PHC Chapter 4: Cardiovascular conditions

4.1 Prevention of ischaemic heart disease and atherosclerosis

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4.1 PREVENTION OF ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS

I20.0-1/I20.8-9/I21.0-4/I21.9/I22.0-1/I22.8-9/I24.0-1/I24.8-9/I25.0-6/I25.8-9/I63.0-6/I63.8-9/I64/I65.0-3/I65.8-9/I73.8-9/G45.0-2/G45.8-9

Patients at risk for cardiovascular events (such as stroke or myocardial infarction) may benefit from lifestyle modification and lipid-lowering medicine therapy. Patients should be managed according to their level of risk, and lipid lowering medicines should be given to those with a high risk of CVD even if cholesterol is within the desirable range.

Indications for lipid lowering medicine therapy

Patients with any of the following factors are at a relatively high risk for a cardiovascular event and should receive lipid lowering therapy:

- Established atherosclerotic disease:
  - ischaemic heart disease.
  - peripheral vascular disease.
  - atherothrombotic stroke.
- Type 2 diabetes with age > 40 years.
- Diabetes for > 10 years. *LoE:IIa*[1]
- Diabetes with chronic kidney disease (eGFR < 60 mL/min).

Patients with any of the following factors are also potentially at risk for cardiovascular disease (other than the categories above)

- Diabetes mellitus.
- Hypertension.
- Central obesity: waist circumference ≥ 94 cm (men) and ≥ 80 cm (women).
- Smoking.
- Age: men > 55 years of age, women > 65 years of age. *LoE:IIIb*[2]
- Psychological stress.

These patients should be managed according to their 10-year risk of a cardiovascular event (See Appendix III: Cardiovascular risk assessment), as calculated using either:

A. BMI - based risk assessment, or
B. Framingham risk score (cholesterol-based assessment).

Management is based on the patient's 10-year risk of a cardiovascular event as follows:

- < 10% risk: lifestyle modification and risk assess patient every 5 years.
- 10–20% risk: lifestyle modification and risk assess patient annually.
- ≥ 20% risk: lifestyle modification and start statin treatment.

Screening for familial hypercholesteroleamia:

In addition to the above cardiovascular risk assessment, measure random total cholesterol in patients with the following features (suggestive of familial hypercholesterolaemia or other heritable dyslipidaemias), regardless of their cardiovascular risk:

- Cardiovascular event < 55 years in men or < 65 years in women.
- Family history of early onset cardiovascular disease in male relatives < 55 years of age and in female relatives < 65 years of age.
- Skin or tendon xanthomata in patient or first degree relative.
- Family history of familial hyperlipidaemia.

Refer patients with random total cholesterol > 7.5 mmol/L for further investigation.

GENERAL MEASURES

All patients with any risk factors for cardiovascular disease should be encouraged to make the following lifestyle changes as appropriate:

- » Maintain ideal weight, i.e. BMI 18 to 25 kg/m^2. Weight reduction in the overweight patient. *LoE:IIIb*[3]
- » Reduce alcohol intake to no more than 2 standard drinks per day for males and 1 for females. (1 standard drink = a can of beer = a glass of wine = a shot of spirits).
- » Follow a prudent eating plan i.e. low fat, high fibre and unrefined carbohydrates, with fresh fruit and vegetables.
- » Regular moderate aerobic exercise, e.g. 30 minutes brisk walking 5-7 times/week (150 minutes/week).
- » Stop smoking.

MEDICINE TREATMENT

- » Lipid lowering medicines should be given to those with a high risk of CVD even if cholesterol is within the desirable range.
- » When lipid-lowering medicines are used, this is ALWAYS in conjunction with ongoing lifestyle modification.

▪ HMGCoA reductase inhibitors (statins), according to table below:

INDICATION	HMGCoA REDUCTASE INHIBITOR (STATIN)
A: Primary prevention - no existing CVD	
» Type 2 diabetes with age >40 years. » Diabetes for >10 years. » Diabetes with chronic kidney disease. » ≥ 20% 10-year risk of cardiovascular event.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night.
» Patients on protease inhibitors. (Risks as above, after switching to atazanavir – see section below).	• Atorvastatin, oral, 10 mg at night.
B: Secondary prevention – existing CVD	
» Ischaemic heart disease. » Atherothrombotic stroke. » Peripheral vascular disease.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Rosuvastatin, 10 mg at night. *LoE:Ia*[4]
» Patients on protease inhibitors.	• Atorvastatin, oral, 10 mg at night. *LoE:Ia*[5]
» Patients on amlodipine (and not on protease inhibitor).	• Simvastatin, oral, 10–20 mg at night. *LoE:IIIb*[6]
» If patient complains of muscle pain.	Reduce dose: ▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 20 mg at night. o If 20 mg not tolerated, reduce to 10 mg. **OR** Consult specialist for further management. *LoE:IIIb*[7]

