

Ministry of Health and Social Services

GUIDELINES FOR MANAGEMENT OF HYPERTENSION

DIRECTORATE: TERTIARY HEALTH CARE AND CLINICAL SUPPORT SERVICES
DIVISION: PHARMACEUTICAL SERVICES
SUB-DIVISION: NATIONAL MEDICINE POLICY CO-ORDINATION

Private Bag 13198
Windhoek
Tel: 061 203 2344
Fax: 061 203 2349

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Foreword

Hypertension (high blood pressure) is one of the major health burdens in Namibia. In the first nine months of 2002 alone over 10,000 new cases of hypertension were diagnosed and approximately 4,000 patients have been admitted to hospital due to problems associated with their hypertension.

Patients with uncontrolled hypertension are at increased risk of having a myocardial infarction (heart attack), cerebrovascular accident (stroke), kidney damage, angina, heart failure, and many other serious health problems. Cerebrovascular accidents ranked as the fourth highest cause of death in Namibia between 1995 and 1999. This is one of the important reasons that it is essential for patients with hypertension to receive effective treatment. However in the ongoing climate of reducing public spending the cost of such treatment can not be ignored. In the financial year 2001-2002 the Ministry spent N\$3.5 million just on medicines to treat patients with hypertension. This makes it doubly important that the correct medicines are prescribed in the correct doses, to avoid wastage of our scarce resources.

The treatment for each patient depends on how high the blood pressure is and also on any concomitant diseases (e.g. diabetes, heart failure, etc.)

These national guidelines for treatment of hypertension are necessary to make sure that each patient with hypertension receives the most appropriate and cost effective treatment. Up until this point in time there have not been national guidelines for any of the chronic, non-infectious diseases that are prevalent in Namibia. Therefore these guidelines for management of hypertension represent a very important step towards the Ministry's goal of "Health for All Namibians by 2000 and beyond".

It is my hope that all medical officers and other health workers will make full use of these guidelines to ensure that all patients with hypertension receive the best care available.

Dr. Libertina Amathila
Minister

Preface

The first guidelines for hypertension in Namibia were compiled by the Department of Medicine, Oshakati Intermediate Hospital in 1998. These guidelines covered medicine treatment of hypertension. The Oshakati guidelines were then adapted by Central Regional Directorate (CRD) in consultation with CRD medical officers and Windhoek Central Hospital (WCH) Internal Medicine Department. Information about diagnosis and classification of hypertension (clinical management) were added to the medicine therapy guidelines. These guidelines were formally adopted by CRD in 1999 resulting in improved management of patients with hypertension and reduced expenditure on antihypertensive medicines.

Requests for changes in the Nemlist prompted the Essential Medicines List Committee (in collaboration with the WCH Internal Medicine Department) to review the CRD guidelines. A section has been added to the guidelines to address management of patients with severe hypertension, which has commonly been mismanaged. These guidelines have now been adopted as national guidelines.

It is essential that all health workers familiarise themselves fully with these guidelines. Medical doctors (who are responsible for management of these patients) and pharmacy staff (who are responsible for issuing the medicines) must pay particular attention to these guidelines.

The document consists of five main sections,

- ◆ Section 1 is the introduction that gives some background to hypertension,
- ◆ Section 2 is about clinical management of hypertension, including classification and diagnosis of hypertension
- ◆ Section 3 gives guidelines on medicine therapy for hypertension, which medicine should be used as first, second, third and fourth line, and special considerations for hypertensive patients with other diseases.
- ◆ Section 4 is about the management of severe hypertension and how to differentiate between and treat hypertensive urgencies and emergencies.
- ◆ Section 5 contains the references used in the formation of this document.

I would like to thank all individuals who contributed to the development and production of these national guidelines. Special thanks must go to Mr. Nick Duncan, VSO Pharmacist Oshakati (97-98) and Dr. Laura Brandt, CMO Otjozondjupa who started the ball rolling and to Ms. Jennie Lates, Chief Pharmacist National Medicine Policy Co-ordination and Dr. Katjitae, Head of Department: Internal Medicine WCH, for finalising these National Hypertension Guidelines for Namibia.

Dr. Kalumbi Shangula
Permanent Secretary

List of Abbreviations

ACE	Angiotensin Converting Enzyme
ALLHAT	The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
bd	Twice Daily
BP	Blood Pressure
CAT	Computerised Axial Tomography
CHD	Coronary Heart Disease
CMS	Central Medical Stores
CNS	Central Nervous System
CRD	Central Regional Directorate
CV	Cardiovascular
CVA	Cerebrovascular Accident
CXR	Chest X-ray
ECG	Electrocardiograph
FBC	Full Blood Count
FH	Family History
g	Gram(s)
GFR	Glomerular Filtration Rate
GIT	Gastrointestinal Tract
h	Hour
HT	Hypertension
ICU	Intensive Care Unit
IV	Intravenous
JVP	Jugular Venous Pulsation
max.	Maximum
mg	Milligram(s)
ml	Millilitre(s)
mm Hg	millimetres of mercury
MO	Medical Officer
MOHSS	Ministry of Health and Social Services
N\$	Namibia Dollar
Nemlist	Namibian Essential Medicines List
NCD	Non-Communicable Disease
od	Once Daily
SLE	Systemic Lupus Erythematosus
tds	Three times a day
TIA	Transient Ischaemic Attack
U&E	Urea and Electrolytes
WCH	Windhoek Central Hospital

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1. INTRODUCTION

Non-communicable diseases (NCDs) are the leading causes of death and disability worldwide. Disease rates from these conditions are accelerating globally, advancing across regions and social classes. The World Health Report 2000 estimates that these disorders together contributed to almost 60% of global mortality (31.7 million deaths) and 43% of the global burden of disease in 1999.

There is still a wide-spread misconception that the problem of NCDs is not relevant for the developing world, that it is a burden of affluent societies only. WHO experts say that scientific evidence testifies to the contrary: for example, in 1998, 77% of the total number of NCD deaths occurred in developing countries, and 85% of the NCD burden was borne by low- and middle-income countries. Surveys of indigenous populations in a number of African countries indicate that hypertension rates are on the rise, as is the prevalence of diabetes.

It is estimated that there are currently between 10 million and 20 million people in the African Region suffering from hypertension. The number of hypertensive patients continues to increase, with a greater number of them to be found in urban rather than rural areas. Approximately five to 15 per cent of all adult deaths in Africa are caused by cardiovascular diseases, mostly consequences of hypertension (stroke and heart failure).

Hypertension is the most common non-communicable disease (NCDs) in Namibia. In the first nine months of 2002 alone over 10,000 new cases of hypertension were diagnosed and approximately 4,000 patients were admitted to hospital due to problems associated with their hypertension (MOHSS 2002b).

