline

Drugs that may reduce the effect of warfarin include:

- barbiturates
- carbamazepine
- nutritional supplements providing vitamin K
- phenytoin
- rifampicin

These drugs act to induce the metabolising enzymes and reduce the efficacy of a given dose. Vitamin K antagonises the action of the anticoagulant directly.

Co-administration of drugs that also increase the risk of bleeding can also present problems. Aspirin, and non-steroidal anti-inflammatory drugs are the commonest examples.

Bleeding from warfarin can be treated with Vitamin K (takes from 2-3 hours to reverse) or more rapidly with fresh frozen plasma or whole blood transfusion.

2.2.2 Aspirin

Aspirin is technically not an anticoagulant but is given for its antiplatelet action. This occurs as a result of the inhibition of prostaglandin synthesis in platelets, which in turn reduces the production of thromboxane A2, the major prostaglandin derivative favouring platelet aggregation. Platelets are irreversibly "labeled" and become refractory to aggregation in an aggregometer. The effect of a single 300 mg (one standard tablet) dose can still be detected in the patient's blood up to 10-14 days later. Prophylactic aspirin should be discontinued for about two weeks prior to surgery

(substituting heparin if necessary). The antiplatelet action of aspirin can be demonstrated with daily oral doses as low as 75 mg at which dose bleeding rarely occurs as a side effect.

2.2.3 Streptokinase

Streptokinase is the only thrombolytic in the Fiji EDL. It acts by binding to plasminogen and this activates uncomplexed plasminogen to plasmin, the endogenous fibrinolytic substance. Fibrin is lysed and generates fibrin degradation products that appear in blood and urine.

Antibodies to streptokinase appear after its use but may also occur through exposure to streptococcal antigens.

Streptokinase can cause allergic and even anaphylactic reactions.

1.8 Lipid-lowering drugs

There has been a proliferation of drugs launched in the world market in recent years for the management of dyslipidaemia. **Simvastatin 10mg and 20 mg capsules are available on the Fiji EDL. Its use is currently restricted to patients with ischaemic heart disease and certain categories of diabetic patients. with eligibility restrictions on availability, inclusion criteria and prescriber.**

It has been shown by previous studies that lipid-lowering drugs can produce substantial benefit in high-risk groups of patients such as those who had a myocardial infarction regardless of the lipid level.

The “statins” are all inhibitors of cholesterol synthesis through inhibition of the activity of hydoxymethylglutaryl CoA reductase, a key enzyme in the synthetic pathway for cholesterol.

Simvastatin is taken once daily (conventionally after the evening meal) in a dose ranging from 10-40 mg according to response. The onset of action is over the succeeding 4-6 weeks and blood lipids should not be re-measured until six weeks have elapsed.

The “statins” are non-toxic in most patients. Safety over a period longer than 10 years is not yet established. The main side effects are muscle pain accompanied by elevation of serum creatine kinase rarely progressing to rhabdomyolysis. Non-symptomatic rise in liver enzymes may also occur. These changes are reversible on discontinuing the drug.

1.9 Antiarrhythmic drugs

1.9.1 Adenosine

This is a natural body constituent and has recently been introduced in non-physiological concentrations for the reversal of supraventricular tachycardias. It has a plasma half-life of only ten seconds and can therefore be given by repeated doses if needed.

The adverse effects are transient. Flushing, headache, hypotension and chest pain may all occur but can be reversed rapidly. Rarely, aminophylline may be used as an antidote to treat adenosine side effects.

It is given by intravenous bolus over a few seconds.

Theophylline acts as an adenosine antagonist and doses of adenosine may need to be increased in patients who are on this drug.

1.9.2 Amiodarone

This drug prolongs refractoriness of most cardiac tissue and has weak beta-blocking activity. It contains organic iodine and some of the adverse effects relate to this. It is used for the treatment of serious arrhythmias unresponsive to other measures. It is the least negatively inotropic of all the antiarrhythmics and therefore is often preferred in heart failure.

Amiodarone has many adverse effects. The most serious are the least reversible. Pulmonary alveolitis and fibrosis may severely impair respiratory function. Hyperthyroidism and hypothyroidism

have been both reported in the literature and are difficult to diagnose as serum thyroxine level may not reflect the true thyroid function of the patient. Less serious adverse effects include photosensitivity, corneal deposits, sleep disturbances and prolongation of the QT interval.

Amiodarone has difficult kinetics. Plasma half-life ranges from one to three months, which means that, in the extreme, steady state may not be reached for over a year. It also implies very slow elimination of the drug once it is stopped. Plasma concentration monitoring is not useful in guiding treatment.

1.9.3 Atropine

This is an anticholinergic compound used to reverse symptomatic bradycardia. As it antagonises the action of acetylcholine at many different sites, it may produce dry mouth and impairment of accommodation leading to visual blurring.

1.9.4 Digoxin

This compound has been used for over two centuries and currently it has no replacement.

Digoxin slows heart rate by depressing conduction through the bundle of His by slowing atrioventricular conduction and by enhancing vagal activity. It strengthens cardiac contraction and is also a mild diuretic.

It has a slow distribution time after both oral and intravenous administration and takes 4-6 hours to express its action. It is therefore of little extra benefit to give the drug parenterally. Hypokalaemia potentiates its effect and may predispose to toxicity.

Adverse effects include, sequentially, bradycardia, ventricular ectopic beats, bigeminy, ventricular tachycardia and, if no action is taken, ventricular fibrillation and death. The systemic features of toxicity are anorexia, nausea, vomiting and xanthopsia (yellow vision).

Digoxin has a half-life of 24-36 hours in patients with normal renal function. It is excreted almost entirely through the kidney and toxicity is more likely in renal failure and in the elderly. Plasma concentration monitoring may be useful in guiding treatment although the correlation between measured concentration and clinical toxicity is not precise. Blood for monitoring should be taken not less than six hours from the previous dose.

1.9.5 Lignocaine

Lignocaine is a Class I antiarrhythmic that blocks inward sodium movement in excitable tissues and can also be used as a local anaesthetic.

Lignocaine has a short half-life of around two hours and is metabolised in the liver to produce two pharmacologically active metabolites that may cause central nervous system toxicity if excessive doses of lignocaine are given. Toxicity includes visual disturbances, paraesthesias and convulsions.

Lignocaine is cleared through the liver and accumulates if hepatic blood flow is reduced as in congestive cardiac failure.

1.10 Cardiovascular drug interactions

Many drug interactions are possible in the management of cardiovascular diseases. Some of the more important ones are described below.

- The action of digoxin is potentiated by diuretics through potassium depletion.
- The negative inotropic action of verapamil is potentiated by beta-blocking drugs.
- The negative chronotropic effect of verapamil is potentiated by beta-blocking drugs.
- There is reduced metabolism of lignocaine with concomitant use of beta-blocking drugs due to reduction in liver blood flow.
- The effect of warfarin is decreased with concomitant use of

barbiturates, carbamazepine, phenytoin and rifampicin. These drugs increase metabolism of warfarin.

- The effect of warfarin is increased with the concomitant use of amiodarone, chloramphenicol, ciprofloxacin, cotrimoxazole, doxycycline, erythromycin, ketoconazole, metronidazole, simvastatin and tetracycline. These drugs inhibit the metabolism of warfarin.
- Plasma concentrations of digoxin are increased with concomitant use of amiodarone and verapamil.

2 Hypertension

Sustained hypertension is the single biggest risk factor for stroke and may also lead to left ventricular and congestive heart failure, chronic renal failure and retinopathy. The importance of hypertension is increased in the presence of other cardiovascular risk factors such as smoking, diabetes mellitus, raised total or low-density lipoprotein (LDL) cholesterol or a family history of premature cardiovascular disease. Therefore, treatment should be more vigorous in the presence of multiple risk factors.

Adequate treatment of hypertension substantially reduces the risk of stroke as well as of heart failure, renal failure and, to a lesser extent, myocardial infarction.

2.1 Definition

The World Health Organization (WHO) defines hypertension as blood pressure (BP) of greater than 140/90 mm Hg. However, for these guidelines, the aim of treatment is to reduce blood pressure to 130/85 or below in most patients.

Mild hypertension is defined as BP of 141-159/91-99 mm Hg; moderate hypertension, BP of 160-179/100-109 mm Hg; and severe as BP of ≥180/110 mm Hg.

Normally not less than two readings should be made at least 30 minutes apart before deciding if a patient has sustained hypertension or not. The appropriate cuff size should be used depending on the arm circumference of the patient. There is usually no urgency to reduce mild or moderate hypertension, unless indicated (see relevant section of text later). Severe hypertension with or without symptoms and any evidence of target organ damage should be treated promptly.

2.2 Types of hypertension

More than 90-95 percent of patients with hypertension are of the

primary or essential type, often with a positive family history. Usually, these patients do not need comprehensive investigations but, whenever possible, urinalysis, blood urea, electrolytes and creatinine are desirable.

For **secondary** hypertension, careful history and examination will provide clues to underlying causes that are worth investigating further. Secondary hypertension is suspected in the following:

- patients less than 40 years old with significant hypertension and no family history of hypertension
- patients with severe hypertension
- patients whose blood pressure is difficult to control despite good drug compliance
- patients with signs and symptoms suggestive of secondary cause
- patients with accelerated hypertension (with retinal changes with or without papilloedema)

Chronic renal disease is the commonest underlying cause for secondary hypertension. The other causes include: renal artery stenosis, phaeochromocytoma, Cushing's disease, primary aldosteronism (Conn's syndrome), coarctation of the aorta, and pregnancy-induced hypertension. Occasionally, hypertension is caused by medications such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives or decongestants.