Table 4.1: Management with HMGCoA reductase inhibitors

Protease inhibitor-induced dyslipidaemia:

» Certain antiretroviral medication, particularly protease inhibitors, can cause dyslipidaemia. Fasting lipid levels should be done 3 months after starting lopinavir/ritonavir. Lopinavir/ritonavir is associated with a higher risk of dyslipidaemia (specifically hypertriglyceridaemia) than atazanavir/ritonavir.

» Patients at high risk (> 20% risk of developing a CV event in 10 years or existing CVD) should switch to atazanavir/ritonavir and repeat the fasting lipid profile in 3 months.

» Patients with persistent dyslipidaemia despite switching, qualify for lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV-uninfected patients. Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.

» Patients at high risk for CVD who fail to respond to lifestyle modification and have dyslipidaemia on atazanavir/ritonavir treat with:

- Atorvastatin, oral, 10 mg at night.

REFERRAL

» Random cholesterol > 7.5 mmol/L (to be evaluated for genetic disorders), after excluding secondary causes such as uncontrolled diabetes, hypothyroidism, or protease inhibitor use.

» Tendon or skin xanthomata (except xanthelasma around the eyes).

» Statins not tolerated by patients, despite lower dose (for consideration of alternative treatment).

4.2 ANGINA PECTORIS, STABLE

I20.20

DESCRIPTION

Characteristic chest pain (burning or heavy discomfort behind the sternum), of duration <15 minutes, due to myocardial ischaemia, usually with exercise and relieved by rest.

GENERAL MEASURES

Lifestyle modification. See Section 4.1: Prevention of ischaemic heart disease and atherosclerosis.

MEDICINE TREATMENT (doctor initiated)

Long-term prophylaxis for thrombosis:

- Aspirin, oral, 150 mg daily. *LoE:Ia*[8]

AND

Relief of angina:

- Nitrates, short acting e.g.:
- Isosorbide dinitrate, sublingual, 5 mg.
  - May be repeated if required at 5-minute intervals for 3 or 4 doses.
  - Instruct patients to keep the tablets in the airtight and lightproof container in which they are supplied.
  - Instruct patients that nitrates are not addictive.

- Instruct patients to use prophylactically, before activities which may provoke angina. LoE:IVb[9]

AND

Step 1

- Beta-blocker
- Atenolol, oral, 50–100 mg daily.
  - Titrate to resting heart rate of approximately 60 beats/minute.

If beta-blocker cannot be tolerated or is contraindicated, consider long-acting calcium channel blocker.

Step 2

ADD

- Long-acting calcium channel blocker e.g.:
- Amlodipine, oral, 5 mg daily.

Step 3

ADD

- Isosorbide mononitrate, oral, 10–20 mg twice daily. LoE:IIIb[10]

OR

- Isosorbide dinitrate, oral, 20–30 mg twice daily.
  - Take either medicine at 8:00 and 14:00 in order to provide a nitrate-free period to prevent tolerance. LoE:IIIb[11]
  - Modify for night shift workers.

Angina is a high-risk condition for cardiovascular disease and an indication for a statin.

- HMGCoA reductase inhibitors (statins), e.g.:
- Rosuvastatin, oral, 10 mg at night. LoE:Ia[12]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg daily. LoE:Ia[13]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10–20 mg at night. LoE:IVb[14]

If patient complains of muscle pain:

Reduce dose e.g.:

- If simvastatin 20 mg not tolerated, reduce to 10 mg.

OR

Refer for further management. LoE:IIIb[15]

REFERRAL

» When diagnosis is in doubt.
» Failed medical therapy.

4.3 ANGINA PECTORIS, UNSTABLE / NON ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

I21.4/ I21.9/I22.0-1/I22.8-9/I24.8-9/I25.6/I25.8-9

DESCRIPTION

Unstable angina is a medical emergency and if untreated can progress to NSTEMI.

Presents as chest pain or discomfort similar to stable angina but with the following additional characteristics:

» angina at rest or minimal effort,
» angina occurring for the first time, particularly if it occurs at rest,
» prolonged angina > 10 minutes, not relieved by sublingual nitrates,
» the pattern of angina accelerates and gets worse.

DIAGNOSIS

» Made from good history.
» ECG may show ST segment depression, transient ST segment elevation or T wave inversion.
» Normal ECG does not exclude the diagnosis. For this reason, history is of paramount importance.

