



**Mercy
Ships[®]**

Bringing Hope and Healing...

Formulary 2009-2011



**An Essential Medicines Dosing Guide
Based on the WHO Model Formulary**

CARDIOVASCULAR SYSTEM

2.01 DIURETICS

WHO MODEL FORMULARY 2008 NOTES:

Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure. Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect. Although **loop diuretics** are the most potent their duration of action is relatively short, whilst **thiazide diuretics** are moderately potent but produce diuresis for a longer period. **Potassium-sparing diuretics** have a relatively weak diuretic effect. Carbonic anhydrase inhibitors are weak diuretics which are rarely used for their diuretic effect and are principally used to lower intraocular pressure in glaucoma (See Chapter 09 Eye Section 9.03 Miotics & Antiglaucoma Meds).

LOOP DIURETICS. Loop diuretics or high-ceiling diuretics, such as **furosemide**, are the most potent and rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30-60 minutes of administration, with max diuretic effect in 1-2 hours. The diuretic action lasts for 4-6 hours. IV furosemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis complete within 2 hours.

Loop diuretics inhibit reabsorption from the ascending loop of Henlé in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics. Because of their shorter duration of action, the risk of *hypokalaemia* may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of *hypokalaemia*. Loop diuretics may cause *hypovolaemia* and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause *hyperuricaemia* and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

THIAZIDE DIURETICS. Thiazide diuretics, such as **hydrochlorothiazide**, are moderately potent and act by inhibiting sodium and chloride reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1-2 hours of oral administration and most have a duration of action of 12-24 hours.

Thiazide diuretics are used in the management of oedema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease (but not effective in poor renal function with creatinine clearance of less than 30 ml per minute). In severe fluid retention a loop diuretic may be necessary. In hypertension, a thiazide diuretic is used at a low dose to lower blood pressure with very little biochemical disturbance; the maximum therapeutic effect may not be seen for several weeks. Higher doses should not be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. If a thiazide alone does not lower blood pressure adequately, it may be combined with another antihypertensive such as a beta-adrenoceptor antagonist. Urinary excretion of calcium is reduced by thiazide diuretics and this property is occasionally utilized in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi. Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume.

High dose thiazide diuretics produce a marked increase in potassium excretion which may cause *hypokalaemia*; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure *hypokalaemia* can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are used as a more effective alternative to potassium supplements for prevention of *hypokalaemia* induced by thiazide diuretics; however supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

POTASSIUM-SPARING DIURETICS. Potassium-sparing diuretics include **amiloride** [not on Mercy Ships list] and **spironolactone**; they are weak diuretics and reduce potassium excretion and increase sodium excretion in the distal tubule. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset of action requiring 2-3 days to achieve maximum diuretic effect, and a similar period of 2-3 days for diuresis to cease after discontinuation of treatment.

Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from *hypokalaemia*. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of *hypokalaemia* and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics is *hyperkalaemia*, which can be life-threatening. These diuretics are thus best avoided or used very carefully in patients who have or may develop *hyperkalaemia*, such as those with renal failure, patients receiving other potassium-sparing diuretics or taking ACE inhibitors or potassium supplements.

OSMOTIC DIURETICS. Osmotic diuretics such as **mannitol** are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 minutes of the start of infusion and lasts for 3-8 hours after the infusion has been discontinued; diuresis occurs after 1-3 hours. Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary oedema can be precipitated in patients with diminished cardiac reserve, acute water intoxication may occur in patient with inadequate urine flow.

ELECTROLYTE IMBALANCE. The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. *Hyponatraemia* is an adverse effect of all diuretics. The risk of *hypokalaemia*, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause *hyperkalaemia*. Other electrolyte disturbances include *hypercalcaemia* (thiazides) *hypocalcaemia* (loop diuretics) and *hypomagnesaemia* (thiazide and loop diuretics). Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias. The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

COMMENT/CAUTIONS:

- **Loop diuretics** act within 1 hour and diuresis is complete within 6 hours. **Thiazide diuretics** act within 1-2 hours and last 12-24 hours. Administer in the morning. May cause postural hypotension especially in the elderly.
- High doses of **thiazides** and **loop diuretics** can cause hypokalaemia (see WHO notes above). **IV furosemide** in large bolus doses may cause ototoxicity, so doses > 50mg should be diluted in 100ml NS and given at a rate not exceeding 4mg/minute.
- **Mannitol:** Solutions >15% concentration may crystallize during storage, crystals must be redissolved by warming solution before use, DO NOT use if any crystals remain; IV sets must have a filter; DO not administer with whole blood or passed through the same transfusion set as blood.
- **Potassium-sparing diuretics** such as spironolactone should be used cautiously in patients on ACE inhibitors as they may cause severe hyperkalaemia. Do not give concurrently with potassium supplements.