If these are suspected, referral should be made to a specialist for further investigation.

2.3 Management of hypertension

The decision to treat hypertension should be based on patient's overall cardiovascular risk rather than the level of blood pressure alone.

2.3.1 Non-pharmacological

Non-pharmacological intervention is recommended for all grades of hypertension. This is the first line of management for mild to moderate hypertension except if the patient has the following:

- multiple cardiovascular risk factors
- diabetes
- renal impairment
- past history of cardiovascular event
- target organ damage

Non-pharmacological measures that have been shown to be effective in clinical trials include:

- weight reduction in obese subjects
- reduction in alcohol intake
- smoking cessation
- regular physical activity
- moderate reduction in dietary sodium intake

2.3.2 Pharmacological

If non-pharmacological measures do not reduce blood pressure to normal (<140/90 mm Hg) after 6-8 weeks in mild to moderate hypertension, drug treatment should be added. However, in patients with diabetes and renal impairment, it is recommended that BP should be less than 130/85 mm Hg.

Unless contraindicated or if there is any specific indication, a diuretic and/or a beta-blocker are the preferred first line of treatment. However, recent trials have shown that ACEI and calcium channel blockers can be used as first line drugs. Ideally, target levels of blood pressure should be achieved using one drug and once daily dosing to enhance patient compliance. This may not always be possible in practice and drug combination is required.

If there are no specific contraindications (e.g. asthma for beta-blockers; gout for thiazides; diabetes is a relative, but not absolute,

contraindication for thiazides), single agent treatment may be started with:

- *Hydrochlorothiazide 12.5- 25 mg orally daily*

  OR

- *Atenololol 25-100 mg orally as a single dose*

  OR

- *Propranolol 40-80 mg orally two- three times daily*

  Doses of hydrochlorothiazide greater than 25 mg produce little extra hypotensive effect but increase the risk of high plasma uric acid or low serum potassium level.

  Loop diuretics (frusemide) produce intense and inconvenient short-term diuresis and are no more effective than thiazides in reducing blood pressure in mild to moderate hypertension. However, frusemide should be used in hypertension complicated by heart failure, severe hypertension, and hypertension related to chronic renal failure.

In general, the control of blood pressure is more important than the class of antihypertensive drug used. Effective drug combinations based on the Fiji EDL include:

- *Atenolol 25-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two- three times daily*
  WITH

  Hydrochlorothiazide 25-50 mg orally daily

- *Atenolol 25-100 mg orally as a single dose*

  OR

  Propranolol 40-80 mg two- three times daily

  WITH

  Nifedipine SR 20-40 mg orally twice daily

- *Nifedipine SR 20-40 mg orally twice daily*

  WITH

  Enalapril 2.5-40 mg orally once daily

- *Enalapril 2.5-40 mg orally once daily*

  WITH EITHER

  Hydrochlorothiazide 25-50 mg orally daily

  OR

  Frusemide 40-80 mg orally daily

  Hydralazine should rarely be used on its own. It produces headache, reflex tachycardia (both prevented by beta-blockade) and fluid retention (prevented or treated by a thiazide diuretic).

  The angiotensin converting enzyme inhibitors (ACEI) can be used as monotherapy or in combination. They should be considered as the drug of first choice in the management of hypertension in the following conditions:

  - complicated by heart failure

- requiring treatment after a myocardial infarction
- associated with left ventricular systolic dysfunction
- occurring in diabetic patients (ideally, renal function should be monitored)

If an ACEI is indicated:

- *Enalapril 2.5-40 mg orally daily*

  If the dose is above 20 mg daily, it can be given as twice daily but the total daily dose should not exceed 40 mg.

Methyldopa should seldom be used as first-line treatment in non-pregnant hypertensives as it may produce mental depression, impotence in males and rarely autoimmune haemolytic anaemia. It is occasionally useful where response to other agents is inadequate or other antihypertensive drugs are not available.

2.4 Hypertensive emergency (urgent blood pressure reduction)

This is seldom needed but may be required in hypertensive encephalopathy, acute hypertensive heart failure, acute myocardial infarction, dissecting aneurysm and phaeochromocytoma. Patients with these conditions should be admitted to the hospital and monitored. The aim is to reduce blood pressure within 60-90 minutes.

While the blood pressure may respond to oral agents (as above), initial parenteral treatment may be needed:

- *Hydrallazine 5 mg bolus intravenously (IV) over 5-10 minutes and repeated every 20 minutes up to a maximum of 20 mg followed by intravenous infusion of hydrallazine (see Appendix).*

  OR

- *Labetalol (100 mg per 20 ml); initial dose of 20-40 mg given intravenously over 1-2 minutes and repeated at intervals of 5-10*

minutes until 200 mg have been given. Alternatively, labetalol may be given as a continuous intravenous infusion at a rate of 2 mg per minute (see Appendix).

After initial stabilisation, the patient should be changed to oral treatment for maintenance.

The practice of opening a nifedipine 10 mg capsule and giving it sublingually is **not supported** as emergency treatment. It delivers an uncertain dose and most of the effect occurs as a result of absorption of the swallowed drug. **On occasions, in older patients, unexpected rapid falls in blood pressure have resulted in stroke or myocardial infarction.** In Fiji, nifedipine 10 mg capsule is restricted to obstetric and paediatric practice.

Please note that in some situations, urgent reduction with intravenous drugs over a short period of time is not recommended (e.g. severe, uncomplicated essential hypertension; severe hypertension postoperatively in a patient suffering from pain; severe asthma). In such situations, oral antihypertensive drugs can be used and blood pressure reduction can be achieved in 48-72 hours.

2.5 Hypertension in children

2.5.1 Definition

Hypertension in children is defined statistically as systolic/diastolic blood pressure levels greater than 95th percentile for age, gender and height. Below are normal blood pressure readings at various ages.

Table 1. Normal blood pressure in children

Age (years)	Systolic blood pressure (95th percentile)	Diastolic blood pressure (95th percentile)
Neonate	95	70
0-5	115	75
6-10	120	80
11-15	135	85

2.2.2 Etiology

Hypertension in the paediatric age group is uncommon. Renal parenchymal disease, renovascular disease and coarctation of the aorta account for 90 percent of all hypertension in children. Essential hypertension is rare before 10 years of age. In adolescence, essential hypertension is the commonest type of hypertension.

2.2.3 Non-pharmacological management

Non-pharmacological interventions are used initially for management of essential hypertension in children. These include:

- weight reduction
- low salt diet
- physical activity

2.5.4 Pharmacological management

a. Asymptomatic hypertension

Refer for work up for secondary causes of hypertension.

b. Symptomatic hypertension

Symptomatic hypertension requires immediate treatment.

In Fiji, post-streptococcal glomerulonephritis is the most common cause of hypertension requiring treatment.

- *Frusemide 1-2 mg per kg intravenously 8-12 hourly*

If blood pressure is not controlled, ADD

- *Nifedipine 0.25-0.5 mg per kg orally (up to a maximum of 10 mg) every 4-8 hours*

In severe cases, ADD

- *Enalapril 0.1 mg per kg orally daily increasing up to 0.5 mg per kg daily over two weeks*

In cases where urgent reduction of blood pressure is necessary:

- If the patient is conscious and not vomiting:

  Nifedipine 5 mg (for patients <2 years) and 10 mg (for patients >2 years) crushed and swallowed with water or given by orogastric tube. Repeat dose every 20 minutes to achieve BP control.

- If level of consciousness is impaired or patient is vomiting:

  Hydrallazine 0.1-0.2 mg per kg intravenously or intramuscularly (IM) stat then 4-6 micrograms per kg per minute by intravenous infusion

  OR

  Labetalol 0.2 mg per kg intravenous push over 2 minutes. If no response in 5-10 minutes, increase to 0.4 mg per kg up to a maximum of 60 mg.

2.6 Isolated systolic hypertension in the elderly

Systolic blood pressure rises (systolic BP of >160 mm Hg and diastolic BP of <90 mm Hg) with age in most, but not in all patients. Recent trials show that reducing isolated systolic hypertension at all ages reduces risk of stroke and heart failure.

- *Hydrochlorothiazide 12.5-25 mg orally daily*

And, if necessary ADD

- *Atenolol 25-100 mg orally daily*

  AND/OR

- *Nifedipine SR 20-40 mg orally twice daily*

Always start with low doses and increase them slowly in the elderly patient. Target systolic pressure is 160 mm Hg or below which can be achieved gradually over several weeks.

2.7 Blood pressure monitoring

Once patients have been stabilised on regular treatment they should normally be reviewed at 2-3 monthly intervals. Serum creatinine and electrolytes need to be measured within the first 6-8 weeks of stable treatment and thereafter annually if there is no special reason for measuring more often (e.g. patients who have shown a bigger than expected reduction in serum potassium on diuretics or those with raised serum creatinine at diagnosis).