MEDICINE TREATMENT

- Oxygen 40% via facemask, if saturation < 94% or if in distress.

CAUTION
Do not administer oxygen to acutely ill patients who are not hypoxic (SPO_2 ≥ 96%)

ADD

LoE:IIb[16]

- Aspirin, oral, 150 mg as a single dose (chewed or dissolved) as soon as possible.

ADD

LoE:Ia[17]

- Nitrates, short acting, e.g.:
- Isosorbide dinitrate, sublingual, 5 mg immediately as a single dose.
  - May be repeated at 5-minute intervals for 3 or 4 doses.

LoE:IVb[18]

ADD

- Morphine 10 mg diluted with 10 mL of water for injection or sodium chloride 0.9%, slow IV (Doctor prescribed).
  - Start with 5 mg; thereafter slowly increase by 1 mg/minute up to 10 mg.
  - Can be repeated after 4–6 hours if necessary, for pain relief.
  - Beware of hypotension.

Continuation of aftercare treatment initiated at higher level of care:
Continue therapy with appropriate lifestyle modification and adherence support.

- Aspirin, oral, 150 mg daily (continued indefinitely in absence of contraindications).

LoE:Ia[19]

<u>When clinically stable without signs of heart failure, hypotension, bradydysrhythmias or asthma:</u>

- Cardio-selective beta-blocker, e.g.:(Doctor initiated)
- Atenolol, oral, 50 mg daily.

AND

- HMGCoA reductase inhibitors (statins), e.g.:
- Rosuvastatin, oral, 10 mg at night.

LoE:Ia[20]

<u>Patients on protease inhibitor:</u>

- Atorvastatin, oral, 10 mg at night.

LoE:Ia[21]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10-20 mg at night. *LoE:IVb*[22]

If patient complains of muscle pain:

Reduce dose e.g.:

If simvastatin 20 mg not tolerated, reduce to 10 mg.

OR

Refer for further management. *LoE:IIIb*[23]

AND

If there is cardiac failure or LV dysfunction (Doctor initiated):

- ACE-inhibitor, e.g.:
- Enalapril, oral, target dose 10 mg 12 hourly (usually titrated from 2.5 mg 12 hourly). *LoE:IVb*[24]

Angioedema is a potentially serious complication of ACE-inhibitor treatment and if it occurs it is a contraindication to continue therapy or to re-challenge.

REFERRAL

Urgent

All suspected or diagnosed cases.

4.4 MYOCARDIAL INFARCTION, ACUTE (AMI)/ ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

I21.0-3/I21.9/I22.0-1/I22.8-9/I24.8-9/I25.6/I25.8-9

DESCRIPTION

AMI/STEMI is caused by the complete or partial occlusion of a coronary artery and requires prompt hospitalisation and intensive care management.

The major clinical feature is severe chest pain with the following characteristics:

- site: retrosternal or epigastric,
- quality: crushing, constricting, or burning pain or discomfort,
- radiation: to the neck and/or down the inner part of the left arm,
- duration: at least 20 minutes and often not responding to sublingual nitrates,
- occurrence: at rest.

May be associated with:

- pallor
- sweating
- arrhythmias
- pulmonary oedema
- a decrease in blood pressure

Note: Not all features have to be present.

EMERGENCY TREATMENT

Before transfer

Cardio-pulmonary resuscitation if necessary (See Section 21.1: Cardiac arrest – cardiopulmonary resuscitation).

- Oxygen 40% via facemask, if saturation < 94% or if in distress.

CAUTION
Do not administer oxygen to acutely ill patients who are not hypoxic ($SPO_2 \geq 96\%$)

AND

- Aspirin, oral, 150 mg as a single dose (chewed or dissolved) as soon as possible. *LoE:IIb*[25] *LoE:Ia*[26]

AND

- Nitrates, short acting, e.g.:
- Isosorbide dinitrate, sublingual, 5 mg immediately as a single dose.
  - May be repeated at 5-minute intervals for 3 or 4 doses. *LoE:IVb*[27]

AND

- Morphine 10 mg diluted with 10 mL of water for injection or sodium chloride 0.9%, slow IV (Doctor prescribed).
  - Start with 5 mg; thereafter slowly increase by 1 mg/minute up to 10 mg.
  - Can be repeated after 4–6 hours if necessary, for pain relief.
  - Beware of hypotension.