WHO MODEL FORMULARY 2008 NOTES:

MANAGEMENT OF ANGINA:

The three main types of angina are: *stable angina* (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest; *unstable angina* (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction; and *Prinzmetal angina* (variant angina), caused by coronary vasospasm, in which attacks occur at rest. Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

STABLE ANGINA Drugs are used both for the relief of acute pain and for prophylaxis to reduce further attacks; they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers), and calcium-channel blockers.

NITRATES. Organic nitrates have a vasodilating effect and are sometimes used alone, especially in elderly patients with infrequent symptoms. Tolerance leading to reduced antianginal effect is often seen in patients taking prolonged action nitrate formulations. Evidence suggests that patients should have a 'nitrate-free' interval to prevent the development of tolerance. Adverse effects such as flushing, headache, and postural hypotension may limit nitrate therapy but tolerance to these effects also soon develops. The short-acting sublingual formulation of **glyceryl trinitrate** is used both for prevention of angina before exercise or other stress and for rapid treatment of chest pain. A sublingual tablet of **isosorbide dinitrate** is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several hours.

BETA-BLOCKERS. Beta-adrenoceptor antagonists (beta-blockers), such as **atenolol**, block beta-adrenergic receptors in the heart, and thereby decrease heart rate and myocardial contractility and oxygen consumption, particularly during exercise. Beta-blockers are first-line therapy for patients with effort induced chronic stable angina; they improve exercise tolerance, relieve symptoms, reduce the severity and frequency of angina attacks, and increase the anginal threshold. Beta-blockers should be withdrawn gradually to avoid precipitating an anginal attack; they should not be used in patients with underlying coronary vasospasm (Prinzmetal angina).

Beta-blockers may precipitate asthma and should not be used in patients with a history of asthma or bronchospasm. Some, including atenolol, have less effect on beta₂ (bronchial) receptors and are therefore relatively cardioselective. Although the cardioselective beta-blockers have less effect on airways resistance they are not free of this effect and should be avoided in patients with asthma or bronchospasm (or in rare situations be given with extreme caution under specialist supervision). Beta-blockers should not be given to patients who have incipient ventricular failure, second- or third-degree atrioventricular block, or peripheral vascular disease. Beta-blockers should be used with caution in diabetes. Beta-blockers can produce hyperglycaemia or they can enhance the hypoglycaemic effect of insulin and may precipitate hypoglycaemia.

CALCIUM-CHANNEL BLOCKERS. A long-acting dihydropyridine calcium channel blocker (such as amlodipine, section 12.3) can be added to betablocker treatment if necessary for control of moderate stable angina. For those in whom a beta-blocker is inappropriate, **verapamil** may be given as an alternative to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve. Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal angina, and in patients in whom alterations in cardiac tone may influence the angina threshold.

UNSTABLE ANGINA requires prompt aggressive treatment to prevent progression to myocardial infarction. Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin. Nitrates and beta-blockers are given to relieve ischaemia; if beta-blockers are contraindicated, verapamil is an alternative, provided left ventricular function is adequate.

PRINZMETAL ANGINA. Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

MANAGEMENT OF HYPERTENSION:

Treatment of hypertension should be integrated into an overall program to manage factors that increase the risk of cardiovascular events (such as stroke and myocardial infarction). Treatment is often life-long. Hypertension was formerly classified as mild, moderate or severe, but a grading system is now preferred. *Grade 1 hypertension* is defined as 140–159 mmHg systolic blood pressure and 90–99 mmHg diastolic blood pressure, *Grade 2 hypertension* 160–179 mmHg systolic and 100–109 mmHg diastolic and *Grade 3 hypertension* more than 180 mmHg systolic and more than 110 mmHg diastolic. The aim of treatment in most patients is an optimal target systolic blood pressure less than 140 mmHg and diastolic blood pressure less than 85 mmHg. For patients with diabetes the aim is systolic blood pressure less than 130 mmHg and diastolic blood pressure less than 80 mmHg. In some patients these targets are not possible despite adequate treatment; however, any decrease in blood pressure reduces the risk of cardiovascular disease.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary sodium, stopping tobacco smoking, and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

There are no significant differences between the major groups of antihypertensive drugs in terms of efficacy, side-effects and quality of life although some differences in response are seen related to age or ethnic group. Therefore, antihypertensive treatment should be selected according to the individual's clinical needs, any conditions that render certain drugs less suitable for the individual, and the availability and cost of drugs.