If inadequately treated, hypertension increases the risk of vascular damage. This leads to cardiac, renal and cerebrovascular morbidity and to mortality. Cerebrovascular accidents ranked as the fourth highest cause of death in Namibia between 1995 and 1999 (MOHSS 2001). Therefore it is essential that patients with hypertension receive effective treatment. However in the ongoing climate of reducing public spending the cost of such treatment can not be ignored. In the financial year 2001-2002 the Ministry spent N\$3.5 million just on medicines to treat patients with hypertension (MOHSS 2002a). This does not take into account the large expenses resulting from long stays in hospital (average length of stay 6.15 days per patient with hypertension (MOHSS 2002b)). The financial implications of treating hypertension and the costs of uncontrolled hypertension make it doubly important that the correct medicines are prescribed in the correct doses, to avoid wastage of our scarce resources.

Hypertension has, until now, not been managed in a uniform way across the country. The quality of hypertensive patients' treatment has depended on the place of training or experience of the managing medical officer. This situation is unacceptable, hence the need to develop clear national guidelines on management of hypertension.

It is critical that medical officers and pharmacy staff closely study this document so that they can make sure hypertensive patients are treated appropriately. There are some significant changes from the traditional ideas regarding treating hypertension which should be noted. For example recent studies have shown that β -blockers can be safely

used in most patients with well controlled diabetes and avoiding β -blockers in these patients may have a negative impact on the patient's prognosis.

Nurses are responsible for screening all out-patients and therefore must also familiarise themselves with the contents of this document so that they are fully aware of the recommended management of hypertension patients. It is also very important so that they can identify dangerous signs that will indicate the need for immediate referral to a medical officer.

The guidelines consist of five main sections;

- ◆ Introduction
- ◆ Clinical Management of Chronic Hypertension,
- ◆ Medicine Therapy for Management of Chronic Hypertension
- ◆ Guidelines for Management of Severe Hypertension
- ◆ References

Special emphasis should be put on Section 2.6 "Management of patients already on hypertensive medication". These hypertension guidelines should not only be applied to newly diagnosed hypertensive patients. All patients currently being treated for hypertension should have their blood pressure and medicines reviewed to ensure that they are receiving the most logical and effective treatment.

Particular note should also be taken of Section 4, as frequently the management of severe hypertension is not according to current medical evidence. This is especially true with regards to the administration of sublingual nifedipine capsules to treat raised blood pressure. This has been shown to be a dangerous practice and should be stopped immediately. For this reason nifedipine capsules are no longer to be available at district hospitals. They have been changed to a Specialist item on the Nemlist, their use being restricted to treatment of Raynaud's Phenomenon under supervision of a Specialist.

The introduction of these guidelines also coincides with several other relevant changes to the Nemlist, most notably the inclusion of an ACE inhibitor in AB class. The ACE inhibitors are an expensive group of medicines but if they are only used strictly according to these guidelines the benefit will outweigh the cost.

These guidelines will be revised in approximately 2-4 years time depending on the rate of emergence of new clinical evidence in the area of management of hypertension. All Hospitals and Regions are encouraged to give comments on these guidelines. Such comments should be forwarded to;

Sub-Division: National Medicine Policy Co-ordination,
Division: Pharmaceutical Services,
Private Bag 13198
Windhoek
Tel: 061 203 2344
Fax: 061 203 2349

2. CLINICAL MANAGEMENT OF CHRONIC HYPERTENSION

2.1 Classification of Hypertension by Blood Pressure

Table 1

Classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	< 140 and	< 90
Mild hypertension	140 -180 and/or	90 -105
Subgroup: borderline HT	140 -160 and/or	90 -95
Moderate HT	>180 - 210 and/or	> 105 - 120
Severe HT	> 210 and/or	> 120
Isolated systolic hypertension	≥ 140 and	< 90
Subgroup: borderline isolated systolic HT	140 -160 and	< 90

2.2 Clinical Assessment of Hypertension

Step 1. Confirm chronic elevation of blood pressure

- ◆ check that cuff size is appropriate and that BP is taken at the level of the heart

Step 2. Take a careful history - Ask about:

- ◆ risk factors (FH of HT and other CV diseases, diabetes; smoking and dietary habits; physical exercise; social environment)
- ◆ indications of secondary HT (FH and personal history of renal disease; drug/substance intake; episodes of sweating, headache, anxiety [pheochromocytoma]; episodes of muscle weakness and tetany [aldosteronism])
- ◆ symptoms of organ damage (headache, vertigo, impaired vision, TIAs, sensory or motor deficit, palpitations, chest pain, shortness of breath, swollen ankles, thirst, polyuria, nocturia, haematuria, cold extremities, intermittent claudication)

Step 3. Careful physical examination - Look for:

- ◆ signs suggesting secondary hypertension (features of Cushing syndrome, skin stigmata of neurofibromatosis, enlarged kidney by palpation, auscultation of abdominal murmurs [renovascular hypertension], auscultation of precordial or chest murmurs, diminished or delayed femoral pulses and reduced femoral BP)
- ◆ signs of organ damage (murmurs over neck arteries, motor or sensory defects, fundoscopic abnormalities, abnormal cardiac rhythms, ventricular gallop, inc. JVP, pulmonary rales, dependent oedema, absence/reduction/asymmetry of pulses, cold extremities, ischaemic skin lesions)

Step 4. Do Laboratory investigations - work-up depends on findings in history and on physical examination; for all patients this could include:

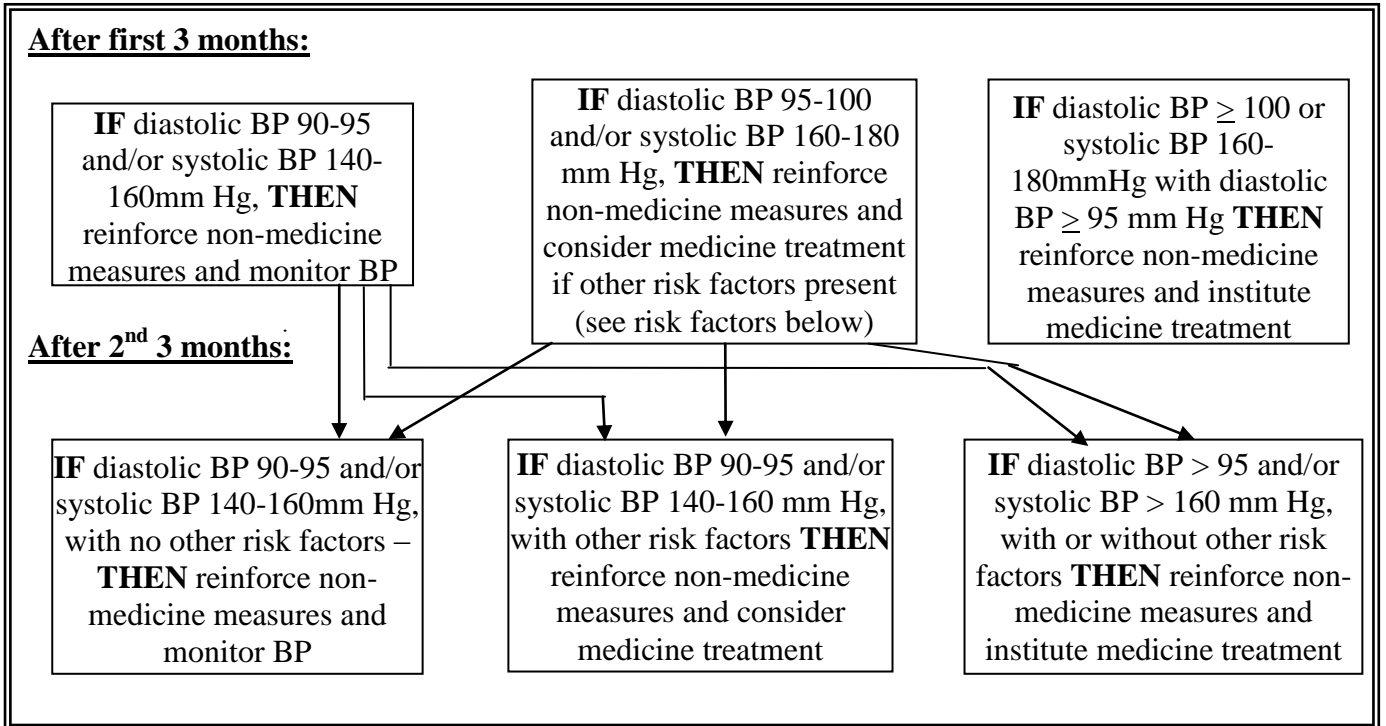
- ◆ Urinalysis (urine dip-stick for protein and blood)
- ◆ Urea and electrolytes, creatinine
- ◆ Blood glucose