AND

- Thrombolytic (see table for time window below) (Doctor initiated), e.g.: *LoE:IIb*[28]
- Streptokinase, IV 1.5 million units diluted in 100 mL sodium chloride 0.9%, infused over 30–60 minutes. **Do not use heparin if streptokinase is given.** *LoE:IIb*[29]
  - Hypotension may occur. If it does, reduce the rate of infusion but strive to complete it in < 60 minutes.
  - Streptokinase is antigenic and should not be re-administered in the period of 5 days to 2 years after 1st administration.
  - Severe allergic reactions are uncommon but antibodies which may render it ineffective may persist for years.

Considerations for initiating thrombolytics	Contra-indications
» <u>For acute myocardial infarction with ST elevation or left bundle branch block:</u> – maximal chest pain is ≤ 6 hours doctor to initiate treatment. – If beyond 6 hours and chest pain, consult a specialist – > 6 hours and no chest pain, thrombolytic not indicated. Manage as above and refer patient. *LoE:Ia*[30]	» <u>Absolute:</u> – streptokinase used within the last year, – previous allergy, – CVA within the last 3 months, – history of recent major trauma, – bleeding within the last month, – aneurysms, – brain or spinal surgery or head injury within the preceding month, or recent (< 3 weeks) major surgery, – active bleeding or known bleeding disorder, – aortic dissection. » <u>Relative (consult specialist):</u> – refractory hypertension, – warfarin therapy, – recent retinal laser treatment, – subclavian central venous catheter, – pregnancy, – TIA in the preceding 6 months, – traumatic resuscitation.

Table 4.2: Streptokinase therapy

Note: Refer all suspected or diagnosed cases urgently.

Continuation of aftercare treatment initiated at higher level of care:
Continue therapy with appropriate lifestyle modification and adherence support.

- Aspirin, oral, 150 mg daily (continued indefinitely in absence of contraindications). *LoE:Ia*[31]

When clinically stable without signs of heart failure, hypotension, bradydysrhythmias or asthma:

- Cardio-selective beta-blocker, e.g.:(Doctor prescribed)
- Atenolol, oral, 50 mg daily.

AND

- HMGCoA reductase inhibitors (statins), e.g.:
- Rosuvastatin, oral, 10 mg at night. *LoE:Ia*[32]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night. *LoE:Ia*[33]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10–20 mg at night. *LoE:IVb*[34]

If patient complains of muscle pain:
Reduce dose e.g.:
If simvastatin 20 mg not tolerated, reduce to 10 mg.
OR *LoE:IIIa*[35]
Refer for further management.
AND

If there is cardiac failure or LV dysfunction (Doctor initiated): *LoE:IVb*[36]

- ACE-inhibitor, e.g.:
- Enalapril, oral, target dose 10 mg 12 hourly (usually titrated from 2.5 mg 12 hourly).

Angioedema is a potentially serious complication of ACE-inhibitor treatment and if it occurs it is a contraindication to continued therapy or to re-challenge.

REFERRAL

Urgent
All suspected or diagnosed cases.

4.5 CARDIAC ARREST, CARDIO-PULMONARY RESUSCITATION

See Chapter 21: Emergencies and injuries.

4.6 CARDIAC FAILURE, CONGESTIVE (CCF)

4.6.1 CARDIAC FAILURE, CONGESTIVE (CCF), ADULTS

I50.0-1/I50.9

DESCRIPTION

CCF is a clinical syndrome and has several causes. The cause and immediate precipitating factor(s) must be identified and treated to prevent further damage to the heart.

Symptoms of CCF include:

- » Progressive effort intolerance (worsening breathlessness, or fatigue with physical activity such as walking uphill, climbing stairs, sweeping or carrying a heavy load). If severe, breathlessness, or fatigue, may occur when doing activities of daily living such as dressing and washing and may even occur at rest.
- » Orthopnoea (breathless when lying down flat).
- » Paroxysmal nocturnal dyspnoea (PND) (sudden awakening with breathlessness).
- » Ankle (or body) swelling.
- » Fatigue.

Signs of CCF include:

- » dyspnoea (breathlessness)
- » ankle swelling with pitting oedema
- » tachycardia
- » raised jugular venous pressure
- » inspiratory basal crackles or wheezing on auscultation of the lungs
- » tachypnoea
  - men: breathing rate > 18 breaths/ minute
  - women: breathing rate > 20 breaths/ minute
- » enlarged liver, often tender

GENERAL MEASURES

- » Monitor body weight to assess changes in fluid balance.
- » Salt (sodium chloride) restriction to less than 2–3 g/day.
- » Regular exercise within limits of symptoms.

MEDICINE TREATMENT

All patients should be assessed by a doctor for initiation or change of treatment.