In the absence of compelling indications for another class of drug, *thiazide diuretics*, such as **hydrochlorothiazide** should usually be considered for antihypertensive therapy; they are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally potassium depletion), reduced glucose tolerance, ventricular ectopic beats and impotence; they should be avoided in gout. These effects can be reduced by keeping the dose as low as possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drug. *Beta-adrenoceptor antagonists (beta-blockers)* such as **atenolol** are effective in all grades of hypertension, and are particularly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease, and heart block. Beta-blockers, especially in combination with a thiazide, are best avoided in

patients with diabetes or those at high risk of developing diabetes. *Angiotensin-converting enzyme inhibitors (ACE inhibitors)* such as **enalapril** are effective and well tolerated by most patients. They can be used in heart failure, left ventricular dysfunction and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse effect is a dry persistent cough. *Dihydropyridine calcium-channel blockers* such as **amlodipine** are useful for isolated systolic hypertension, in populations unresponsive to other antihypertensives (for example Africans). *Drugs acting on the central nervous system* are also effective antihypertensive drugs. In particular, **methyldopa** [not on Mercy Ships list] is effective in the treatment of hypertension in pregnancy. A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a stepwise manner until blood pressure is controlled.

HYPERTENSIVE EMERGENCIES. In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, IV infusion of **sodium nitroprusside** is effective. Over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction.

HYPERTENSION IN PREGNANCY. This is defined as sustained diastolic blood pressure of 90 mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is > 95 mmHg, **methyldopa** [not on Mercy Ships list] is the safest drug. Beta-blockers should be used with caution in pregnancy, since they can restrict fetal growth if used for an extended period; intrauterine growth restriction is minimized if use is limited to the third trimester. ACE inhibitors are contraindicated in pregnancy since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately.

Pre-eclampsia and eclampsia. If pre-eclampsia or severe hypertension occurs after week 36 of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia, IV **hydralazine** can be used. **Magnesium sulfate** is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

MANAGEMENT OF HEART FAILURE:

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations, and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics, cardiac glycosides and vasodilators. In addition, measures such as weight reduction, moderate salt restriction, and appropriate exercise should be introduced.

The primary treatment of heart failure is with *angiotensin-converting enzyme inhibitors (ACE inhibitors)* such as **enalapril** which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease. A *thiazide diuretic* such as **hydrochlorothiazide** is used in the management of mild to moderate heart failure when the patient has mild fluid retention and severe pulmonary oedema is not present; however thiazides are ineffective if renal function is poor. In these patients, and in more severe fluid retention, a *loop diuretic* such as **furosemide** is required. See Section 2.01 Diuretics for more notes on using diuretics in heart failure. Note that **spironolactone** may be considered for severe heart failure patients already receiving an ACE inhibitor and a diuretic (low dose spironolactone 25 mg daily reduces symptoms and mortality rate). Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's clinical condition. The *beta-blockers* bisoprolol and carvedilol [not included on WHO Model List] can be used in stable heart failure and left-ventricular systolic dysfunction. Treatment with beta-blockers should only be undertaken by those experienced in the management of heart failure. **Digoxin**, a *cardiac glycoside*, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial vasodilation. It produces symptomatic improvement, increases exercise tolerance, and reduces hospitalization, but it does not reduce mortality. It is considered for patients with atrial fibrillation and for selected patients who remain symptomatic despite treatment with an ACE inhibitor, a diuretic, and a suitable beta-blocker. *Vasodilators* are used in heart failure to reduce systemic vascular resistance. **Isosorbide dinitrate** (Section 2.06) produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. **Hydralazine** produces mainly arterial vasodilation, which reduces left ventricular afterload, and increases stroke volume and cardiac output. Isosorbide dinitrate and hydralazine can be used in combination when an ACE inhibitor cannot be used, but this combination may be poorly tolerated. **Dopamine**, an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage is critical; at low doses it stimulates myocardial contractility and increases cardiac output, however, higher doses (more than 5 micrograms/kg per minute) cause vasoconstriction, with a worsening of heart failure.

2.02 ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Enalapril Maleate Tab 10mg (Renitec)	IDA EML	Hypertension: <i>By mouth</i> Adult initially 2.5-5mg in the morning (first dose at night), usual maintenance 10-20mg daily, max 40mg daily.

COMMENT/CAUTIONS:

- **ACE Inhibitors** may cause very rapid falls of blood pressure in volume-depleted patients. Discontinue or reduce diuretic dose 2-3 days before ACE inhibitor initiation. Administer first dose at bedtime. Diuretics may be resumed if needed after a few weeks. If diuretics cannot be stopped, supervise medically for 2 hours after first dose/until stable blood pressure.
- **Renal function:** Monitor baseline creatinine and assess within 1 week of initiating therapy. If >10% increase in creatinine levels review therapy. Reassess regularly (3-4 times during the year). Concomitant treatment with NSAIDs increases the risk of renal damage.