8.8 Resistant hypertension

Apparent resistance to antihypertensive drugs may be due to several different causes and these should be explored. They include:

- non-compliance with treatment (almost certainly the commonest cause)
- failure to detect a primary cause especially renal artery stenosis or primary hyperaldosteronism
- ingestion of drugs interacting with the antihypertensive treatment, e.g. NSAIDs, steroids
- ingestion of a large sodium load or consumption of a large amount of alcohol

8.8 Hypertension in pregnancy

Hypertension less than 20 weeks of pregnancy is due to either:

- chronic hypertension or
- chronic hypertension with superimposed pre-eclampsia

After 20 weeks of pregnancy, hypertension can be due to:

- pregnancy- induced hypertension (PIH) – hypertension without proteinuria

- mild pre-eclampsia
- severe pre-eclampsia
- eclampsia

8.8.1 Mild pre-eclampsia

Mild pre-eclampsia is defined as hypertension that occurs after 20 weeks of pregnancy and characterized by the following:

- two readings of diastolic blood pressure of 90-110 mm Hg taken at least four hours apart
  PLUS
- proteinuria 2+ and
- no signs or symptoms of severe disease (see below)

It is recommended that patient be admitted if:

- BP ≥ 150/100 mm Hg on two occasions
- there are symptoms of severe disease (see below) and
- there is concern about foetal well being
- follow-up and accessibility of obstetric care is a concern

Mild pre-eclampsia does not usually require treatment. However, if the BP is >160/100 mm Hg,

- *Methyldopa 250-500 mg orally two-three times a day*

  AND, if necessary, ADD

- *Hydrallazine 25 mg three orally times daily*

It is recommended that BP should be maintained at 130-140/80-90 mm Hg.

8.8.1 Severe pre-eclampsia

Severe pre-eclampsia is defined as hypertension that occurs after

20 weeks of pregnancy and characterized by the following:

- diastolic BP >110 mm Hg
- proteinuria 3+
- presence or absence of epigastric tenderness, headache, visual changes, hyperreflexia, pulmonary oedema, oliguria and convulsions

Severe pre-eclampsia needs urgent referral and transfer to the hospital.

In the hospital, the management of severe eclampsia includes the following:

- If the diastolic BP >110 mm Hg

  Nifedipine 10 mg orally stat and repeat dose as necessary to maintain diastolic BP at 90-109 mm Hg

  OR

  Hydrallazine 5 intravenously as a bolus dose

- Start intravenous fluids, e.g. 500 ml plasma expander over one hour.
- Maintain strict fluid balance chart.
- Monitor BP, pulse and respiration regularly.
- Insert indwelling catheter and maintain urine output at >30 ml/hr.

For maintenance of blood pressure:

- *Nifedipine 10-20 mg orally as required to a maximum of 60 mg daily to keep diastolic BP <110 mm Hg*

  OR

- *Hydrallazine by slow intravenous infusion, 50 mg in 100 ml of dextrose saline in a chamber titrated in order to keep diastolic BP <110 mm Hg*

It is not necessary to reduce BP to normal levels, rather it is more important to maintain BP at "safe" level of diastolic BP of <110 mm Hg. The definitive treatment for pre-eclamptic toxaemia (PET) is delivery of the baby. This should be undertaken as soon as it is practicable, preferably in a referral hospital.

If convulsion occur or is imminent, administer magnesium sulphate as described below.

- If infusion pump is available:

  Magnesium sulphate 4 grams as loading dose diluted in 100 ml of dextrose 5% to be infused slowly over 20 minutes. This is to be followed by maintenance dose of magnesium sulfate 12.5 grams in 100 ml of dextrose 5% to be infused at 1gram per hour (see Appendix).

- If infusion pump is not available:

  Magnesium sulphate 50%, 4 grams in 20 ml (8 ml in 12 ml of diluent) intravenously over 10-15 minutes

  PLUS

  Magnesium sulphate 50% (10 ml) intramuscularly and 0.5 ml 1% lignocaine in each buttock

After delivery of the baby (24-48 hours) when the patient's condition is stable, blood pressure can be maintained with either:

- *Methyldopa 250-500 mg orally two-three times daily*

  OR

- *Nifedipine SR 20-40 mg orally twice daily*

  OR

- *Hydrallazine 25-50 mg orally three times daily.*

3 Ischaemic heart disease

Myocardial ischaemia results from disparity between the oxygen demand and oxygen supply. The commonest cause of myocardial ischaemia is atherosclerotic disease of the coronary arteries. The major risk factors for coronary atherosclerosis include: positive family history (premature mortality due to coronary artery disease in first degree relatives), smoking, sedentary lifestyle, obesity, diabetes, hypertension and hyperlipidaemia.

However, there are many other conditions that usually in the presence of pre-existing coronary artery disease can precipitate myocardial ischaemia and identifying them are important in the management. Some of these conditions include: anaemia, arrhythmias, thyrotoxicosis and valvular heart disease. Therefore, simply treating the presenting syndrome and ignoring the associated risk factors is a poor and inadequate approach to the patient with coronary artery disease.

3.1 Prevention of cardiovascular disease

The burden of cardiovascular disease is increasing in many developing countries including Fiji. Paradoxically, this is happening at a time when the mortality and morbidity from coronary artery disease are diminishing in many developed countries. Possibly, this discrepancy can be explained by the varying emphasis placed on primary prevention strategies between developed and developing countries.

This section deals with preventive intervention for the **individual patient**. This is distinct from complementary social interventions that are needed to reduce risks at a population level, e.g. tobacco taxation, food standards to lower population fat intake or access to safe places for physical activity.

The major non-modifiable risk factors are age, gender and family history. These together with the modifiable risk factors (i.e. smoking, diabetes mellitus, dyslipidaemia and hypertension) account for most cases of

cardiovascular disease. Risk factors should be assessed in any appraisal of a patient with coronary artery (or any other arterial) disease.

3.1.1 Primary prevention

Strategies that are considered to be beneficial include:

- smoking cessation
- treatment of hyperlipidaemia
- treatment of hypertension
- management of diabetes mellitus

A balanced and appropriate diet exerts a protective effect. Patients should be helped to achieve ideal body weight (body mass index between 20 and 25 kg/m^2) and should reduce dietary saturated fat and added salt. Less than 30 percent of the total dietary energy content should come from fats. There is evidence that at least two serves of fish a week provide further benefit.

Physical activity may not be an independent protective factor but may have an impact on obesity, cardiorespiratory fitness and elevated blood pressure.

The major risks associated with lipids are elevated LDL cholesterol and reduced HDL cholesterol. There can be little doubt about the need to treat elevated LDL cholesterol in patients with familial hypercholesterolaemia and a poor family prognosis. However, debate currently centers on the appropriate cut off point for starting lipid lowering treatment in the population at large.

In some developed countries, it is recommended to treat patients with multiple cardiovascular risk factors who have a total cholesterol at or above 5.5 mmol/L. First-line treatment should be dietary management but thereafter pharmacotherapy often based on the use of statins is advocated.

Guidelines and studies on which to base them are lacking for most developing countries.

2.2.2 Secondary prevention

It is not too late to improve the natural history of cardiovascular disease even after it is clinically apparent as angina, claudication, transient ischaemic attacks or occlusive events.

As described above, modification of modifiable risk factors together with the near routine use of aspirin, beta-blockers, statins and in most cases ACEIs is supported by good quality clinical trials which demonstrate improved survival after myocardial infarct.

3.2 Principles of management

The principles of management of ischaemic heart disease are:

- patient education
- modification of risk factors
- identification and management of precipitating factors
- drug therapy
- consideration for coronary revascularization

3.3 Management of coronary pain syndromes

Pain attributable to coronary artery obstruction occurs in each of the three coronary pain syndromes-**stable angina, unstable angina and myocardial infarction. However, there are patients who are asymptomatic but have evidence of myocardial ischaemia.**

3.3.1 Stable angina

Angina pectoris is pain, usually felt in the central chest, which may radiate to the neck, both arms and occasionally, the back that occurs during exercise or emotional stress and is rapidly relieved by rest. Angina is stable if, for at least one month, it has been brought on by the same amount of exertion and is not accompanied by pain at rest – unless caused by emotional stress.

a. Drug therapy

i. Acute attack

- *Glyceryl trinitrate 300-600 micrograms sublingually*

Repeat every 5 minutes if pain persists up to a maximum of three tablets. If pain persists, check that tablets are active (a tingling sensation if put on the tongue). If no response and tablets are of good quality, treat as for unstable angina. Patients should sit or lie down when first using glyceryl trinitrate because of the possibility of symptomatic hypotension. Glyceryl trinitrate should not be exposed to light.

ii. Subsequent treatment

Patients should be on aspirin and will usually require further treatment to improve exercise tolerance. Initially, use

- *Aspirin 100-150 mg orally daily*

AND

- *Atenolol orally 50-100 mg daily*

OR

- *Propranolol 40-80 mg orally two-three times daily*

The other drugs that can be considered in uncontrolled angina include:

- *Isosorbide dinitrate 10-40 mg orally three times daily*

To prevent the development of nitrate tolerance, there

should be an interval of eight hours between the night dose and the first dose the next day.

- *Verapamil 40-120 mg orally 2-3 times daily*

  OR

- *Nifedipine SR 20-40 mg orally twice daily*[1]

Please note that the combination of a beta-blocker and verapamil is contraindicated.

iii. Use of glyceryl trinitrate as prophylaxis

Nitrates may be used prophylactically for any form of physical or emotional stress.

- *Glyceryl trinitrate 300-600 micrograms sublingually*

iv. Refractory stable angina

Occasionally, patients will not respond to preventive treatment even if a combination of beta-blocker, calcium channel blocker (nifedipine) and nitrates is prescribed.

If pain persists despite addressing the modifiable risk factors and optimum drug therapy, it is recommended that the patient be referred for further cardiac assessment with the view of possible echocardiography, exercise stress test and coronary revascularization procedures.

3.3.2 Unstable angina

This coronary syndrome is characterised by anginal pain which is severe, of recent onset, or which has recently become abruptly worse. Angina occurring at rest or following recent myocardial infarction is also classified as unstable angina.

1Isosorbide monotitrate and diltiazem are drug options but they are not available in the Fiji EDL.