- » Many of the medicines used can affect renal function and electrolytes.
- » Monitor sodium, potassium and serum creatinine.

STEP 1: Diuretic plus ACE-inhibitor

Mild volume overload (mild CCF) and normal renal function – thiazide diuretic

- Hydrochlorothiazide, oral 25–50 mg daily. *LoE:IIb*[37]
  - Caution in patients with gout.
  - Less effective in impaired renal function.
  - Higher doses can cause hyponatremia.
  - Caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

Significant volume overload or abnormal renal function – loop diuretic

- Furosemide, oral, daily (Doctor initiated).
  - Initial dose: 40 mg daily.
  - If dose > 80 mg/day is required, change dose interval to 12 hourly.
  - Higher doses may be needed if co-morbid kidney impairment is present.
  - Once CCF has improved, consider switching to hydrochlorothiazide.
  - Monitor electrolytes and creatinine.

Acute pulmonary oedema

- Furosemide, IV. See Section 21.2.8: Pulmonary oedema, acute.

Note:

» Use a lower diuretic dose when given in combination with an ACE-inhibitor.

» Routine use of potassium supplements with diuretics is not recommended. They should only be used short-term to correct documented low serum potassium level.

All patients with CCF, unless contraindicated or poorly tolerated

- ACE-inhibitor, e.g.:
- Enalapril, oral, 2.5 mg 12 hourly, up to maximum of 10 mg twice daily.
  - Titrate dosages gradually upwards until an optimal dose is achieved.
  - Absolute contraindications include: (refer to package insert for a complete list)
  - cardiogenic shock,
  - bilateral renal artery stenosis, or stenosis of an artery to a dominant/single kidney,
  - aortic valve stenosis and hypertrophic obstructive cardiomyopathy
  - pregnancy,
  - history of angioedema associated with previous ACE-inhibitor or angiotensin II receptor blocker (ARB) therapy.

STEP 2: After titration of ACE-inhibitor add carvedilol (alpha 1 and non-selective beta blocker) unless contra-indicated (Refer to package insert for full prescribing information).

Note: Do not use atenolol for cardiac failure.

- Carvedilol, oral (Doctor initiated). *LoE:IIIb*[38]
  - Starting dose: 3.125 mg twice daily.
  - Increase dose at two-weekly intervals by doubling the daily dose until a maximum of 25 mg twice daily, if tolerated.
  - If >85 kg and target heart rate has not been achieved, titrate to a maximum of 50 mg twice daily, if tolerated. *LoE:IIIb*[39]
  - If not tolerated, i.e., worsening of cardiac failure manifestations, reduce the dose to the previously tolerated dose.
  - Up-titration may take several months.
  - Should treatment be discontinued for > 14 days, reinstate therapy as above.
  - Absolute contraindications include: (Refer to package insert)
  - cardiogenic shock, bradycardia, various forms of heart block
  - severe fluid overload
  - hypotension
  - asthma

OR

- Spironolactone, oral, 25 mg daily (Doctor initiated).

CAUTION

Spironolactone can cause severe hyperkalaemia and should only be used when serum potassium and renal function can be monitored. Check potassium levels within one month of starting therapy and thereafter, as per clinical need. Routine monitoring of potassium levels is essential if spironolactone is used with an ACE-inhibitor, other potassium sparing agents or in the elderly. Avoid concomitant potassium supplements and use of NSAIDs. **Do not use in kidney failure (Do not use if eGFR < 30 mL/min).**

STEP 3:

- Spironolactone, oral, 25 mg daily (Doctor initiated).

OR *LoE:IVb*[40]

- Carvedilol, oral (Doctor initiated).
  - Starting dose: 3.125 mg twice daily.
  - Increase dose at two-weekly intervals by doubling the daily dose until a maximum of 25 mg twice daily, if tolerated.
  - If >85 kg and target heart rate has not been achieved, titrate to a maximum of 50 mg twice daily, if tolerated
  - If not tolerated, i.e. worsening of cardiac failure manifestations, reduce the dose to the previously tolerated dose.
  - Up-titration can take several months.
  - Should treatment be discontinued for > 14 days, reinstate therapy as above.
  - Absolute contraindications include: (Refer to package insert)
  - cardiogenic shock, bradycardia, various forms of heart block
  - severe fluid overload
  - hypotension
  - asthma

STEP 4:

Symptomatic CCF despite above-mentioned therapy:

- Refer to hospital for step up therapy with digoxin.

CAUTION

Patients with CCF on diuretics may become hypokalaemic.
Digoxin therapy should not be initiated if the patient is hypokalaemic.