2.03 BETA-BLOCKERS

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Atenolol Tab 50mg (Tenormin)	MSL IDA EML	Hypertension: <i>By mouth</i> Adult 50mg daily (higher dose rarely necessary). Angina: 100mg daily in 1 or 2 doses. Arrhythmias: 50-100mg daily.
Labetalol HCl Inj 100mg/20ml (Trandate)		Hypertension: <i>by IV Inj</i> 50mg, repeat after 5 minutes if needed; <i>by IV infusion</i> at a max rate of 2mg/minute titrated to patient response; max total dose 200mg both routes. Inject slow IV undiluted over 1-2 minutes, for IV infusion further dilute 100mg with 100-200ml of D5/NS and infuse over 50-60 minutes.
Metoprolol Tab 100mg (Betaloc/Lopressor)	EML	Hypertension, angina or arrhythmia: <i>By mouth</i> Adult 50-100mg twice daily, max 300mg daily. Adjunct in hyperthyroidism: 50mg 4 times daily.

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Propranolol Tab 40mg (Inderal/Avlocardyl)	IDA EML	Hypertension: <i>by mouth</i> 80mg twice daily, max 320mg daily (half dose for portal hypertension). Angina: 40mg 2-3 times daily to 240mg/DAY. Arrhythmia, anxiety tachycardia, thyrotoxicosis (adjunct): 10-40mg 3-4 times daily. Child, arrhythmia 2-6mg/kg/DAY, hypertension 0.5-1mg/kg/DAY, in divided doses every 6-12 hours. Max: 16mg/kg/DAY.
Propranolol HCl Inj 1mg/ml (Inderal/Avlocardyl)		Arrhythmias, thyrotoxic crisis: <i>by IV inj</i> 1mg (undiluted over 1 minute); repeat every 2-4 minutes if needed according to response; max 10mg (5mg in anaesthesia).

COMMENT/CAUTIONS:

- **Beta-blockers** are effective in all grades of hypertension and are particularly useful in angina and following myocardial infarction. See WHO notes above under Treatment of Angina for cautions about use in asthma, incipient ventricular failure, peripheral vascular disease and diabetes.
- Avoid using with **verapamil** since risk of precipitating heart failure.
- **Labetolol**: Severe hepatocellular damage reported, monitor liver function.
- **Propranolol IV**: Excessive bradycardia can be countered with IV injection of atropine sulphate 0.6-2.4mg in divided doses of 600 micrograms.

2.04 CALCIUM CHANNEL BLOCKERS

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Amlodipine Tab 5mg & 10mg (Istin, Amlostin)	IDA	Angina, hypertension: <i>By mouth</i> initially 5mg once daily; max 10mg once daily.
Diltiazem HCl Cap modified-release 240mg (Adizem XL)	D	Angina, mild/moderate hypertension: <i>by mouth</i> modified-release 240mg once daily. Non modified-release formulations: 60mg 3 times daily (elderly initially twice daily); max 360mg daily in divided doses.

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Nifedipine Tab modified-release 20mg (Adalat LA or MR)	IDA EML	Hypertension, angina prophylaxis: <i>By mouth</i> Adult 20mg-100mg daily with food in 1-2 divided doses, see individual product leaflet since doses may differ between different modified-release formulations.
Verapamil HCl Tab 40mg (Isoptin/Securon)	EML	Angina: <i>by mouth</i> Adult 80-120mg 3 times daily. Arrhythmias: 40-120mg 3 times daily. Hypertension: 240-480mg daily in 2-3 divided doses.
Verapamil HCl Tab modified-release 240mg (Securon SR)		Angina or hypertension: <i>by mouth</i> 240mg daily, max 240mg twice daily. Prophylaxis after MI where beta-blockers are inappropriate: 240mg in the morning, 120mg in the evening.
Verapamil HCl Inj 5mg/2ml (Isoptin/Securon)	EML	Arrhythmias: <i>slow IV inj</i> 5-10mg (over 2-4 minutes) of max conc 2.5mg/ml in NS/D5, with ECG monitoring; paroxysmal tachyarrhythmias: further 5mg after 5-10 minutes if needed. DO NOT administer to patients recently given beta-blockers (hypotension/asystole risk).

COMMENT/CAUTIONS:

- The general first-line medicines for hypertension treatment are **thiazide diuretics, beta-blockers & ACE inhibitors**. However, **calcium-channel blockers** may be considered first-line in specific populations e.g. Africans, Afro-Caribbeans or the elderly, who respond less well to the former drugs.
- **Adverse effects:** Flushing and headache (less obtrusive after a few days), ankle swelling (may respond only partially to diuretics), hypotension. Constipation is more common with **verapamil**. Avoid abrupt withdrawal which may induce hypertensive crisis or rebound.
- **Diltiazem** and **verapamil** should be avoided in heart failure as they may further depress cardiac function causing clinically significant deterioration.
- **Nifedipine:** Short-acting formulations should be avoided as they may evoke reflex tachycardia and cause large variations in blood pressure.