- ◆ ECG
- ◆ Lipids (cholesterol and triglycerides)
- ◆ Fasting glucose
- ◆ Consider CXR

2.3 Management of MILD HYPERTENSION

If three BP readings are in the mild range listed above over a 4-week period, institute *non-medicine treatment* and monitor blood pressure for 3 months. Then follow the flow-chart below:

Box 1



Non-medicine treatment includes lifestyle counselling in the following areas:

- ◆ Overweight patients: weight loss
- ◆ Sedentary patients: institute mild regular exercise (walking)
- ◆ Alcohol users: reduction of alcohol consumption
- ◆ All patients: decrease sodium intake - cook with less salt and do not add salt at the table. N.B. stress importance of using iodised salt if any salt is used.
- ◆ All patients, but especially diabetics: decrease saturated fat (from animal sources, e.g. meat and milk products) intake. Avoid frying food, cut excess fat off meat, reduce intake of foods such as fat cakes, omelette and mayonnaise.
- ◆ All patients: increase consumption of polyunsaturated and monounsaturated fats. Good sources of these are oily fish (e.g. sardines), nuts (e.g. macadamia or macadamia nuts) and vegetable oils (e.g. sunflower, olive or ointanga oil)
- ◆ All patients: increase fruit and vegetable consumption, ideal is 5 portions per day
- ◆ Smokers (to decrease the chance of stroke and CHD): stop smoking
- ◆ With all patients: stress the advantages of avoiding long-term medicine therapy.

Risk factors that might indicate that *earlier medicine treatment of mild hypertension is required*:

- ◆ Consider medicine treatment sooner in men and in post-menopausal women
- ◆ Presence of cardiovascular complications (e.g. Left Ventricular Hypertrophy, evidence of ischaemic heart disease, previous CVA)
- ◆ Raised serum creatinine and proteinuria
- ◆ Presence of any other stage II or III disease (see Table 2 below)
- ◆ Diabetes mellitus, especially with the presence of microalbuminuria
- ◆ Continued cigarette smoking
- ◆ Family history of hypertension, premature stroke, heart disease or sudden cardiac death
- ◆ Elderly patient (>60 years old)

Classification of hypertension by extent of organ damage

Table 2

Stage	Sign
I	No objective signs of organic changes
II	At least one of the following signs of organic damage: left ventricular hypertrophy (x-ray, ECG, echocardiogram) generalised and focal narrowing of retinal arteries proteinuria or slightly raised plasma creatinine concentration or both sonar or radiographic evidence of atherosclerotic plaques (carotid arteries, aorta, iliac and femoral arteries)
III	Both symptoms and signs have appeared as a result of organ damage including: heart: angina pectoris, myocardial infarction, heart failure brain: transient ischaemic attack, stroke, hypertensive encephalopathy optic fundi: retinal haemorrhages + exudates with or without papilloedema kidney: high plasma creatinine concentration, renal failure vessels: dissecting aneurysm, symptomatic arterial occlusive disease

2.4 Management of MODERATE HYPERTENSION

Patients with average BP readings in the moderate range should be evaluated immediately, following which medicine and non-medicine measures should be instituted concurrently.

2.5 Management of SEVERE HYPERTENSION

Patients with average BP readings in the severe range should be treated according to **Section 4 - Guidelines for Management of Severe Hypertension.**

2.6 Management of ISOLATED SYSTOLIC HYPERTENSION (ISH)

ISH is defined as systolic pressure ≥ 140 mm Hg with a diastolic pressure is < 90 mm Hg. It carries a marked risk of CV disease. The majority of persons with ISH have inadequately controlled blood pressure. Low-dose thiazides are the accepted first-line treatment for the elderly. (Lever & Ramsay 1995)

There is no firm evidence to guide policy for patients with systolic BP between 140–160 mm Hg and diastolic BP <90 mm Hg (borderline ISH). Treatment is advised when there are cardiovascular complications or evidence of target organ damage. (British Hypertension Society 2002)

2.7 Management of Patients ALREADY ON HYPERTENSIVE MEDICATION

The pharmacotherapy of each and every hypertension patient currently on treatment should be systematically reviewed and an attempt made to simplify therapy (for instance, reducing the number of medicines prescribed and changing to medicines allowing single daily dosage). In addition note should be taken of *cost* and every effort should be made to exchange expensive therapy (such as Methyldopa) for equally effective inexpensive therapy as discussed in Section 3 on medicine therapy for management of hypertension.

Just as it is not possible to swap a patient straight from one anti-epileptic medicine to another, caution must also be exercised when changing a patient's antihypertensive medication. The dose of the medicine being withdrawn must be gradually reduced. If a new medicine is being introduced this should be done gradually at the same time as the old medicine is being withdrawn. Special care should be taken when withdrawing methyldopa, doxazosin or reserpine as these can cause rebound hypertension if they are withdrawn too quickly.

Obviously the patient will need to be followed more closely by the doctor for these periods. The resultant reductions in and simplification of therapy will benefit patients as well the MOHSS budget.

2.8 Chronic Follow-up of Hypertension Patients

The most efficient and effective way to follow-up hypertension patients is to hold special hypertension (or "chronic disease") clinics on specified days in the week. Ideally one or two doctors and nurses who take a special interest in hypertension could run the clinics routinely. In all cases, patients should be given appointments for dates when their check-ups are due. All patients should be reviewed monthly, looking for control of BP and side effects of medications. If the doctor is satisfied that the patient is under good control, (patient is entirely stable on his/her treatment and has no complaints) the doctor may write a prescription for a month's medication x 3. The nurse may then do the monthly checks for the next 2 months and only refer if there are problems. During the 3-monthly visit the doctor should note in addition any signs/symptoms of end-organ damage. Should a patient miss an appointment, he/she should be referred to the doctor to allow the doctor to impress upon the patient the importance of routine check-ups and adherence to medication.