REFERRAL

Urgent

» Patients with prosthetic heart valve.
» Suspected infective endocarditis.
» Fainting spells.

Non urgent

» Initial assessment and initiation of treatment.
» Poor response to treatment.

4.6.2 CARDIAC FAILURE, CONGESTIVE (CCF), CHILDREN

I50.0/I50.1-9

DESCRIPTION

The congestion of the systemic or pulmonary venous systems due to cardiac dysfunction of various different causes; including congenital heart disease and acquired cardiac and lung conditions (e.g. cor-pulmonale due to bronchiectasis in children living with HIV). Often mistaken for respiratory infection.

Signs and symptoms

Infants

- » rapid breathing
- » rapid heart rate
- » cardiomegaly
- » enlarged tender liver
- » chest indrawing
- » crackles or wheezing in lungs
- » active cardiac impulse

Often presents primarily with shortness of breath, difficulty in feeding and sweating during feeds. Oedema is usually not an obvious feature.

Children

- » rapid breathing
- » rapid heart rate
- » cardiomegaly
- » enlarged tender liver
- » chest indrawing
- » crackles or wheezing in lungs
- » active and displaced cardiac impulse
- » oedema of the lower limbs or lower back

GENERAL MEASURES

While arranging transfer:

- Oxygen, using nasal cannula at 2–3 L per minute.

OR

- Oxygen 40%, using face mask at 2–3 L per minute.
  - Semi-Fowlers position.

Note: If hypertensive, consider glomerulonephritis in children.

MEDICINE TREATMENT

While arranging transfer:

If CCF is strongly suspected

- Furosemide, IV, 1 mg/kg, over 5 minutes. See Section 23: Paediatric dosing tables.
  - Do not put up a drip or run in any IV fluids.

REFERRAL

All children with suspected congestive cardiac failure.

4.7 HYPERTENSION

4.7.1 HYPERTENSION IN ADULTS

I10

DESCRIPTION

A condition characterised by an elevated blood pressure (BP) measured on 3 separate occasions, a minimum of 2 days apart:

» Systolic BP ≥ 140 mmHg

and/or

» Diastolic BP ≥ 90 mmHg.

However, when BP is severely elevated (refer to the table below), a minimum of 3 BP readings must be taken at the 1st visit to confirm hypertension. Ensure that the correct cuff size is used in obese patients.

LEVELS OF HYPERTENSION IN ADULTS

Level of hypertension	Systolic mmHg	Diastolic mmHg
Mild	140–159	90–99
Moderate	160–179	100–109
Severe	≥ 180	≥ 110

Table 4.3: Classification of hypertension

The aim of hypertension management is to achieve and maintain target BP: Systolic < 140 mmHg and diastolic < 90 mmHg (applicable to patients of all ages with uncomplicated hypertension).

LoE:IIb[41]

MONITORING

At every visit:

- » Weight
- » Blood pressure

Baseline:

- » Serum creatinine concentration (and eGFR) – see Section 8.1: Chronic Kidney Disease (CKD)
- » Urine protein by dipstix to screen for secondary causes of hypertension.
  - In patients with diabetes see Section 9.2: Type 2 diabetes mellitus.
- » BMI for cardiovascular risk assessment (See Section 4.1: Prevention of ischaemic heart disease and atherosclerosis).
- » Abdominal circumference.
- » Serum potassium concentration, if on ACE-inhibitor or eGFR < 30 mL/min. (See Section 9.2.2: Type 2 Diabetes Mellitus, Adults).

Six monthly:

- » Serum potassium concentration in patients on spironolactone or eGFR < 30 mL/min.

Annually:

- » Finger prick blood glucose (see Section 9.2.2: Type 2 Diabetes Mellitus, Adults).
- » Urine protein by dipstix (see Section 8.1: Chronic Kidney Disease (CKD)).
- » Serum creatinine concentration (and eGFR) in patients who have:
  - proteinuria 1+ or more,
  - existing cardiovascular disease,
  - hypertension present for 10 years or more
  - if uncontrolled hypertension,
  - chronic kidney disease (eGFR < 60 mL/min).

GENERAL MEASURES

Screen all patients for cardiovascular disease risk factors (see Section 4.1: Prevention of ischaemic heart disease and atherosclerosis) and prescribe a statin if required.

Screen for presence of compelling indications (see table below) and manage patients accordingly.

Lifestyle modification

All people with hypertension should be encouraged to make the following lifestyle changes as appropriate.