2.06 NITRATES

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Isosorbide Dinitrate Tab modified-release 20mg (Isoket Retard)	EML	Prophylaxis of angina <i>by mouth</i> <u>modified-release</u> : 20-40mg 12 hourly <u>Non modified-release</u> : angina 30-120mg, left ventricular failure 40-160mg (max 240mg), given daily in divided doses.
Nitroglycerin Sublingual Spray 400 microgram/dose, 200 doses (Glytrin/Nitrolingual) [Glyceryl trinitrate (GTN)]	MSL	Angina: treatment or prophylaxis, spray 1-2 doses under tongue and then close mouth.
Nitroglycerin Inj 1mg/ml (Nitrocine/Nitronal) [Glyceryl trinitrate (GTN)]		Angina, left ventricular failure, myocardial infarction: <i>By IV infusion</i> 10-200 micrograms/minute titrated to patient response. If using PVC IV sets start at 25 micrograms/minute (higher initial dose to offset drug loss through PVC absorption). Non-PVC IV sets and glass parenteral bottles are preferred, avoid use of filters. Dilute 1mg in 10ml D5/NS to give 100 micrograms/ml, for dose 10 micrograms/minute run at 6 ml/hour. Max conc 400 micrograms/ml.

COMMENT/CAUTIONS:

- **Adverse effects:** flushing, headache, and postural hypotension.
- Glyceryl Trinitrate sublingual tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, containing no cotton wool wadding, and discarded after 8 weeks in use.
- Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day.

WHO MODEL FORMULARY 2008 NOTES:

MANAGEMENT OF ARRHYTHMIAS:

Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment. Antiarrhythmic drugs must be used cautiously since most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalaemia. When antiarrhythmic drugs are used in combination, their cumulative negative inotropic effects may be significant, particularly if myocardial function is impaired.

ATRIAL FIBRILLATION. The increased ventricular rate in atrial fibrillation can be controlled with a **beta-adrenoceptor antagonist** (beta-blocker) or **verapamil**. **Digoxin** slows the ventricular response and is particularly appropriate if atrial fibrillation is accompanied by congestive heart failure. Intravenous digoxin is rarely of value for rapid control of the ventricular rate because response may take many hours. If adequate control at rest or during exercise cannot be achieved readily verapamil may be introduced with digoxin, but it should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease, and in the elderly. **Warfarin** is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the previous 48 hours and there does not appear to be a danger of thromboembolism, antiarrhythmic drugs, such as **procainamide** or **quinidine** [not on Mercy Ships list], may be used to terminate the fibrillation or to maintain sinus rhythm after cardioversion.

ATRIAL FLUTTER. **Digoxin** will sometimes slow the ventricular response. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with an anticoagulant should be considered before cardioversion to prevent emboli. IV **verapamil** reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial IV dose may be followed by oral treatment; hypotension may occur with high doses. It should not be used for tachyarrhythmias where the QRS complex is wide unless a supraventricular origin has been established beyond doubt. If the flutter cannot be restored to sinus rhythm, antiarrhythmics such as **quinidine** [not on Mercy Ships list] can be used.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA. In most patients this remits spontaneously or can revert to sinus rhythm by reflex vagal stimulation. Failing this, IV injection of a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective. Verapamil and a beta-blocker should **never** be administered concomitantly because of the risk of hypotension and asystole.

VENTRICULAR TACHYCARDIA. Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients intravenous **lidocaine** or **procainamide** may be used. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective.

Torsades de pointes is a special form of ventricular tachycardia associated with prolongation of the QT interval; it may be congenital but is often drug induced. Initial treatment with IV infusion of **magnesium sulphate** (usual dose 2 g over 10–15 minutes, repeated once if necessary) together with temporary pacing is usually effective. Prolonged QT interval may be treated with a beta-adrenoceptor antagonist (beta-blocker) (but *not* sotalol) and pacing; antiarrhythmic drugs (including lidocaine) should be avoided as they can further prolong QT interval.

BRADYARRHYTHMIAS. Sinus bradycardia (less than 50 beats/minute) associated with acute myocardial infarction may be treated with atropine. Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease and permanent pacing is usually required.

CARDIAC ARREST. In cardiac arrest, **epinephrine** (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1 in 10 000 solution) as part of the procedure for cardiopulmonary resuscitation.

[Mercy Ships note: IV Amiodarone is available and may be considered for paroxysmal, supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. IV Adenosine is available for emergency use for terminating paroxysmal supraventricular tachycardia. See also current local and national standard treatment guidelines.]