The routine for follow-up visits should be simple:

- ◆ measure blood pressure and weight
- ◆ enquire about general health, side-effects and treatment problems
- ◆ reinforce advice on non-pharmacological measures
- ◆ test urine for proteinuria annually
- ◆ urea & electrolytes, and creatinine should also be done annually.

3. MEDICINE THERAPY FOR MANAGEMENT OF CHRONIC HYPERTENSION

3.1 Treatment Options

Box 2

Step 1 Thiazide diuretic:

Amiloride 2.5mg + Hydrochlorothiazide 25mg - **½-1 tablet od.**

Step 2 Add Reserpine **0.125mg od** (*max. to avoid side effects: 0.25mg od*) or Atenolol 50mg od

Step 3 Add (or substitute) the medicine not chosen in step 2

If β -blocker (Atenolol) ineffective or contraindicated, then use Calcium channel blocker instead: Verapamil 80 mg tds

Step 4 Consider:

ACE inhibitor - currently available: Perindopril 2-4mg od initially. Max. 8mg od.

Alpha-blocker – Doxazosin 1mg od initially, increase to 2mg od after 1-2 weeks and thereafter to 4mg od if necessary; max 16mg daily.

Methyldopa 250mg bd-tds initially. Increase gradually to a max of 1g daily

changing thiazide to loop diuretic [Furosemide 40-80mg od]

Step 5 Consider Minoxidil, usually in combination with a β -blocker and diuretic.

3.2 Information for Prescribers

- ◆ **The target blood pressure** for most patients is normal (< 140/90 mm Hg. The target BP in patients with diabetes is 130/85 mm Hg (Guidelines Subcommittee, WHO 1999) However it should be noted that a meta-analysis of 1 million adults in 61 studies of blood pressure and mortality (Prospective Studies Collaboration 2002) showed that at age 40-69 years, each increase of 20mm Hg in “usual” systolic BP is associated with more than a 2 fold increase in the rate of death from stroke and a 2 fold increase in death rates from ischaemic heart disease and other vascular diseases. Therefore the patients’ BP should be brought as close as the patient can tolerate to 120/80 mm Hg.
- ◆ Most patients will require more than one medicine to control their blood pressure and the combination should include a low dose thiazide diuretic (Furberg et al, 2002). This also applies to people with diabetes mellitus in whom doctors have been reluctant to prescribe thiazide diuretics, a reluctance that is no longer justified.
- ◆ Verapamil is the calcium-channel blocker of choice. Isradipine is a specialist medicine and very expensive.
- ◆ Verapamil and β -blockers should not be used together, especially in patients with impaired myocardial function.
- ◆ Reserpine, methyldopa, and doxazosin all cause fluid retention and should be given in combination with a diuretic.
- ◆ It may take up to 3/52 for the antihypertensive effect of reserpine to be seen.

- ◆ Reserpine and methyldopa have a similar mode of action. Therefore reserpine should be used in preference and they should **never** be co-administered.
- ◆ Where methyldopa cannot be avoided, the daily dose should be kept below 1g to minimise side-effects. To reduce problems with drowsiness it can be administered as two unequal doses, with the higher dose at bedtime.
- ◆ When starting therapy with an alpha blocker or ACE inhibitor consider giving the first dose at bedtime to reduce problems associated with first dose hypotension.
- ◆ Nifedipine is no longer recommended for acute treatment of hypertension and therefore is now only available for treatment of Raynaud's Phenomenon by Specialists.

3.3 Medicine Information

Table 3

Medicine	Nemlist category	"Average" dose	Cost of 1 month's treatment (N\$)	Class of anti-hypertensive medicine
Reserpine	ABC#	0.125mg od	0.45	centrally acting
Amiloride + Hydrochlorothiazide	ABC#	25/2.5mg od	2.26	thiazide diuretic and K- sparing diuretic mix
Furosemide	AB	40mg od	1.82	loop diuretic
Atenolol	AB	50mg od	3.77	β-blocker
Indapamide	AB	2.5mg od	2.75	thiazide diuretic
Doxazosin	AB	4 mg od	39.47	alpha-blocker
Verapamil	AB	80mg tds	19.63	calcium channel blocker
Perindopril	AB	4mg od	20.31	ACE inhibitor
Methyldopa	AB	500mg bd	46.88	centrally acting
Isradipine	S	2.5mg bd	68.33	calcium channel blocker
Minoxidil	S	5 mg bd	114.83	vasodilator

NB: Propranolol is not in the table because it should not be used to treat hypertension
 Nifedipine is not included in table as it is not to be used in treatment of hypertension (see section 4 - Guidelines for the Management of Severe Hypertension)
 Costs quoted are as per CMS data 25 Oct 2002

3.4 Prescribing for Patients with Other Medical Conditions

Diabetes There is now agreement that low dose thiazide diuretics (Furberg et al 2002; Curb et al 1996) and β-blockers are effective in reducing morbidity and mortality in patients with diabetes and hypertension. (Grossman et al 2000; Pahor et al 1998) Caution should be used when prescribing β-blockers for insulin dependent diabetic patients. β-blockers should be **avoided** in patients who experience no warning signs of hypoglycaemia, patients with peripheral vascular disease, autonomic

neuropathies, multiple organ damage or those who suffer frequent episodes of hypoglycaemia (Joint Formulary Committee (eds) 2001). ACE inhibitors may be of particular benefit because they can slow progression of diabetic nephropathy.

- Renal failure** Thiazide diuretics are ineffective if GFR <30ml/min, so use furosemide instead. May require dose reduction of other agents.
- Heart failure** Avoid calcium-channel blockers. Furosemide (40-80mg od) is preferable to amiloride + hydrochlorothiazide. Consider ACE inhibitor at an early stage. β -blockers can be used with caution in chronic stable heart failure but should only be initiated under specialist supervision and the dose titrated upwards very slowly (Joint Formulary Committee (eds) 2001).
- Airways disease** Avoid β -blockers.
- Pregnancy** Methyldopa is the agent of choice. Calcium-channel and β -blockers may also be considered. Avoid ACE inhibitors, diuretics and reserpine.
- Breast feeding** Avoid doxazosin, isradipine, perindopril, and reserpine

3.5 Counselling Points

- ◆ Methyldopa and reserpine can cause drowsiness and may affect one's ability to drive or operate machinery.
- ◆ Perindopril should be taken ½-1 hour before food
- ◆ Patients receiving doxazosin or perindopril for the first time should be told to take the first dose after getting into bed at night. This is because it can cause a marked fall in blood pressure.

3.6 Classes of Medicines for use in Treatment of Hypertension

In deciding on appropriate treatment options the focus should be on issues of *efficacy, tolerability and cost*. Each class of medicines will be discussed in turn:

Diuretics

The recently released results of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (Furberg et al, 2002) clearly indicate that low dose thiazide-type diuretics such as *Hydrochlorothiazide* should be considered first-line pharmacological therapy in patients with hypertension. They are unsurpassed in lowering BP, reducing clinical events, and tolerability, and they are less costly. Thiazide diuretics have been shown to be particularly effective in black patients, (DiPiro et al 1996; Beers and Berkow 1999) especially the elderly. (Sani 1997) This may be because black patients tend to have a low renin status, which predicts a good response to diuretic therapy. (DiPiro et al 1996; Goodman Gilman et al 1996) Low doses are recommended since higher doses have little additional hypotensive effect and increase the incidence of adverse effects, (Gibbon 1997) including sudden cardiac death. (Goodman Gilman et al 1996) Only in the treatment of severe hypertension that is unresponsive to 3 or more other medicines should a dose of 50 mg hydrochlorothiazide be considered.