- » Smoking cessation.
- » Maintain ideal weight, i.e. BMI 18 to 25 kg/m^2. Weight reduction in the overweight patient. *LoE:IIIb*[42]
- » Salt restriction with increased potassium intake from fresh fruits and vegetables (e.g. remove salt from the table, gradually reduce added salt in food preparation and avoid processed foods). Dietician's advice recommended.
- » Reduce alcohol intake to no more than 2 standard drinks per day for males and 1 for females.
- » Follow a healthy eating plan i.e. low fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables. Dietician's advice recommended.
- » Regular moderate aerobic exercise, e.g. 30 minutes brisk walking at least 5-7 times a week. *LoE:IIIb*[43]

MEDICINE TREATMENT

Initial medicine choices are dependent on the presence or absence of compelling indications for specific medicines. See Table 4.5: Treatment of hypertension with compelling indications, for a list of compelling indications and recommendations for specific medicines.

In the absence of compelling indications, see Table 4.4: Stepwise approach of treating hypertension without compelling indications.

Advise patient to take medication regularly, including on the day of the clinic visit, but a single missed dose does not account for severe elevations in BP.

Note:

- » Check adherence to antihypertensive therapy by doing pill counts and questioning family members.
- » The use of fixed dose combination medication for control of hypertension results in greater adherence and such agents should be used when they are available. *LoE:IIIb*[44]
- » The prescribing of antihypertensive medication should be guided by the time of day that is most convenient for patients and that would optimize adherence and minimize side effects for individual patients
- » Monitor patients monthly and adjust therapy if necessary, until the BP is stable.
- » Check adherence to medication before escalating therapy.
- » After target BP is achieved, patients may be seen at 3–6 monthly intervals.

Mild hypertension

When there are no cardiovascular risk factors, initiate lifestyle modification measures (Step 1). If there is poor response to lifestyle modification measures after 3 months, initiate medicine therapy (Step 2).

If mild hypertension with the presence of risk factors (see Section 4.1: Prevention of ischaemic heart disease and atherosclerosis), initiate medicine therapy as well as lifestyle modification (Step 2).

Moderate hypertension
Confirm diagnosis within 2 weeks. Initiate treatment after confirmation of diagnosis (medicine and lifestyle modification) at Step 2.

Severe hypertension
Confirm diagnosis within 1 hour.
In patients who are not symptomatic, initiate treatment (medicine and lifestyle modification) at Step 3.
Patients with symptoms of progressive target organ damage or associated clinical conditions: See hypertensive urgency, below and Section 4.7.2: Hypertensive emergency.

Special cases

Pregnancy-induced hypertension
See Section 6.4.2: Hypertensive disorders of pregnancy.

Asymptomatic severe hypertension
- » These patients have severe hypertension, are asymptomatic and have no evidence of progressive target organ damage.
- » Observe the patient in the health care setting and repeat BP measurement after the patient has rested for 1 hour.
- » If the second measurement is still elevated at the same level, start oral treatment with 2 agents (Step 3), one of which should be low dose hydrochlorothiazide and the second medicine is usually a calcium channel blocker, e.g. amlodipine.
- » Patient should be followed up within a week.
- » Refer to doctor if BP >160/100 mmHg after 4 weeks.

Hypertensive urgency
- » Most have a systolic BP > 180 mmHg and/or diastolic BP > 110 mmHg.
- » Patients are symptomatic, usually with severe headache, shortness of breath and oedema, but there are no immediate life threatening neurological or cardiac complications such as are seen in hypertensive emergencies (see Section 4.7.2: Hypertensive emergency).
- » Start treatment with 2 oral agents (Step 3) with the aim to lower diastolic BP to 100 mmHg slowly, over 48–72 hours.
- » Amlodipine and furosemide or hydrochlorothiazide should be used, if there is renal insufficiency or evidence of pulmonary congestion (See Section 4.6.1: Cardiac failure, congestive (CCF), adults).
- » All patients with hypertensive urgency should be referred to a hospital.

Stroke
BP is often elevated in acute stroke. Do not treat elevated BP at PHC, but refer patient urgently.

Elderly
In patients without co-existing disease, initiate medicine treatment only when the BP > 160/90 mmHg.

CAUTION
Lower BP over a few days. A sudden decrease in BP can be dangerous, especially in the elderly.

RISK ASSESSMENT OF HYPERTENSIVE PATIENTS

» Cardiovascular risk should be assessed in all hypertensive patients based on BP levels, additional risk factors, hypertension-mediated organ damage (HMOD), and previous disease, before starting treatment. Refer to the simplified classification of hypertension risk, below.

» **Other risk factors** include: Age (>65 years), sex (male>female), heart rate (>80 beats/min), increased body weight, diabetes, high LDL-C/triglyceride, family history of CVD, family history of hypertension, early-onset menopause, smoking habits, psychosocial or socioeconomic factors.