There is evidence that the reason for unstable angina is a sudden change in a previously stable plaque within an atheromatous coronary artery. Rupture of the endothelium over and around the plaque leads to vasoconstriction, platelet adhesion and an inflammatory response. If the vessel becomes completely occluded, a myocardial infarct will result. However, commonly, occlusion is not complete and the area around the plaque settles down over a period of a few weeks.

All patients diagnosed to be suffering from unstable angina should be referred for admission preferably to the Coronary Care Unit (CCU).

The most important distinction to make is between unstable angina and an acute myocardial infarction. The factors favouring an acute myocardial infarction include pain of more than 15-20 minutes duration; pain not responsive to nitrates or requiring narcotics; systemic features such as pallor, sweating, vomiting and hypotension. If any or all of these are present, refer immediately for admission to the hospital. An electrocardiogram (ECG) is critically important in making the diagnosis.

The aim of treatment in unstable angina is to relieve the pain and to modify the environment around the "active" plaque to reduce the likelihood of coronary artery occlusion. However, it should be borne in mind that chest pain might be secondary to other serious conditions like acute myocardial infarction, pericarditis, aortic dissection and pulmonary embolism.

For initial treatment:

- Oxygen therapy
- *Aspirin 150-300 mg orally stat*

  AND

- *Morphine 2.5-10 mg intravenously as needed*

  AND

- *Atenolol 50-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two-three times daily*

If pain persists and if the patient's hemodynamic status allows, ADD:

- *Nifedipine SR 20-40 mg orally twice daily*

  AND, if required, ADD

- *Isosorbide dinitrate 10-40 mg orally three times daily*

If pain still persists, in addition, heparin should be given as follows:

- *Heparin 5,000 units by bolus dose intravenously followed by 1,000 units per hour by intravenous infusion*

  Subsequent doses should be adjusted to keep the APTT (activated partial thromboplastin time) between 60 and 85 seconds. The APTT should be measured 6-hourly until stable, then daily.

  Heparin will normally be required for at least three days and possibly longer depending on clinical response.

If symptoms persist despite all of the above treatment, cardiological intervention, if available, is required with a view to further investigation and revascularisation.

3.3.3 Myocardial infarction

Complete occlusion of a coronary artery leads to the death of the cardiac muscle it supplies. Occlusion of a large, proximal vessel may cause myocardial ischaemia of such an extent that the patient dies rapidly of pump failure. Alternatively, a ventricular arrhythmia

(tachycardia, fibrillation) may reduce cardiac output to such a drastic extent that, if the abnormal rhythm cannot be reversed, death is most likely.

Severity of pain by itself is a poor indicator of the extent of myocardial damage especially in a diabetic patient. Poor cerebral function, peripheral circulatory signs such as pallor, sweating and hypotension combined with extensive ECG changes with or without arrhythmias point to a large infarct.

The aims of immediate management are to:

- relieve pain
- achieve coronary reperfusion and minimise infarct size
- prevent and treat complications
- allay the patient's anxiety

All patients with suspected myocardial infarction should be admitted to hospital and preferably to a unit where cardiac monitoring can be performed.

a. Immediate management

Unless the patient is very anxious, routine use of a sedative drug (e.g. diazepam) is not recommended.

i. Pain relief

- *Morphine 2.5-10 mg intravenously with repeat doses as necessary*

AND

- *Glyceryl trinitrate 600 micrograms sublingually with a repeat dose in 5 minutes if no response*

It should not be given in hypotension and if right ventricular infarction is suspected.

ii. Limiting infarct size

- *Aspirin 300 mg* chewed or dissolved before swallowing
- *Oxygen 4-6 L per minute* by mask
- Thrombolytic therapy – *streptokinase*

The indications for thrombolytic therapy includes chest pain that has developed within the previous 12 hours with either ST-segment elevation myocardial infarction (STEMI) or development of new left bundle branch block (LBBB) or both.

Streptokinase

Administer streptokinase 1.5 million International Units (IU) by intravenous infusion over 30-60 minutes. If blood pressure falls as a result of the infusion, reduce the rate or stop briefly and restart at half the previous rate.

Streptokinase induces antibody formation that makes it unsuitable for use in subsequent episodes of coronary occlusion. It may also produce allergic symptoms (i.e. bronchospasm, angio-oedema, urticaria, flushing and musculo-skeletal pain).

The contraindications to thrombolytic therapy are shown in Table 1.

Patients most likely to benefit from thrombolytic treatment are those presenting early with large anterior infarcts especially if complicated by heart failure. Those presenting after 24 hours have less chance of benefit and increased risk of cardiac rupture.

For mild or moderate allergic reactions to streptokinase:

- *Promethazine 25 mg intravenously*

  OR

- *Hydrocortisone 100 mg intravenously*

Table 2. Contraindications to thrombolytic therapy

Absolute contraindications	Relative contraindications
Active internal bleeding Recent surgery, biopsy or trauma Prior cardiopulmonary resuscitation Known bleeding disease (haemophilia, platelet disorders Recent or disabling stroke Neurosurgery within 6 months A previous intracranial bleed Severe uncontrolled hypertension (a blood pressure greater than 180/110 mm Hg during presentation) Aortic dissection Coma Oesophageal varices	Previous peptic ulcer disease Warfarin therapy Liver disease Previous streptokinase therapy within the last four years Previous hypersensitivity to streptokinase Heavy perivaginal bleeding Diabetic proliferative retinopathy Pregnancy

Severe allergic reactions should be treated as for anaphylaxis.

- *Adrenaline 1 in 1,000 solution, 0.5- 1 ml (0.5-1 mg) intravenously over 5 minutes*

If response is poor, increase dose to:

- *Adrenaline 1 in 1,000 solution 2 to 5 ml (2-5 mg) intravenously over 5 minutes*

  AND ADD

- *Promethazine 25 mg intravenously*

  OR

- *Hydrocortisone 100 mg intravenously*

b. Management in the post-infarct period

i. Beta-blockers

- *Atenolol 25-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two-three times twice daily*

The benefit persists long-term and beta-blockade should be continued indefinitely.

ii. Angiotensin converting enzyme inhibitors (ACEI)

- *Enalapril 5-40 mg orally daily*

Outcome is improved after myocardial infarction with these agents. ACEIs should be started 24-48 hours after the acute episode in patients with a previous myocardial infarct, diabetes mellitus, hypertension, anterior infarct or evidence of persisting left ventricular dysfunction. Persistent hypotension and/or renal dysfunction are the only major contraindications.

iii. Antiplatelet agent

- *Aspirin 150-300 mg orally daily*

iv. "Statin" (hydroxymethylgutaryl CoA reductase inhibitor) drug

These compounds which inhibit one of the crucial steps in the biosynthesis of cholesterol have a limited and as yet not fully defined place in the primary prevention of cardiovascular disease (see text later). Recent large-scale trials have demonstrated a substantial role for them in the secondary prevention of coronary thrombosis and myocardial infarction. The benefits may not be fully explained by their lipid-lowering action so it is possible that an alternative mode of action may be involved. Survival benefits have been shown in patients with comparatively low, as well as elevated, total cholesterol at the outset.

The statins are relatively free from serious adverse effects although safety beyond 10 years has yet to be established. The commonest adverse effect is reversible myalgia with elevated plasma creatine kinase levels and, rarely, rhabdomyolysis.

The statin group of drugs is not available in the Fiji EDL at the time of this publication. The following drugs can be used: lovastatin (10-20 mg daily), simvastatin (10-40 mg) and atorvastatin (10-40 mg). Note that other statins are probably equally effective and the choice should rest on the local cost.

Thus a combination of lifestyle modification, and ongoing treatment with aspirin, beta blockade, a statin, and, in many cases, ACEIs has been justified by clinical trials of adequate size and duration.

The administration and supervision of this potentially complex regimen is best organised through a cardiac rehabilitation program for the first few months after the myocardial infarction.

c. On discharge

At the time of discharge, a cardiac rehabilitation program is recommended. The program should include the following:

- drug therapy
- patient education
- modification of risk factors
- avoidance of precipitating factors
- dietary management
- resumption of work, driving and sexual activity
- advice on air travel
- further investigations, e.g. stress test, echocardiography, and coronary angiography with a view to possible intervention

4 Heart failure

Heart failure is a clinical condition due to inability of the heart to pump adequate blood to meet the metabolic demands of the tissues. It is a syndrome and not a disease in itself. The development of chronic heart failure can take months to years during which various compensatory mechanisms come into play in response to the initial pathological process.

Heart failure is always the result of a primary underlying cause and this should always be looked for and, if possible, treated in the course of investigation and management. More often, the heart failure is in a compensated state and symptoms develop due to one or many precipitating factors. Identification and management of these precipitating factors are very important. Hence, in the treatment of heart failure it is vital to address both the underlying etiology and the precipitating factors.