Thiazide diuretics can have a number of metabolic adverse effects [hyperglycaemia, hyperuricaemia, increased cholesterol]. However, there is now agreement that thiazide diuretics (Furberg et al 2002; Curb et al 1996) are effective in reducing morbidity and mortality in patients with diabetes and hypertension. The recent ALLHAT results (Furberg et al, 2002) showed that the thiazide diuretic (chlorthalidone) was superior to the ACE inhibitor (lisinopril) for several cardiovascular disease outcomes and superior to the calcium channel blocker (amlodipine) for heart failure in both diabetic and non-diabetic participants.

In those patients that do have problems with the adverse metabolic effects of amiloride & hydrochlorothiazide tablets *Indapamide* may be substituted. Indapamide produces no adverse effects on blood glucose and insulin levels and on the lipid profile. (Association of British Pharmaceutical Industry 1996).

Loop diuretics are less potent anti-hypertensives than thiazides (Sani 1997) but are indicated when there is concomitant heart or renal failure. (Thiazides are ineffective if GFR<30ml/min. (Gibbon 1997)) In addition, they are preferred to thiazides in the treatment of resistant hypertension. (Sani 1997)

β-Blockers

The efficacy of β-blockers in black patients is a contentious issue. The mode of action of β-blockers may involve a reduction in plasma renin levels (Goodman Gilman et al 1996) and this has led some authors to state that they are less efficacious in black patients, where renin levels tend to be low anyway. ; (Beers and Berkow 1999; Goodman Gilman et al 1996) However, this has been disputed (DiPiro et al 1996; Sani 1997) and although black patients may respond less well to monotherapy with β-blockers (Gibbon 1997) it would appear that diuretic therapy combined with β-blockers is equally efficacious in hypertensive blacks and whites. (DiPiro et al 1996) Consequently it is reasonable to use β-blockers in combination with diuretics in patients who do not respond adequately to diuretics alone or with reserpine.

There is now agreement that β-blockers are effective in reducing morbidity and mortality in patients with diabetes and hypertension. (Grossman et al 2000; Pahor et al 1998) Caution should be used when prescribing β-blockers for insulin dependent diabetic patients. β-blockers should be **avoided** in patients who experience no warning signs of hypoglycaemia, patients with peripheral vascular disease, autonomic neuropathies, multiple organ damage or those who suffer frequent episodes of hypoglycaemia (Joint Formulary Committee (eds) 2001).

Atenolol is to be used in preference to *Propranolol* for the following reasons: it is less expensive; there is improved compliance since there are fewer tablets for the patient to take; and there are fewer side effects since atenolol is cardioselective and water soluble. The recommended dose of atenolol is 50mg od. It is no longer considered necessary to increase the dose to 100mg (Joint Formulary Committee 2001) since the added benefit of the higher dose is slight. (Gibbon 1997)

Calcium-channel blockers

Calcium-channel blockers have proven efficacy in all types of hypertensive patients (Goodman Gilman et al 1996). However ALLHAT (Furberg et al, 2002) showed that thiazide diuretics are superior to Calcium channel blockers (by about 25%) in preventing heart failure. Therefore they can not be recommended as a first line agent.

Although they are a disparate group, they are all similar in their antihypertensive effectiveness. (DiPiro et al 1996; Beers and Berkow 1999; Goodman Gilman et al 1996) *Verapamil* is the agent of choice. *Nifedipine* capsules are no longer recommended for use in acute severe hypertension (Varon and Marik 2000) and therefore should not be used (see section 4 – Guidelines for the management of Severe Hypertension). *Isradipine* is very expensive and its use is not justified.

Verapamil and β -blockers should not generally be used together, especially if myocardial function is impaired. They have an additive cardiac depressant effect, thus increasing the risk of hypotension, asystole and cardiac failure. (Gibbon 1997; Joint Formulary Committee 2001)

Centrally Acting

Reserpine is our 2nd line medicine in combination with thiazides. It was used in one of the landmark studies that demonstrated the beneficial effects of medicine treatment of hypertension (Goodman Gilman et al 1996) but subsequently fell out of favour due to a poor side effect profile. However, it is now gaining in popularity since the lower doses now used are associated with fewer adverse effects (e.g. drowsiness, depression). (Gibbon 1997) For example, at low doses (not exceeding 0.25mg daily) the rate of depression is equivalent to that of β -blockers, diuretics or placebo, (DiPiro et al 1996) and in combination with a diuretic, Reserpine is as well tolerated as combinations of a diuretic with Propranolol or Methyldopa. (Goodman Gilman et al 1996) The major advantage of Reserpine is that it is much less expensive than other anti-hypertensives.

Methyldopa is not favoured owing to frequent side effects (depression, drowsiness) and the potential for immunological abnormalities (haemolytic anaemia) and organ toxicity (it is hepatotoxic). (Goodman Gilman et al 1996) It requires multiple daily doses and can impair the quality of life of the patient. (Gibbon 1997) In addition, it is very expensive when compared to other anti-hypertensive agents. To minimise the side effects of methyldopa the daily dose should ideally be kept below 1g (Joint Formulary Committee 2001) and it should be given in combination with a diuretic (to avoid fluid retention). To reduce problems with drowsiness it can be administered as 2 unequal doses, with the higher dose at bedtime. It is safe in asthmatics, heart failure and pregnancy.

Alpha adreno-receptor blocker

Doxazosin is an alpha-adrenoceptor antagonist and should not be used as a first line agent in hypertension. The trial arm for doxazosin in the ALLHAT study (Furberg et al, 2000) was stopped early due to the fact that the alpha-adrenoceptor antagonist treatment resulted in increased risk of stroke and heart failure. For this reason doxazosin should only be used as a 4th line treatment. It should not be used in patients with urinary incontinence (British Hypertension Society 2002). It should be used in combination with a diuretic and activity

is enhanced when given with a β -blocker or diuretic. (Goodman Gilman et al 1996) It may improve the lipid profile by decreasing total cholesterol and triglyceride levels and increasing HDL levels. (Robinson 1995)

First-dose hypotension can be a problem. Initiate treatment with 1mg daily. Increase after 1-2 weeks to 2mg daily and then to 4 mg daily if necessary (maximum 16mg).