2.08 OTHER ANTIARRHYTHMIAS

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Adenosine Inj 3mg/ml, 2ml (Adenocor)		Emergency use, rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardia: <i>By rapid IV injection into central or large peripheral vein</i> 6mg over 2 seconds with cardiac monitoring; if necessary followed by 12mg after 1-2 minutes, and then by 12mg after a further 1-2 minutes; increments should not be given if high level AV block develops at any dose.
Amiodarone Inj 50mg/ml, 3ml (Cordarone)	EML	Advanced cardiac life support (ACLS): <i>by slow IV injection</i> 300mg over at least 3 minutes; if necessary supplementary doses of 150mg may be considered; max 2g in 24 hours. Arrhythmias: <i>By IV infusion</i> via caval catheter, initially 5mg/kg over 20-120 minutes with ECG monitoring, subsequent infusion given if needed according to response up to max 1.2g in 24 hours. Dilute 300mg in 300ml of D5 to give 1mg/ml solution. Max IV infusion rate 30mg/minute, usual conc 1-6mg/ml; for > 2mg/ml give via central line.

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Procainamide Inj 100mg/ml (Pronestyl)		<p>Ventricular arrhythmias: <i>by slow IV injection</i> Adult 100mg diluted, given at max rate 50mg/minute with ECG monitoring, repeat at 5-minute intervals until arrhythmia is controlled, max total dose 1g; maintenance dose <i>by IV infusion</i> dilute and give at rate 2-6mg/minute.</p> <p>For IV injection, dilute 100mg with 25-50 ml of D5 and inject slowly over 2-5 minutes. For IV infusion, dilute 200mg with 50-100 ml of D5, give over 30-100 minutes.</p>

COMMENT/CAUTIONS:

- All anti-arrhythmics are potentially pro-arrhythmic. If using more than one antiarrhythmic care is needed as fatal interactions can occur. Avoid rapid changes and combinations.
- **IV Amiodarone** is intended for use only in patients with life-threatening arrhythmias because of substantial toxicity. See product leaflet for detail of its adverse effects and monitoring requirements in longer term therapy.

2.09 INOTROPIC & VASOCONSTRICTOR SYMPATHOMIMETICS

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Dobutamine HCl Inj 250mg/20ml	D	<p>Cardiogenic shock in myocardial infarction: <i>By IV infusion</i> Adult 0.5-1 micrograms/kg/minute initially then adjusted according to response, to 2-20 micrograms/kg/minute.</p> <p>For IV infusion, dilute 250mg/20ml vial in at least 50ml of D5/NS/RL, usually 250mg in 250ml of D5/NS/RL to give 1000 micrograms/ml solution, max conc 5000 micrograms/ml.</p>

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Dopamine HCl Inj 200mg/5ml	IDA EML	Cardiogenic shock in myocardial infarction: <i>By IV infusion</i> via a large vein (dilute 200mg in 50-100ml D5/NS/RL, max conc 6mg/ml), Adult initially 2-5 micrograms/kg/minute, increase by increments of 5-10 micrograms/kg/minute and titrate according to blood pressure, cardiac output and urine output; max rate 50 micrograms/kg/minute.
Ephedrine HCl Inj 30mg/ml	IDA EML	Hypotension prevention in epidural/spinal anaesthesia: <i>by slow IV inj</i> 3-6mg (max 9mg) repeated every 3-4 minutes, max cumulative dose 30mg For slow IV injection dilute 30mg in 10-20ml WFI, max conc 3mg/ml.
Epinephrine Inj 100micrograms/ml (0.1mg/ml), pre-filled syringe 10ml (1mg/10ml) [Adrenaline 1:10 000] Caution different dilutions used for different admin routes.	EML	Cardiac Arrest: <i>by IV inj</i> through a central line, 1mg (in 10ml) repeated at 3-minute intervals if necessary, max 100 micrograms/kg every 3-5 minutes; <i>IM/SC inj</i> 100-500 micrograms (undiluted 1-5ml) every 10-15 minutes; or <i>by IV cont infusion</i> 1 mg diluted in 50-100ml of NS (max conc 64 micrograms/ml), given at a rate of 1-10 micrograms/kg/minute. Anaphylaxis: see chapter 03 pg 41.
Norepinephrine Inj 1mg/ml, 4ml [Noradrenaline]	EML	Cardiac Arrest: <i>by IV infusion</i> in a large vein, Adult initially 8-12 micrograms/minute, maintenance 2-4 micrograms/minute adjusted according to response; or 0.5-1microgram/minute initially, patients with refractory shock may require 8-30 micrograms/minute. For IV infusion dilute 4mg/4ml in 1000ml D5 (NS not recommended).

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Phenylephrine Inj 1% 10mg/ml (Neosynephrine)		Acute hypotension: <i>By SC/IM inj undiluted</i> 2-5mg, repeat doses if needed at 15 minute intervals to max total 10mg; or <i>by slow IV inj</i> of a 1mg/ml solution (diluted in D5/NS), 100-500 micrograms over 3 minutes, repeat if needed after 15 minutes.