4.1 Causes of heart failure

The common causes of heart failure are:

- ischaemic heart disease (see relevant section)
- valvular heart disease remains a common and important cause of heart failure in Fiji
- hypertension is a treatable cause that is also common
- hyperthyroidism – cardiac manifestation might be the only manifestation of this condition
- cardiomyopathy that can occur from several different causes

The less common causes of heart failure are:

- congenital heart disease
- infective endocarditis
- myocarditis
- cor pulmonale
- pericardial diseases

4.2 Precipitating factors of heart failure

Many factors may cause an already compromised heart to fail. These include:

- poor drug compliance
- excess dietary salt
- fluid excess
- drugs – NSAIDs, steroids, antidepressants, verapamil
- arrhythmias – tachyarrhythmias or bradyarrhythmias (most commonly atrial fibrillation)
- intercurrent infections particularly respiratory infections
- acute myocardial infarction
- infective endocarditis
- anaemia
- hyperthyroiroidism
- uncontrolled hypertension
- physical overexertion
- pregnancy

4.3 General management of chronic heart failure

The principles in the management are:

- non-pharmacological treatment
- pharmacological treatment
- treatment of underlying etiology
- treatment of precipitating factors
- other general measures

4.3.1 Non-pharmacological

- weight reduction
- salt restriction – ideally, no added salt is advised
- water restriction – this is not necessary unless there is dilutional hyponatraemia; in this situation, reduction to minimum of 1.5 liter per day is recommended

4.3.2 Pharmacological

The aims of drug treatment are to improve the prognosis and to relieve and control the symptoms and signs of heart failure. The commonly used drugs in the treatment of heart failure include:

- diuretics – frusemide, spironolactone, thiazides
- angiotensin converting enzyme inhibitors – unless contraindicated, virtually all patients with heart failure should be on ACEI
- digoxin
- beta-blockers – carvedilol, metoprolol and bisoprolol have been proven in clinical trials to be effective in heart failure (these drugs are not available in the Fiji EDL)
- isosorbide dinitrate
- hydrallazine

a. Mild to moderate heart failure

Diuretics and angiotensin converting enzyme inhibitors (ACEI) are both first-line treatment for heart failure Conventionally, treatment is commenced with diuretics and ACEI added to potentiate the response.

- *Frusemide 40-80 mg orally daily*

- *Enalapril 2.5 mg daily followed by gradual increments to a maximum of 20 mg daily*

Hypotension can result after the first dose in the elderly, patients who are already dehydrated from previous diuretic therapy, in the presence of pre-existing hyponatraemia, and concurrent treatment with other anti-hypertensive drugs.

If heart failure is not controlled by these drugs, ADD

- *Digoxin 0.0625-0.5 mg orally daily according to age and renal function.*

Digoxin is recommended if the patient is in atrial fibrillation and the ventricular rate is not controlled.

If ACEI cannot be used in patients with heart failure because of angioedema, worsening renal function or intractable cough, alternative treatments is:

- *Hydrallazine 25-50 mg orally two-three times daily*

  PLUS

- *Isosorbide dinitrate 10-20 mg three times a day*

b. Severe heart failure

If despite the above treatment the heart failure worsens or fails to respond, hospitalization is recommended. Treatment in the hospital includes:

- *Frusemide up to a maximum of 1 gram daily in divided doses*

  Absorption of oral diuretics is often impaired in severe heart failure and frusemide starting with 80 mg IV BD is advised. Patients having significant renal impairment will require higher doses of frusemide.

  PLUS

- *Enalapril orally as above*

  PLUS

- *Spironolactone 25-50 mg orally daily*

  PLUS

- *Digoxin 0.0625-0.5 mg orally daily according to age and renal function*

If these treatments are inadequate, the following can occasionally be required:

- *Hydrocholorothiazide 25-50 mg orally daily*

  OR

- *Hydrallazine 25-50 mg orally three times daily*

  PLUS

- *Isosorbide dinitrate 10-20 mg orally three times daily*

  Frusemide and hydrocholorothiazide act at different sites in the nephron and will supplement each other's action if used together.

4.3.3 Treatment of underlying etiology and precipitating factors

In all cases, the underlying etiology and precipitating factors must be treated.

4.3.4 General measures

The general measures in the treatment of chronic heart failure may include:

- bed rest
- oxygen therapy
- regular weight monitoring
- patient education
- therapeutic aspiration of fluids from serous cavities
- heparin 5,000 units subcutaneously BD till patient is mobilized as prophylaxis for deep vein thrombosis (DVT)

4.4 The role of beta-blockers in heart failure

Beta-blockers are used to counteract the effect of the activated sympathetic nervous system in heart failure.

Studies have shown that beta-blockers are useful in all stages of heart failure from various causes except in decompensated heart failure. The beneficial effects include improvement in survival, reduction in all cause mortality and hospitalization rate, and improvement of ejection fraction and functional class.

It is recommended that beta-blockers should be started in small doses and increments made to maximum tolerable dose.

The drugs that have shown efficacy in clinical trials are carvedilol, metoprolol and bisoprolol. All these drugs are not available in the Fiji EDL. To date, the use of other beta-blockers (i.e. atenolol and propranolol) in heart failure has not been studied.

4.5 Acute cardiogenic pulmonary oedema

Immediate treatment should include:

- bed rest
- maintain airway
- administer oxygen 4-6 L per minute by mask
- fusemide 40-80 mg IV repeated in 30 minutes if needed
- morphine 5-10 mg IV
- salbutamol nebulizer 2.5-5 mg 4-hourly, if there is evidence of bronchospasm (e.g. wheezing)
- sublingual glyceryl trinitrate if patient is not hypotensive
- other treatments that may be required when there is significant hypotension:
  - dobutamine infusion (Refer to Appendix)
  - dopamine infusion if patient is hypotensive (refer to Appendix)
- ventilatory support if required

The underlying etiology and precipitating factors must be treated and the general measures discussed above have to be followed.

4.6 Diastolic heart failure

Patients with classical signs and symptoms of heart failure but normal cardiac (left ventricular) ejection fraction on investigation may have:

- fluid overload (or renal failure producing the same picture)
- a mechanical cause for the heart failure such as severe mitral regurgitation
- principally diastolic heart failure resulting in poor diastolic filling and correspondingly poor forward perfusion

The main causes of this relatively uncommon form of heart failure include:

- pericardial disease
- myocardial hypertrophy with fibrosis (e.g. long-standing hypertension)
- atrial fibrillation and any other causes of poor diastolic filling
- infiltrative diseases (e.g. amyloidosis, sarcoidosis, haemochromatosis)

The importance of diastolic heart failure and its recognition lie in the fact that patients with this condition are very sensitive to the effects of diuretics and vasodilators both of which can precipitate severe reductions in cardiac output and in blood pressure.

> In a case of suspected diastolic heart failure referral to a consultant physician is advised.

5 Cardiac arrhythmias

Cardiac arrhythmias range from trivial ectopic beats to the life-threatening ventricular fibrillation. Whether or not an arrhythmia requires intervention depends largely on its capacity to make a significant impact on cardiac output.

In a patient whose myocardial function is already impaired (e.g. by a large infarct) a change from normal sinus rhythm to atrial fibrillation with a ventricular rate of 140 beats per minute may be sufficient to cause heart failure. By contrast, a young person with a normal myocardium may sustain a supraventricular tachycardia at the same rate for days without any evidence of cardiac decompensation.

> The urgency for intervention and the nature of that intervention are dictated equally by the situation in which the arrhythmia occurs and by the nature of the arrhythmia itself.

5.1 Causes of cardiac arrhythmias

The common and/or important causes of arrhythmias are:

- ischaemic heart disease
- valvular heart disease
- cardiomyopathy
- hypoxia
- electrolyte disturbance – hypokalaemia, hyperkalaemia, hypocalcaemia, hypomagnesaemia
- endocrine – hyperthyroidism, phaechromocytoma
- drugs – digoxin, tricyclic antidepressants
- congenital conduction abnormalities

5.2 Aims of treatment

In general, there are four aims in the treatment of cardiac arrhythmias:

- return the heart to normal sinus rhythm, if possible
- control the heart rate
- treat any associated risks (e.g. anticoagulant therapy in atrial fibrillation)
- treat the underlying cause

Most arrhythmias are benign and injudicious use of antiarrhythmic drugs can be harmful as many of them are proarrhythmic on their own.

5.3 Tachyarrhythmias

5.3.1 Atrial

a. Sinus tachycardia

This implies a persistent heart rate over 100 per minute in a resting patient.

It usually has an underlying cause such as anxiety, thyroid overactivity or systemic illness. The first approach should be to identify and treat the underlying cause.

If no obvious underlying cause is apparent, treatment is generally not needed.

b. Atrial premature complexes

Treatment is seldom required. If patient is symptomatic,

- *Atenolol 25-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two- three times daily*

c. Paroxysmal supraventricular tachycardia (PSVT)

This occurs intermittently and sometimes can be converted to sinus rhythm by carotid sinus massage, by the Valsalva manoeuvre or by holding ice cold water in the mouth. If these are ineffective,

- *Verapamil 5 mg intravenously slowly; repeat if needed up to 15 mg*

  OR

- *Adenosine 6 mg bolus intravenously over 5-10 seconds followed by 12 mg intravenously 2 minutes later and if needed, 18 mg intravenously thereafter.*

  Adenosine can produce chest pain and large falls in blood pressure. The half-life of the drug is short and recovery will occur within one minute normally without intervention. If the symptoms persist, aminophylline intravenously can be used.

If above drugs are not available,

- *Digoxin 0.25-0.50 mg orally stat,*
  repeat same dose orally six hours later,
  followed by 0.25 mg orally six hours after the second dose, and followed by 0.25 mg orally six hours after the third dose and continue at 0.25 orally mg daily.

  If rapid control is needed, digoxin may be given intravenously (see below under section on atrial fibrillation).

  The maintenance digoxin dose should be adjusted depending on the patient's renal function and serum potassium level.

Verapamil must never be given to a patient with a wide-complex undiagnosed tachycardia – QRS > 0.12 seconds. If there is any possibility that the rhythm is a ventricular tachycardia either use adenosine or treat as for ventricular tachycardia.

d. Prophylaxis for paroxysmal supraventricular tachycardia (PSVT)

A few patients may require prophylaxis if attacks are frequent. This may require electrophysiological investigation if available.