ACE inhibitors

Some authors state that ACE inhibitors, like β -blockers, may not be the best choice of antihypertensive for black patients with low renin status. (Beers and Berkow 1999; Goodman Gilman et al 1996) However, the relative resistance among black to these medicines can be overcome by concurrent use of a low-dose diuretic, (DiPiro et al 1996; Goodman Gilman et al 1996) with which there is a strongly additive effect. (Sani 1997)

ACE inhibitors have generally been thought to be advantageous in diabetics (slowing the development of diabetic nephropathy) (Goodman Gilman et al 1996) and in heart failure, where they improve prognosis substantially. (Joint Formulary Committee 2001) However the results of ALLHAT (Furberg et al, 2002) showed that for the diabetic population, ACE inhibitors appeared to have no special advantage for most CVD and renal outcomes when compared with thiazide diuretics. This finding agrees with the results of the UK Prospective Diabetes Study Group (1998) that showed that atenolol and captopril were equally effective in reducing the risk of non-fatal and fatal diabetic complications. The study also showed that there was no difference in the renal protection provided by atenolol or captopril.

Renal function should be monitored. ACE inhibitors are relatively expensive so should not be used as first or second line treatment in normal hypertensive patients.

Vasodilator

Minoxidil is a potent vasodilator reserved for the treatment of resistant hypertension. When used alone there is a significant risk of tachycardia, flushing, fluid retention and headache. These effects may be reduced by combining minoxidil with a diuretic (usually furosemide) and a β -blocker. (Joint Formulary Committee 2001; Sani 1997) It is generally unsuitable for female patients due to the side effect of hirsutism. (Gibbon 1997)

3.7 Resistant Hypertension

Hypertension should be considered resistant if blood pressure cannot be reduced to below 140/90 mm Hg in patients who are adhering to an adequate and appropriate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near maximal doses. One of the most common causes of true resistance is volume overload due to inadequate diuretic therapy. If goal blood pressure cannot be achieved without intolerable adverse effects, even suboptimal reduction of blood pressure contributes to decreased morbidity and mortality. Patients who have resistant hypertension should be referred to a specialist to evaluate for precipitating factors.

N.B. Lack of adherence to both medicine and non-medicine treatment regimens are common causes for failure to reach target blood pressure. These problems should be addressed before a patient is considered to have resistant hypertension.

4. GUIDELINES FOR THE MANAGEMENT OF SEVERE HYPERTENSION

Severe hypertension is a common clinical problem, encountered in various clinical settings. Although various terms have been applied to severe hypertension, such as hypertensive crises, emergencies, or urgencies, they are all characterized by acute elevations in BP that may be associated with end-organ damage (hypertensive crisis). The immediate reduction of BP is only required in patients with acute end-organ damage. Hypertension associated with cerebral infarction or intracerebral hemorrhage only rarely requires treatment. The short-acting calcium channel blocker nifedipine is associated with significant morbidity and should be avoided.

4.1 Introduction

A number of different terms have been applied to severe acute elevations of BP. However, most authors have defined hypertensive crises or emergencies as a sudden increase in systolic and diastolic BP associated with end-organ damage of the CNS, the heart, or the kidneys; the term *hypertensive urgencies* has been used for patients with severely elevated BP without acute end-organ damage (Calhoun and Oparil 1990; Fergusson and Vlasses 1986; Gifford 1991; Reuler and Magarian 1988). Box 3 lists those clinical conditions that meet the diagnostic criteria of hypertensive crises. It is important to note that the clinical differentiation between hypertensive emergencies and hypertensive urgencies depends on the presence of target organ damage, rather than the level of BP. Another frequently encountered term, *malignant hypertension*, is defined as a syndrome characterized by elevated BP accompanied by encephalopathy or nephropathy (Joint National Committee of prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997). A systolic pressure > 169 mm Hg or a diastolic > 109 mm Hg in a pregnant woman is considered a hypertensive emergency requiring immediate pharmacologic management (Rey et al 1997).

Box 3

Diagnostic Criteria for Hypertensive Emergencies

- ◆ Hypertensive encephalopathy
- ◆ Acute aortic dissection
- ◆ Acute pulmonary oedema with respiratory failure
- ◆ Acute myocardial infarction/unstable angina
- ◆ Eclampsia
- ◆ Acute renal failure
- ◆ Microangiopathic haemolytic anaemia

4.2 Clinical Manifestations

Most patients with severe hypertension (diastolic pressure \geq 110 mm Hg) have no acute, end-organ damage. Rapid antihypertensive therapy in this setting may be associated with significant morbidity (Bannan et al 1990; Bertel et al 1987; Reed and Anderson 1986).

There are, however, true hypertensive emergencies in which the rapid (controlled) lowering of BP is indicated (McRae and Liebson 1986).

The manifestations of hypertensive crises are those of end-organ dysfunction. Box 3 above lists those conditions that, when associated with severely elevated BP, are referred to as hypertensive crises/ emergencies. Organ dysfunction is uncommon with diastolic BPs <130 mm Hg, although it may occur.

Headache, altered level of consciousness, and less-severe degrees of CNS dysfunction are the classic manifestations of hypertensive encephalopathy (Garcia and Vidt 1987; Hickler 1988). Advanced retinopathy with arteriolar changes, hemorrhages and exudates, as well as papilloedema, are commonly seen on examination of fundi in patients with hypertensive encephalopathy. Cardiovascular manifestations of hypertensive crises may include angina or acute myocardial infarction. Cardiac decompensation may lead to symptoms of dyspnea, orthopnea, cough, fatigue or frank pulmonary oedema (Bennett and Shea 1988). Severe injury to the kidney may lead to renal failure with oliguria and/or hematuria.

4.3 Initial Evaluation of the Patient With Severe Hypertension

The key to successful management of patients with severely elevated BP is to differentiate hypertensive crises from hypertensive urgencies. This is accomplished by a targeted medical history and physical examination supported by appropriate laboratory evaluation (Vidt 1986). Prior hypertensive crises, antihypertensive medications prescribed, and BP control should be ascertained. Particular inquiry should include the use of monoamine oxidase inhibitors and recreational drugs (*ie*, cocaine, amphetamines, phencyclidine). The BP *in all limbs* should be measured by the physician. In obese patients, appropriately sized cuffs should be used. Funduscopic examination is mandatory in all cases to detect the presence of papilledema.

FBC, U&Es, creatinine, and urinalysis should be obtained in all patients presenting with hypertensive crises (Vidt 1986). A peripheral blood smear should be obtained to detect the presence of a microangiopathic hemolytic anemia. In addition, a chest radiograph and ECG should be done. Some patients may benefit from a CAT scan if available, depending on neurological signs. An echocardiogram should be obtained to assess left ventricular function and evidence of ventricular hypertrophy. In many instances, these tests are performed simultaneously with the initiation of antihypertensive therapy.

4.4 Therapeutic Approach

Patients with hypertensive emergencies require immediate control of the BP to terminate ongoing end-organ damage, *but not to return BP to normal levels* (Calhoun and Oparil 1990; Fergusson and Vlasses 1986; Gifford 1991; Reuler and Magarian 1988). The elevated BP in patients with hypertensive emergencies should be treated in a controlled fashion in an ICU if possible. In patients with hypertensive urgencies, BP is lowered gradually over a period of 24 to 48 h, usually with oral medication (recommend atenolol, ACE inhibitor, verapamil or methyldopa). If the patient's history shows that they have not been taking their prescribed medication regularly then the patient should be restarted on the routine regimen, providing it has previously been effective.