COMMENT/CAUTIONS:

- **Dopamine** dosage is critical. Low dose stimulates myocardial contractility and increases cardiac output; higher doses (> 5 micrograms/kg/minute) cause vasoconstriction, with a worsening of heart failure.
- **Epinephrine/adrenaline:** Caution as different dilutions are used for different routes of administration. For cardiac arrest, if central line is not in place, give same dose via peripheral vein then flushed through with at least 20ml NS to expedite entry into circulation.
- **Norepinephrine** may be useful in advanced cardiovascular life support (ACLS) as an adjunct to maintain adequate blood pressure when severe hypotension and low total peripheral resistance persist (in those unresponsive to less potent adrenergics e.g. dopamine/phenylephrine) and renal and cerebral perfusion remain inadequate after an effective heartbeat, palpable pulse, and ventilation have been established.
- **Phenylephrine** has a long duration of action, use with caution, excessive vasopressor response may cause prolonged rise in blood pressure.

2.10 ANTICOAGULANTS & HAEMOSTATICS

WHO MODEL FORMULARY 2008 NOTES:

Anticoagulants are used to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore used widely in the prevention and treatment of deep-vein thrombosis in the legs, prophylaxis of embolization in rheumatic heart disease and atrial fibrillation and to prevent thrombi forming on prosthetic heart valves.

Heparin is a parenteral anticoagulant that initiates anticoagulation rapidly but has a short duration of action. The low molecular weight heparins have a longer duration of action. For patients at high risk of bleeding, heparin is more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping the infusion. For the treatment of deep venous thrombosis (DVT) and

pulmonary embolism (PE) heparin is given as an IV loading dose followed by continuous IV infusion (using an infusion pump) or by intermittent subcutaneous injection. An oral anticoagulant is started at the same time as heparin. The heparin needs to be continued for at least 5 days, until the oral anticoagulant has taken effect and the INR (international normalized ratio) has been in the therapeutic range for 2 consecutive days. Laboratory monitoring is essential, on a daily basis. Heparin is also used in regimens for the management of myocardial infarction, unstable angina, acute peripheral arterial occlusion and in dialysis. In patients undergoing general surgery, low-dose heparin by SC injection is used to prevent postoperative DVT and PE in high risk patients (obesity, malignant disease, history of DVT/PE, over 40 yo, established thrombophilic disorder or undergoing major or complicated surgery). It is also of value in high-risk medical patients e.g. obesity, heart failure, confined to bed. If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of heparin effects is required, **protamine sulfate** is a specific antidote.

Oral anticoagulants take at least 48-72 hours for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly. **Warfarin** is indicated in DVT, PE, for patients with atrial fibrillation who are at risk of embolization and for those with mechanical prosthetic heart valves (to prevent emboli developing on the valves); oral anticoagulants should not be used in cerebral thrombosis or peripheral arterial occlusion as first-line therapy. The main adverse effect of oral anticoagulants is haemorrhage. Prothrombin time (usually reported as INR should be checked on a daily basis initially then at longer intervals depending on response. If severe haemorrhage occurs, stop warfarin and give **phytonadione** (vitamin K) by slow IV injection.

MANAGEMENT OF MYOCARDIAL INFARCTION:

Management includes two phases: *initial* management of acute attacks; then *long term* management including prevention of further attacks.

INITIAL MANAGEMENT

Oxygen (all patients, except in severe chronic obstructive pulmonary disease). Pain and anxiety are relieved by slow IV injection of an opioid analgesic such as **morphine** (section 5.02). **Metoclopramide** (section 1.02) may also be given by IM injection to prevent and treat nausea and vomiting caused by morphine. **Acetylsalicylic acid** 150-300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect. Thrombolytic drugs such as **streptokinase** (section 2.10) help to restore perfusion and thus relieve myocardial ischaemia (give within 1 hour of infarction, use after 12 hours only on specialist advice). Antibodies to streptokinase appear 4 days after use and streptokinase should not be given to the patient again after this time. **Nitrates** (section 2.06) may also be given to relieve ischaemic pain. Early administration

of beta-blockers such as **atenolol** (section 2.03) has been shown to reduce both early mortality and MI recurrence rate; initial IV administration is followed by long-term oral treatment (unless the patient has contraindications). **ACE inhibitors** (section 2.02) have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 hours, and if possible continued for 5-6 weeks. If arrhythmias occur, they should be treated aggressively, but the likelihood decreases rapidly over the first 24 hours after infarction. Treat ventricular fibrillation immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic **lidocaine** (section 2.08) should be given. All patients should be closely monitored for hyperglycaemia; those with diabetes mellitus or raised blood-glucose concentration should receive **insulin**.