- *Atenolol 25-100 mg orally daily*

OR

- *Propranolol 40-80 mg orally three times daily*

If the above drugs are not effective or beta-blockers are contraindicated,

- *Amiodarone 200-400 mg orally three times daily for two weeks, followed by 200 mg daily or the minimum dose required to control the arrhythmia*
  and continue it indefinitely.

e. Atrial flutter and fibrillation

Atrial flutter usually presents with a 2:1 atrioventricular block and a regular rate of around 150 beats per minute. Atrial fibrillation presents with a similar rate which is however quite irregular. The aims of treatment are discussed below.

i. Control ventricular rate

This is only required if the ventricular rate is >100 per minute. The urgency to control the rate depends on the pre-existing ventricular rate.

- ***Digitalization***

  Digoxin 0.5-1.0 mg orally, followed by 0.25-0.5 mg every 4-6 hours up to a maximum of 1.5-2.0 mg in the first 24 hours.

Maintenance treatment thereafter will require digoxin 0.0625-0.5 mg daily depending on age, renal function and plasma digoxin level, if available. The intravenous route is rarely necessary because oral digititalization is just as effective.

However, if rapid digitalization is needed, digoxin may be given intravenously. The total loading dosage is 0.5-1.5 mg. A loading dose of 0.5 mg in 20 ml of normal saline is given as an intravenous infusion for 20 minutes. The remaining dose is also given intravenously over 20 minutes at intervals of 4-6 hours depending on the response over a period of 24 hours. The total digitalizing dose will need to be reduced if the patient has had digoxin in the preceding two-week period.

OR

- *Verapamil 5 mg intravenously up to 15 mg with careful monitoring of pulse and blood pressure*

For long-term control, digoxin can be used. If the ventricular rate is not controlled, a beta-blocker can be added.

- *Atenolol 25-100 mg orally daily*

OR

- *Propranolol 40-80 mg orally two-three times daily*

If beta-blockers are contraindicated,

- *Verapamil 40-80 mg orally three times daily*

ii. Treatment of underlying cause

Whenever possible, the underlying cause should be identified and treated (e.g. hypokalaemia, thyrotoxicosis).

iii. Reversal to sinus rhythm

For atrial fibrillation of recent onset, consideration should be given to convert it to sinus rhythm by electrocardioversion. Medical therapy with amiodarone or sotalol might be effective. In chronic AF, recent evidence suggests that rate control is just as effective as rhythm control.

iv. Anticoagulant therapy

Unless contraindicated and impractical (i.e. poor patient compliance, difficulty in monitoring), anticoagulant therapy should be considered in every patient with chronic AF to prevent thromboembolic event. If warfarin cannot be used for one reason or another, aspirin can be used as alternative but is not as effective as warfarin. The risk of thromboembolism increases in patients with previous thromboembolism, mitral valve disease, heart failure, hypertension and in older patients – especially women over the age of 75 years.

2.2.2 Ventricular arrhythmias

a. Premature ventricular ectopics including bigeminy

These are benign unless patients have underlying heart disease. If no obvious cause is found, the following measures are advisable:

- reduction coffee and tea intake
- cessation of smoking
- reduction alcohol intake

Drug treatment is not normally required but in symptomatic cases beta-blockade may be of value.

- *Atenolol 25-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two- three times daily*

b. Ventricular tachycardia (VT)

i. Non-sustained ventricular tachycardia

In hospitals where ECG monitoring is possible, treat only prolonged episodes that cause cardiovascular haemodynamic instability.

- *Lignocaine 2% , 50-100 mg intravenously over 1-2 minutes followed by 4 mg per minute intravenous infusion for a maximum of one hour then 1-2 mg per minute by intravenous infusion for 24 hours (see Appendix).*

If patient is unresponsive or if lignocaine is contraindicated use

- *Amiodarone 5 mg per kg intravenously via central venous line over 1-2 hours, followed by 10-15 mg per kg infused over a 24- hour period (see Appendix).*

ii. Sustained ventricular tachycardia

(a) With haemodynamic stability

Treatment is the same as for non-sustained ventricular tachycardia.

(b) With haemodynamic instability ("pulseless VT")

The treatment for this condition is immediate

intervention by defibrillation. Maintenance of sinus rhythm after electrocardioversion requires drug therapy:

- *Lignocaine 2%, 50-100 mg intravenously over 1-2 minutesfollowed by 4 mg per minute intravenous infusion for a maximum of one hourthen 1-2 mg per minute by intravenous infusion for 24 hours (see Appendix).*

If patient is unresponsive or if lignocaine is contraindicated:

- *Amiodarone 5 mg per kg intravenously by central venous line over 1-2 hours, followed by 10-15 mg per kg infused over a 24-hour period (see Appendix).*

If long-term oral drug treatment is required to maintain sinus rhythm:

- *Amiodarone 200-400 mg orally three times daily for two weeks as a loading dose followed by 200 mg orally daily or the minimum dose required to control the arrhythmia and continue it indefinitely.*

  OR

- *Atenolol 25-100 mg orally daily*

  OR

- *Propranolol 40-80 mg orally two- three times daily*

In difficult cases, sotalol can be considered but it is not available in the Fiji EDL.

c. Torsades de pointes

This is a rare, polymorphic ventricular tachycardia in which the QRS axis is constantly shifting (turning, "torsade"). Patients usually have a prolonged QTc (greater than 0.45 seconds) on the ECG. The rhythm is particularly prone to occur as a result of drug therapy including treatment with tricyclic antidepressants, phenothiazines, erythromycin and ketoconazole. Any drug suspected of causing the arrhythmia should be stopped immediately.

Patients should be managed in hospital with ECG monitoring. No consensus exists about the most effective treatment.

Lignocaine can be effective:

- *Lignocaine 1%, 75-100 mg intravenously over 1-2 minutes followed by 4 mg per minute for a maximum of one hour. Maintenance infusion thereafter of 1-2 mg per minute by intravenous infusion (see Appendix).*

Alternatively,

- *Magnesium sulphate 50%, 2 g intravenously over 10-15 minutes followed, if necessary, by 0.5-0.75 g per hour by intravenous infusion for 12-24 hours*

DO NOT use amiodarone to treat this arrhythmia as it may provoke it.

d. Ventricular fibrillation (see under cardiac arrest)

e. Ventricular asystole

Institute CPR.

- *Adrenaline 1mg (1 ml of a 1:1,000 solution) intravenously and repeat at 5 minute intervals until the return of spontaneous circulation is achieved*

- *Atropine 3 mg intravenously with a saline flush of 20 ml*

f. "Pulseless" ventricular activity

Treatment is as for ventricular asystole with the addition of the need to exclude potentially reversible causes such as:

- hypoxia
- hypovolaemia
- hypothermia or hyperthermia
- hypokalaemia or hyperkalaemia and metabolic disorders
- cardiac tamponade
- tension pneumothorax
- toxins, poisons, drugs
- thrombosis – pulmonary or coronary

5.3.3 Cardiac arrest (see also *Emergency Drug Guidelines)*

This is due to ventricular tachycardia, fibrillation, asystole or "pulseless" ventricular activity.

On the assumption that no immediate ECG diagnosis can be made of the underlying rhythm, immediately:

- Institute and continue cardio-pulmonary resuscitation (CPR).
- Defibrillate at 200 joules and, if no response, twice more at 360 joules (for children: 4 joules per kg).
- Secure airway and ventilate at maximum oxygen percentage achievable.
- Obtain an ECG tracing while maintaining CPR.
- Give adrenaline 1 mg (1 ml of a 1:1,000) as an intravenous bolus followed by 20 ml saline flush.
- Repeat defibrillation at 360 joules three times in succession.
- Repeat intravenous adrenaline. If venous access cannot be obtained in order to administer adrenaline, give adrenaline 5mg (5 ml of a 1:1,000 solution) diluted to 10 ml of normal saline may be given through the endotracheal tube.

- Repeat defibrillation at 360 joules on three successive occasions.

If no response has been achieved at this point, the chances of recovery are slight. Acidosis will certainly have occurred and may be treated with:

- *Sodium bicarbonate 8.4% (1 mmol per ml) 1 mmol per kg intravenously over 5-15 minutes*

  Sodium bicarbonate is also indicated in cases where arrhythmia is secondary to hyperkalaemia.

Control of rhythm may be attempted with:

- *Lignocaine 1%, 75-100 mg intravenously over 1-2 minutes followed by 4 mg per minute for the next hour and decreasing to a maintenance dose of 1-2 mg per minute thereafter (see Appendix).*

However, the mainstay of management remains effective CPR followed by urgent defibrillation. The primary drug in emergency treatment is adrenaline.

5.4 Bradyarrhythmias

5.4.1 Sinus bradycardia

Treat only if symptomatic. Exclude hypothyroidism, pituitary failure and drugs (e.g. beta-blockers, digoxin, and verapamil).

If intervention is required:

- *Atropine 0.6-1.8 mg intravenously and repeat as needed*

5.4.2 Atrioventricular block

Drugs (digoxin, beta-blockers or verapamil) may be the cause and

should be withheld if this appears to be the case.

a. First degree AV block

There is prolonged PR interval on ECG. This requires no treatment.

b. Second degree AV block

There are two types.

i. Wenckebach phenomenon (Mobitz type I)

In this type of AV block, there is successive prolongation of the PR interval followed by a dropped beat and the whole cycle repeats.

ii. Mobitz type II

There is a fixed ratio between the atrial and ventricular contractions in this type of arrhythmia, e.g. 2:1 or 3:1.