The use of sublingual nifedipine must be strongly condemned; this agent may result in a precipitous and uncontrolled fall in BP. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a benefit, the use of nifedipine capsules for hypertensive emergencies and “pseudoemergencies” should be abandoned (Gonzalez-Carmona et al 1991; Grossman et al 1996; Schillinger 1987; Spah and Grosser 1988).

The immediate goal of IV therapy is to reduce the diastolic BP by 10 to 15%, or to about 110 mm Hg. In patients with acute aortic dissection, this goal should be achieved within 5 to 10 min. In the other patients, this end point should be achieved within 1-2 hours. Once the end points of therapy have been reached, the patient can be started on a regimen of oral maintenance therapy.

It should be emphasized that only patients with hypertensive crises/emergencies (see Box 3 above) require immediate reduction of a markedly elevated BP. In all other patients, the elevated BP can be lowered slowly using oral agents. In patients who have suffered a major cerebrovascular event, the BP should not be lowered, except in exceptional circumstances (see below).

4.5 Hypertension After a Cerebrovascular Accident

The current recommendations of the American Heart Association is that hypertension in the setting of acute ischemic stroke should be treated **only “rarely and cautiously”** (Emergency Cardiac Care Committee and Subcommittees 1992). It is generally recommended that antihypertensive therapy be reserved for patients with a diastolic pressure > 120 to 130 mm Hg, aiming to reduce the pressure by no more than an arbitrary figure of 20% in the first 24 h (Lavin 1986; O’Connell and Gray 1994; O’Connell and Gray 1996). In patients with intracerebral hemorrhage, the value of early antihypertensive therapy in preventing rebleeding or reducing vasogenic oedema has not been demonstrated. However, with radiological evidence of a major intracerebral bleed, cautious lowering of a systolic BP > 200 mm Hg or a diastolic BP > 120 mm Hg is generally suggested (Lavin 1986; O’Connell and Gray 1994). This recommendation is supported by a recent study that demonstrated that rapid decline in BP within the first 24 h after an intracerebral hemorrhage was associated with increased mortality (Qureshi and Bliwise 1999).

4.6 Preeclampsia

The presentation of a patient with pregnancy-induced hypertension may range from a mild to a life-threatening disease process. The process can be ended only by delivery. The decision to continue or to deliver the pregnancy will be made by consultation between medical and obstetric personnel. A **systolic pressure > 169 mm Hg or a diastolic > 109 mm Hg** in a pregnant woman is considered a hypertensive emergency requiring immediate pharmacologic management (Rey and LeLorier 1997). Most preeclamptic patients are vasoconstricted and haemoconcentrated. After initial therapy, volume expansion and haemodilution occur.

Magnesium sulphate is considered the standard of therapy as a prophylaxis for seizure activity (Varon and Marik 2000); the loading dose is 4 to 6 g in 100 mls dextrose 5% in 0.2% sodium chloride solution over 15 to 20 min. A constant infusion of 1 to 2 g/h should

then be maintained depending on urine output and deep tendon reflexes that are checked on an hourly basis. Detailed intake and output records must be maintained. Since renal function is frequently impaired, an increase in total body water can result in pulmonary edema. In rare cases, if hyponatraemia is allowed to occur, cerebral oedema may be observed. Dihydralazine and hydralazine have been used traditionally in the treatment of eclampsia. See below for administration details.

4.7 Management of Hypertensive Emergencies with Dihydralazine Injection

- ◆ The initial dose is 6.25mg (1/4 of an ampoule), administered by slow (2 minutes) intravenous or intramuscular injection in order to avoid precipitous decreases in mean arterial pressure with a critical reduction in cerebral or uteroplacental perfusion.
- ◆ If it is necessary to repeat the injection, this should be done after an interval of 2 hours, throughout which the blood pressure and heart rate should be monitored.
- ◆ Prior to injection, the dry, active substance should be completely dissolved in 2ml water for injection. The freshly prepared solution should be used immediately.
- ◆ For the preparation of infusion solution this fresh solution should be diluted with 0.9% sodium chloride solution or with plasmolyte B solution packed in **glass containers only**, since there is a possibility of an interaction with plastic containers. Glucose solution should not be employed for this purpose, because contact between dihydralazine and glucose causes the active substance to be rapidly broken down.
- ◆ The dosage for a drip infusion is one ampoule (25mg). The drip must be started very slowly and the dose titrated upwards until a suitable response is seen.
- ◆ Constant monitoring of blood pressure is essential during treatment with dihydralazine. If the blood pressure falls too far then the dihydralazine must be stopped immediately and fluid replacement started.
- ◆ Oral antihypertensive therapy should be initiated as soon as the patient's condition is stabilised because the oral agents have a slow onset of action.

Other Medicine Information about Dihydralazine Injection 25mg/ml (Nepresol®) (Data from Nepresol ® package insert)

Indications:

- ◆ Hypertensive crises, including in late pregnancy (pre-eclampsia and eclampsia)

Contra-Indications:

- ◆ Hypersensitivity to dihydralazine or hydralazine.
- ◆ Idiopathic systemic lupus erythematosus (SLE)
- ◆ Tachycardia and heart failure with a high cardiac output (eg. in thyrotoxicosis)
- ◆ Myocardial insufficiency due to mechanical obstruction (eg. in the presence of aortic or mitral stenosis or constrictive pericarditis).
- ◆ Isolated right ventricular heart failure due to pulmonary hypertension (cor pulmonale)
- ◆ Dissecting aortic aneurysm.
- ◆ Porphyria.

Management of overdose:

Symptoms: The chief manifestations are cardiovascular disorders such as pronounced tachycardia and hypotension, which are accompanied by nausea, dizziness and sweating and which can result in circulatory collapse, also possible are myocardial ischaemia with angina pectoris and cardiac arrhythmias. Further signs and symptoms include impairment of consciousness, headache and vomiting as well as possibly tremor, convulsions, oliguria and hypothermia.

Rx: No specific antidote. Treatment is symptomatic mainly by administering a plasma expander.

Side-Effects:

- ◆ Tachycardia, palpitations, anginal symptoms, flushing, headache, dizziness, nasal congestion, GIT disturbances are seen more frequently at the start of treatment, especially if the dosage is raised rapidly. However such reactions generally subside in the further course of treatment.
- ◆ **CARDIOVASCULAR SYSTEM:** More frequently: Tachycardia, palpitations, flushing, hypotension, anginal symptoms. Less frequently: Oedema, heart failure.
- ◆ **LIVER AND BILIARY SYSTEM:** Less frequently: Jaundice, abnormal liver function, hepatitis.
- ◆ **MUSCULO-SKELETAL SYSTEM:** More frequently: Arthralgia.
- ◆ **SKIN AND APPENDAGES:** Less frequently: Rash, pruritus.
- ◆ **CENTRAL AND PERIPHERAL NERVOUS SYSTEM:** More frequently: Headache, dizziness. Less frequently: Peripheral neuritis, paraesthesiae (these unwanted effects can be reversed by administering pyridoxine)
- ◆ **BLOOD:** Less frequently: Anaemia, leucopenia, thrombocytopenia.
- ◆ **GIT:** More frequently: GIT disturbances, diarrhoea, nausea, vomiting.
- ◆ **HYPERSENSITIVITY REACTIONS:** Less frequently: SLE like syndrome.
- ◆ **PSYCHE:** Less frequently: Agitation, anorexia, nervousness, restlessness, anxiety, depressive mood disorders.
- ◆ **OTHER:** Less frequently: Fever, malaise.