LONG-TERM MANAGEMENT

Acetylsalicylic acid (section 2.10) should be given to all patients in a dose of 75-150 mg daily by mouth, unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction. Treatment with **beta-blockers** (section 2.03) should be continued for at least 2 to 3 years. **Verapamil** is sometimes useful if a beta-blocker cannot be used. ACE inhibitors such as **enalapril** (section 2.02) should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction. **Nitrates** (section 2.06) may be required for patients with angina. The use of **statins** (section 2.11) may also be considered in patients with high risk of recurrence.

MANAGEMENT OF STROKE:

Stroke (cerebrovascular accident) may be *ischaemic* or *haemorrhagic*; precise diagnosis is essential as management for the two types of stroke is quite different. Primary prevention of both types includes reduction of high blood pressure, stopping smoking, weight reduction, and cholesterol reduction. Atrial fibrillation, acute myocardial infarction, and valvular disease may produce embolism and ischaemic stroke. Prophylaxis in patients at risk of *ischaemic* stroke includes antiplatelet drugs such as acetylsalicylic acid or oral anticoagulants such as warfarin (section 2.10). Treatment of acute ischaemic stroke includes use of **acetylsalicylic acid** (aspirin) 150–300 mg as a single dose given within 48 hours of onset, and, in selected patients, anticoagulants such as heparin. Long-term therapy with acetylsalicylic acid 75–150 mg daily reduces the risk of having another stroke. Antiplatelet drugs are **not** used in the management of haemorrhagic stroke, as they can exacerbate bleeding. Treatments include careful lowering of very high blood pressure and surgery where appropriate. Acetylsalicylic acid is normally given for at least one year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
<p>Low Molecular Weight Heparin (LMWH) – Nadroparin 7500AxalCU/0.3ml, 10 000 AxalCU/0.4ml, & 15 000 AxalCU/0.6ml (Fraxiparine)</p>	<p>D</p>	<p>Surgical prophylaxis, for 7 days: general <i>by SC inj</i> 0.3ml daily, first injection 2-4 hours pre-surgery; orthopaedic 100 AxalCU/kg/DAY for 3 days, given 12 hours pre- & post-surgery, then 150AxalCU/kg/DAY from fourth post-op day onwards. DVT Treatment <i>by SC inj</i> 0.1ml/10kg every 12 hours for at least 10 days.</p>
<p>Low Molecular Weight Heparin (LMWH) – Enoxaparin 20mg/0.2ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml (Clexane)</p>	<p>D</p>	<p>Surgical prophylaxis: Low/moderate risk 20 mg once daily for 7-10 days, initial dose should be given 2 hours pre-operatively. Higher risk, e.g. orthopaedic surgery, 40 mg daily initial dose administered 12 hours before surgery. DVT Treatment <i>by SC inj</i> 1.5mg/kg once daily for 5 days <i>or</i> 1mg/kg every 12 hours for 5 days.</p>
<p>Phytomenadione (Vitamin K₁) Inj 10mg/ml [Phytonadione] [ADULT USE ONLY]</p> <p>NOTE: Some commercial preps unsuitable for IV use.</p>	<p><i>MSL</i> <i>IDA</i></p> <p><i>EML</i></p>	<p>Hypoprothrombinaemia, warfarin overdose: no or minor bleeding <i>by slow IV inj</i> Adult 500 micrograms; less severe bleeding <i>IM</i> undiluted 10-20mg; severe haemorrhage <i>by slow IV inj</i> 2.5-5mg, max 50mg (dilute in D5, max rate 1mg/minute).</p>
<p>Protamine Sulphate Inj 10mg/ml, 5ml (Prosulf)</p>	<p><i>IDA</i></p> <p><i>EML</i></p>	<p>Heparin overdose: By slow IV Inj (undiluted or dilute in D5/NS) over 10 minutes, 1mg neutralises 80-100 units heparin when given within 15 minutes; if longer time, less protamine needed (heparin is rapidly excreted); max total dose 50mg.</p>
<p>Streptokinase Inj 1 500 000 units vial (Streptase)</p>	<p><i>EML</i></p>	<p>MI: <i>By IV infusion</i> 1 500 000 units over 60 minutes. Reconstitute vial with 5ml of D5/NS and further dilute in 45ml of D5/NS. Use reconstituted solution within 8 hours.</p>

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GENERIC (TRADE) NAME	CAT.	INDICATION/DOSE
Simvastatin Tab 20mg (Zocor)	IDA EML	<i>By mouth</i> 10mg at night, adjusted at intervals of not less than 4 weeks; max 80mg/DAY.

COMMENT/CAUTIONS:

- Rhabdomyolysis associated with lipid-regulating drugs may be increased in patients with renal impairment, hypothyroidism, and patients on concomitant ciclosporin treatment. Concomitant treatment with a fibrate and a statin may also increase risk of serious muscle toxicity. Advise patients to report promptly unexplained muscle pain, tenderness and weakness.