Generally, both types of AV block do not require treatment. Rarely, pacing may be required in Mobitz type II AV block.

c. Third degree heart block

This may be an acute and potentially spontaneously reversible complication of, for example, an acute **anterior or inferior** myocardial infarction. In centers where cardiac pacing is possible, this is the treatment of choice.

If pacing is not available give

- *Isoprenaline 20 micrograms intravenously,*
  repeat according to clinical response and
  follow with an infusion of 1-4 micrograms per minute or occasionally higher in patients who have been on beta-blockers (see Appendix).

There is anecdotal evidence for the efficacy of ephedrine, salbutamol and theophylline in maintaining response if the block has responded to isoprenaline.

The treatment of choice for chronic heart block is permanent cardiac pacing.

d. Sinoatrial block and sick sinus syndrome

These conditions require pacemaker therapy if persistent.

6 Peripheral vascular disease (PVD)

Atherosclerotic disease of the limb vessels is part of the overall spectrum of atheromatous disease. Risk factor modification therefore becomes as much a strategy in managing PVD as in the primary or secondary prevention of coronary artery disease and stroke.

6.1 Acute limb ischaemia

The signs and symptoms of this condition are:

- pain
- paresthaesia
- paralysis
- pulseless
- pallor

6.1.1 Causes

The common causes of acute limb ischaemia are:

- embolization from the heart
- thromboembolism from a large atheromatous vessels or an aneurysm
- *in situ* thrombosis of a diseased vessel
- use and abuse of ergot derivatives for migraine

This is an emergency. Urgent investigation and surgical consultation are required.

The limb should be protected using a bed cage and heel pad but should not be elevated.

6.1.2 Drugs

- *Morphine 2.5-5 mg intravenously as required to control pain*

  AND

- *Heparin sodium 5,000 units intravenously as a loading dose followed by 1,000 units per hour by intravenous infusion, and thereafter adjusted according to the APTT.*

If viability of the limb is restored:

- *Warfarin for 3-6 months aiming at an INR of 2.0 to 3.0*

There should be efforts to determine and treat the cause of the thromboembolic event. Depending on the cause, (e.g. atrial fibrillation), warfarin might need to be taken for an indefinite period.

Following a local thrombus rather than an embolic event:

- *Aspirin 150-300 mg orally, daily, which may be preferable to warfarin.*

All cases must be assessed by the surgical team as there may be a place for embolectomy.

6.2 Chronic limb ischaemia

The gradual loss of circulation caused by atheroma and local thrombosis may present with resting ischaemic pain often worsening, over a few weeks (and needing increasing amounts of analgesic), to ulceration and gangrene of the feet and toes.

The aims of management are:

- pain relief
- improvement and preservation of circulation
- treatment of sepsis
- modification of risk factors

6.2.1 Pain relief

Pain is often very severe and may require:

- *Morphine 2.5-10 mg intravenously repeated 4-hourly or more often until pain is controlled.*

6.2.2 Improvement and preservation of the circulation

- Surgical intervention will normally be required. Early consultation should be requested.
- Elevate the head of the bed.
- Reduce antihypertensive medication, if possible, to permit a high normal blood pressure.
- Withdraw any beta-blocking drugs, including eye drops.
- Sympathectomy may provide some symptomatic relief but will not improve ultimate outcome.
- Anticoagulation.

6.2.3 Treatment of sepsis

Patients should be referred to a hospital and early consultation with the staff of the divisional hospital is needed.

Organisms are commonly of several sorts but anaerobes will be present. It is recommended that culture of specimens from the ischaemic limb be taken prior to empirical antibiotic treatment:

- *Metronidazole 400 mg orally 8-hourly*

  PLUS

- *Flucloxacillin 500 mg orally 6-hourly*

  OR

- *Cephalothin 1-2 grams intravenously 6-hourly*

In patients hypersensitive to penicillin, erythromycin or chloramphenicol can be used.

The antibiotic may need to be modified once the culture results are available.

If the patient is not receiving heparin intravenously as treatment, this drug should be used prophylactically:

- *Heparin sodium 5,000-7,500 units subcutaneously every 12 hours*

6.2.4 Modification of risk factors

All modifiable risk factors listed under the section on Ischaemic Heart Disease should be addressed, i.e. **smoking is a major preventable risk.**

6.3 Intermittent claudication

Intermittent claudication refers to pain felt in the legs on exertion that is relieved by rest (as differentiated from spinal claudication where the pain persist even with rest). Most patients do not suffer loss of a limb as a result of this disease. Life expectation is dictated primarily by co-existing atheroma elsewhere - especially in the coronary circulation.

The single most important management strategy is **modification of risk factors.** The other modalities of treatment are:

- A graded exercise program, e.g. walking 50-60 minutes per day can extend claudication distance

- *Aspirin 150-300 mg orally daily*

6.4 Raynaud's phenomenon

Episodic blanching of the fingers, especially on exposure to the cold, is commonly benign but may be a symptom of an underlying connective tissue disease. Again, there should be efforts in identifying and treating the underlying cause.

The first line drug therapy is:

- *Nifedipine SR 20-40 mg orally twice daily*

If not successful in relieving symptoms and frequency of the attacks:

- *Glyceryl trinitrate 2% ointment 0.5 cm applied at the base of the affected fingers*

7 Cerebrovascular disease

Cerebrovascular disease is common. However our ability to treat stroke and reverse neurological damage once it has occurred is strictly limited. This makes it all the more important to institute **primary prevention** in the hope of reducing stroke incidence in the community.

7.1 Risk factors

The risk of stroke doubles with each succeeding decade above 20 years (although the absolute risk of stroke at 20 is very low). The major modifiable risk factors are:

7.1.1 Hypertension

Stroke risk increases linearly with initial height of blood pressure. Effective treatment of all forms of hypertension reduces stroke risk. Isolated systolic hypertension, common in the elderly and once thought to be benign, also constitutes a stroke risk.

7.1.2 Smoking

Smoking is clearly identified as a major risk factor for cerebrovascular disease, as it is for peripheral vascular and coronary artery disease.

7.1.3 Diabetes mellitus

While tight control of blood sugar has been shown to delay the progression of retinopathy and nephropathy, this evidence is not so strong for the occurrence of cerebrovascular disease.

7.1.4 Dyslipidaemias

Association exists between high low-density lipoprotein (LDL) cholesterol and stroke. While evidence exists for the protective effect of lowering lipids for coronary artery disease, similar evidence is fragmentary for cerebrovascular disease. It seems reasonable to

modify dyslipidaemia as part of risk factor management.

7.1.5 Pre-existing cardiovascular disease

Asymptomatic carotid artery stenosis increases stroke risk.

Atrial fibrillation with or without valvular disease of the heart disease or valve prosthesis is a major risk factor. Treatment with aspirin or warfarin reduces stroke substantially.

7.1.6 Drugs

Excessive alcohol consumption is a modifiable risk factor for stroke.

Oral contraceptives (irrespective of oestrogen dose) in women over 35 years of age who also smoke are a documented risk for cerebrovascular disease even though the absolute risk of stroke in this age group is low.

If patient has multiple risk factors:

- *Aspirin 150-300 mg orally daily*

7.2 Transient ischaemic attack (TIA)

A TIA is an episode of neurological impairment of sudden onset with a duration of less than 24 hours unassociated with symptoms of migraine. Common primary causes are emboli from a cardiac source or from major atheromatous extracranial vessels – especially the carotid arteries.

The risk of stroke after a TIA is 5-7 percent per year and as high as 10-18 percent per year for patients with greater than 70 percent carotid stenosis on the relevant side.

All patients should be considered for Doppler imaging of the carotid vessels and cardiac investigation for a source of emboli (including transoesophageal echocardiography if indicated and available).

The medical management in the **absence** of a source for embolism involves anti-platelet therapy:

- *Aspirin 150-300 mg orally daily*

If the TIA is due to a demonstrable cardiac cause and no evidence of cerebral hemorrhage by CT scan, warfarin may be commenced immediately. Surgical management of carotid stenosis (carotid endarterectomy and stenting) is an option in specialized centers.

7.3 Completed stroke

7.3.1 Diagnosis

The advent of CT and MRI (not available in Fiji) scans has given a more precise awareness of the causes of stroke. Clinical diagnosis unsupported by brain imaging has been shown to be less reliable than was earlier thought. This is important if causes with specific therapy are to be detected and treated early.

The two most important categories that have therapeutic importance are **thromboembolic disease** and **haemorrhage.**

2.2.2 Management of ischaemic stroke

The aims of management are:

- to reverse ischaemia
- to protect brain cells from the effects of ischaemia
- to rehabilitate the patient
- to introduce vigorous secondary prevention

a. Reversing ischaemia

The use of streptokinase has shown no benefit and the risk of bleeding is high. Tissue plasminogen activators administered early (within three hours) may confer greater benefit than harm but precise indications are lacking. Any thrombolytic therapy can only be given

after urgent brain imaging to exclude haemorrhage. Thrombolytic therapy is not an option in Fiji at present.

b. Protecting cells from ischaemic injury

Brain cells die not only from ischaemia itself but also from the local release of excitotoxic molecules in response to the ischaemia. Therefore, adequate hydration and oxygenation is important. In ischaemic stroke, it is advisable not to be aggressive to lower the blood pressure (i.e. maintain diastolic BP at 100-110 mm Hg) rapidly during the first ten days. However, in hemorrhagic stroke, BP of less than 140/90 is advisable.

c. Rehabilitation

Rehabilitation should be commenced as soon as urgent diagnostic and therapeutic measures have been taken. Therefore, referral to a physiotherapist and eventually, if possible, to a rehabilitation unit is recommended.

d. Secondary prevention

There is clear evidence that modifying risk factors after a completed stroke confers benefit.