Management of Side-Effects:

The severity of any side effects must be weighed against the risk of potential end organ damage upon stopping the dihydralazine administration before the blood pressure has been lowered by 10-15%. In most cases the side effects are transient and can be minimised by starting with a low dose and slowly titrating the dose upward. Peripheral neuritis and paraesthesiae can be reversed by administration of pyridoxine 20-50mg three times a day.

Precautions:

- ◆ In patients with renal impairment (creatinine clearance < 30ml/min or serum creatinine concentrations > 2.5mg/100ml or 221 micro-mol/l) the dose or dosing interval has to be adapted according to clinical response, in order to avoid accumulation of the "apparent" active substance.
- ◆ Caution in patients with cerebrovascular disease.

- ◆ When undergoing surgery, patients on this medicine may show a fall in blood pressure, in which case one should not use adrenaline to correct the hypotension, since it enhances the cardiac accelerating effects of dihydralazine.
- ◆ When initiating therapy in heart failure, particular caution should be exercised and the patient, kept under careful surveillance and/or haemodynamic monitoring for early detection of postural hypotension or tachycardia.
- ◆ Where discontinuation of therapy in heart failure is indicated, dihydralazine should be withdrawn gradually (except in serious situations, such as SLE syndrome or blood dyscrasias) in order to avoid precipitation and/or exacerbation of heart failure.

WARNINGS:

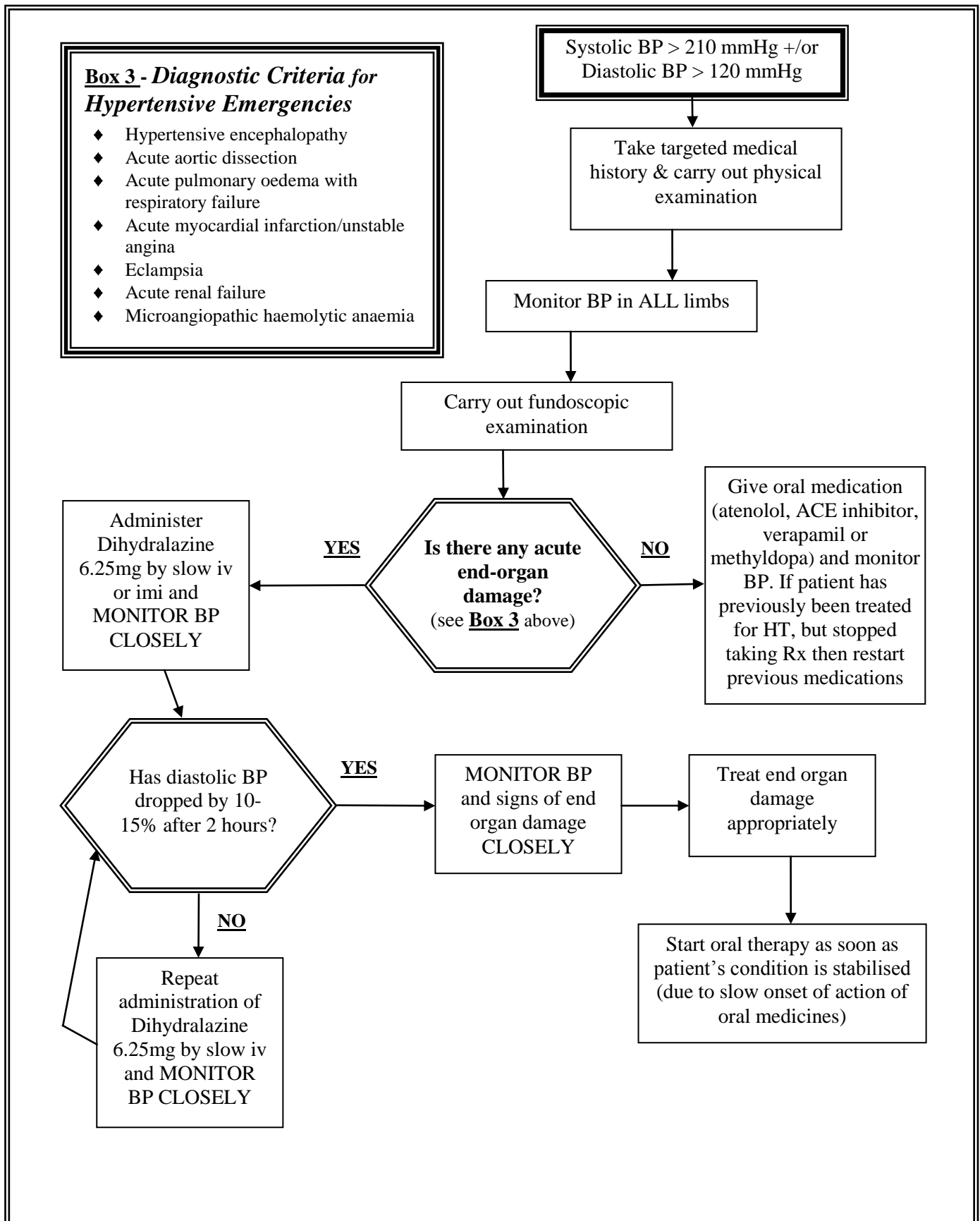
- ◆ The overall hyperdynamic state of circulation induced by dihydralazine may accentuate certain clinical conditions.
- ◆ Myocardial stimulation may prolong or aggravate angina pectoris.
- ◆ Patients with confirmed or suspected coronary heart disease should therefore be given dihydralazine only under the cover of a β -blocker or in combination with other suitable sympatholytic agents. It is important that the β -blocker medication should be commenced a few days before the start of treatment with dihydralazine. Patients who have survived myocardial infarction should not be given dihydralazine until a post-infarction stabilisation phase has been achieved.
- ◆ Patients with hepatic dysfunction should be carefully monitored in case of rare but serious adverse effects on the liver.
- ◆ Dihydralazine and hydralazine are closely similar structures; cases of lupus erythematosus (LE) like syndrome have been reported in patients treated with dihydralazine. For maintenance therapy with dihydralazine the lowest dosage that still proves effective should be employed.
- ◆ Dihydralazine has shown mutagenic potential in bacterial test systems. However in several other tests, including in vivo experiments, no evidence of mutagenicity has been demonstrated.

Pregnancy:

- ◆ As a general principle the medicine may be employed in pregnancy only if there is no safer alternative or when the disease itself carries a serious risks for the mother or child eg. pre-eclampsia or eclampsia.
- ◆ Caution should be exercised in maternal hypotension as I/V administration may lead to foetal death.
- ◆ Dihydralazine passes into breast milk.

Box 4

MANAGEMENT OF SEVERE HYPERTENSION



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