7.4 Management of haemorrhagic stroke

The underlying cause of hemorrhagic stroke should be identified and treated accordingly (i.e. control blood pressure in hypertensive intracerebral bleed).

7.5 Stroke related to subarachnoid haemorrhage

Many patients with subarachnoid haemorrhage have a primary cause potentially amenable to intervention – in particular aneurysm. Vasospasm in this condition may produce reversible neurological deficits which can persist and even lead to death. Vasospasm

manifests as an altered conscious state or increased neurological defect.

The management of subarachnoid haemorrhage is discussed in the *Emergency Management Guidelines.*

8 Non-hypertensive cardiovascular disease in pregnancy

The ideal time to evaluate a woman with cardiovascular disease is before she becomes pregnant. This allows time to make or confirm the diagnosis and make a management plan. “Pre-pregnancy” clinics are being introduced in many countries to reduce the need for urgent decisions taken when the pregnancy is already well advanced.

Enormous changes occur in the cardiovascular system in normal pregnancy. Vasodilatation occurs very early. Cardiac output increases by up to 40 percent at 20 weeks, yet the impact of vasodilatation is so great that blood pressure continues to fall to its minimum at mid-term and only slowly returns to normal as term approaches. Blood volume increases slowly in response to vasodilation and reaches its maximum in the final trimester after 30 weeks.

All these changes are normally reversed within 5-7 days of delivery.

These changes put demands on a normal cardiovascular system and can lead to heart failure if, for example, severe valvular disease is present.

8.1 Valvular heart disease

Mitral stenosis is the most important valvular lesion to be encountered in pregnancy. It may present with pulmonary oedema or sudden onset of atrial fibrillation.

The same treatment principles apply as in the non-pregnant patient (see relevant section on heart failure).

Although diuretics are not recommended in the treatment of pregnancy-related hypertension, in pulmonary oedema or congestive heart failure they should be used and are safe. Digoxin may also be given if indicated.

Angiotensin converting enzyme inhibitors should not be used in pregnancy.

Vasodilatation ("cardiac unloading"), if required, is best achieved with:

- *Hydrallazine 25-50 orally three times daily*

  PLUS

- *Isosorbide dinitrate 10-40 mg three times daily if additional therapy is required*

Mitral valvuloplasty may be performed in pregnancy, if the clinical state warrants this.

Mitral valve prolapse is a common valvular abnormality in pregnancy. As blood volume expands, the murmur and click may disappear. This lesion does not normally produce any haemodynamic problems.

8.2 Antibiotic prophylaxis at delivery

Normal vaginal delivery and elective caesarean section do not require prophylactic antibiotics in a patient with a normal heart or with mitral valve prolapse. However, delivery in the presence of a prolonged labour or pre-existing infection does require antibiotic prophylaxis.

Antibiotic prophylaxis is **routinely** indicated for patients with **established valvular disease**.

Delivery should occur at an appropriate maternity unit.
A suggested regimen for a patient arriving in labour is:

- *Gentamicin 2 mg per kg intravenously*
  PLUS

- *Ampicillin 1 gram intravenously followed by ampicillin 500 mg intravenously 6 hours later*

The same regimen can be used in patients:

- not admitted in labour; given just before vaginal delivery or caesarian section
- with spontaneous membrane rupture; give antibiotics on admission to the unit
- at rupture of the membranes to induce labour; the first dose being given just before the procedure occurs

For patients known to be hypersensitive to penicillin:

- *Vancomycin 1 gram intravenously over one hour*

8.3 Cardiac arrhythmias in pregnancy

The same principles apply as in the non-pregnant patient (see Chapter 4). If beta-blocking drugs are required, propranolol should be preferred over atenolol in pregnancy.

The following list is a guide to antiarrhythmic drug safety in pregnancy. For most of the drugs, experience is too limited for a firm recommendation to be made.

Table. 3 Recommendations for antiarrhythmic therapy in pregnancy

Drug	Recommendation
Adenosine	Safe
Amiodarone	Avoid
Atenolol	Associated with foetal growth retardation
Atropine	Safe
Digoxin	Safe
Lignocaine	Safe
Propranolol	Safe; may induce foetal bradycardia
Verapamil	Insufficient data; avoid if possible

While beta-blocking drugs are commonly listed as drugs to avoid in pregnancy, clinical trials with oxprenolol in pregnancy-related hypertension have revealed no excess of foetal abnormalities despite prolonged exposure *in utero*.

Appendix

Drug to be infused	Formulation	Preparation	Infusion rate
Hydrallazine	20 mg/ampoule	Reconstitute 20 mg ampoule by adding 2 ml of sterile water (concentration: 10 mg of hydrallazine/ml). Add hydrallazine solution above to 98 ml of normal saline in a metered chamber (concentration: 1 mg of hydrallazine/ml).	Infuse initially at 0.2-0.3 mg/min (12-18 ml/hr). Maintenance dose: 0.05-0.15 mg/min (3-9 ml/hr).
Magnesium sulphate	50%, 2 ml (1 g) ampoule; 10 ml (5 g) ampoule	Loading dose: Magnesium sulfate 50%, 4 g (8.0 ml) diluted in 100 ml of dextrose 5%. Maintenance dose: Magnesium sulfate 50% (25 ml) in 100 ml dextrose 40%.	Loading dose: Use infusion pump and run at 300 ml/hr and set total volume at 108 ml. Maintenance dose: Infuse at 1 g/hr. Set infusion pump to run at 10 ml/hr and set total volume at 125 ml.

Drug to be infused	Formulation	Preparation	Infusion rate
Labetalol	100 mg/20 ml (5 mg/ml)	Add 100 mg (20 ml) of labetalol in 80 ml of dextrose 5% in a metered chamber (concentration: 1 mg of labetalol /ml).	Recommended dose: 0.5–2.0 mg/min Infusion rate: 30 ml/hr (0.5 mg/min) initially then titrate until diastolic blood pressure of 110 mm Hg is achieved to a maximum dose of 120 ml/hour (2 mg/min).
Dobutamine	1 vial = 250 mg (in powder form)	Add 10 ml of sterile water to the 250 mg vial of dobutamine. Add the dobutamine solution to 90 ml of normal saline or dextrose 5% in a metered chamber (concentration: 2.5 mg of dobutamine/ml or 2,500µg of dopamine/ml).	2.5-10 µg/kg/min For example, in a 60-70 kg patient, the rate of the dobutamine infusion will be 4-20 ml/hr.

Drug to be infused	Formulation	Preparation	Infusion rate
Dopamine	1 vial = 200 mg/5 ml	Add 200 mg of dopamine in 95 ml of normal saline or dextrose 5% in a metered chamber. After reconstitution, the concentration of dopamine in the chamber will be 200 μg/ml [1 ml = 60 microdrops (μgtts) or 33 μg/μgtts].	To achieve enhanced renal perfusion: 2-5 μg/kg/min (120-300 μg/min) For antihypotensive effect: 5-50 μg/kg/minute (300-3,000 μg/min) For example, the infusion rate in a 60 kg patient will be: - Renal perfusion dose: 4-10 μgtts/min (4-20 ml/hr) - Antihypotensive effect: 10-100 ml/hr
Streptokinase	1 vial = 1.5 million units	Add 2 ml of normal saline to the vial containing 1.5 megaunits streptokinase. Mix the streptokinase solution to 98 ml of normal saline in a metered chamber.	100 ml/hr

<table>
<tr><th>Drug to be infused</th><th>Formulation</th><th>Preparation</th><th>Infusion rate</th></tr>
<tr><td>Lignocaine 2%</td><td>2% solution (20 mg/ml) vial</td><td>Discard 200 ml from 1 liter of dextrose 5% and add 2 grams (200 ml or 20 vials) of lignocaine 2% (concentration: 4 mg of lignocaine/ml).</td><td>
<table>
<tr><th>Time</th><th>Rate (ml/hour)</th><th>Dose (mg/hour)</th></tr>
<tr><td>1st hour</td><td>60</td><td>4</td></tr>
<tr><td>2nd hour</td><td>45</td><td>3</td></tr>
<tr><td>After the 2nd hour for 24 hours</td><td>30</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Lignocaine 1%</td><td>1% solution (10 mg/ml) vial</td><td>Discard 400 ml from 1 liter of dextrose 5% and add 4 grams (400 ml or 40 vials of lignocaine 1% (concentration 4 mg of lignocaine/ml).</td><td>
<table>
<tr><th>Time</th><th>Rate (ml/hour)</th><th>Dose (mg/hour)</th></tr>
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</table>

Drug to be infused	Formulation	Preparation	Infusion rate
Amiodarone	50 mg/ml ampoule	Loading dose: Mix calculated loading dose of amiodarone (5 mg/kg) in 250 ml of dextrose 5%. Maintenance dose: Mix calculated maintenance dose of amiodarone (10-15 mg/kg) in 500 ml of dextrose 5%.	Loading dose: Infuse for 1-2 hours (125-250 ml/hr). Maintenance dose: Infuse for 24 hours (20 ml/hr).
Isoprenaline	2 mg/ampoule (1 mg/ml)	Add 2 mg (1 ampoule) of isoprenaline to 99 ml of normal saline or dextrose 5% in a metered chamber (concentration: 0.02 mg of isoprenaline/ml or 20 μg of isoprenaline/ml).	Initially at 3 ml/hr (1 μg/min) then titrate accordingly based on response of heart rate, blood pressure, urine output, central venous pressure and peripheral circulation up to a maximum of 60 ml/hr (20 μg/min).