» **HMOD** includes: LVH (LVH on ECG), moderate-severe CKD (eGFR <60 mL/min/1.73m^2), any other available measure of organ damage.

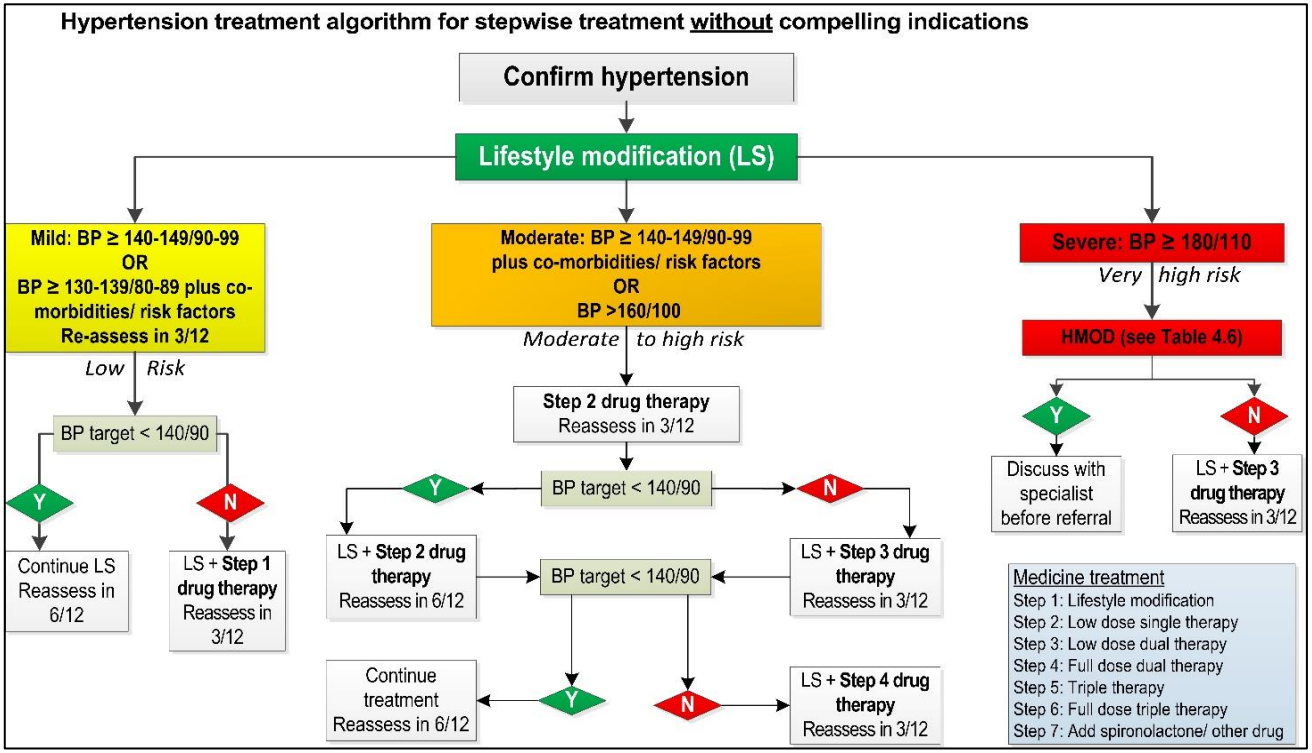
» **Previous disease includes:** previous coronary heart disease (CHD), CCF, stroke, peripheral vascular disease, atrial fibrillation, CKD stage 3+.

LoE:IIIb[45]

Other risk factors, HMOD, or disease	BP (mmHg) grading			
	High normal SBP 130-139 DBP 85-89	Mild SCP 140-159 DBP 90-99	Moderate SBP 160-179 DBP 100-109	Severe SBP≥180 Or DBP ≥110
No other risk factors	Low risk	Low risk	Moderate risk	High risk
1 or 2 risk factors	Low risk	Moderate risk	Moderate to High risk	High risk
≥ 3 risk factors	Low to Moderate risk	Moderate to High risk	High risk	High risk
HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to High risk	High risk	High risk	High to very high risk
Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Figure 4.1: Simplified classification of hypertension risk

Source: Williams B, et al. Authors/Task Force Members:. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension.. J Hypertens. 2018 Oct;36(10):1953-2041.



***Caution**: Consider monotherapy in low-risk grade 1 hypertension and patients > 80 years or the frail (monitor for postural hypotension).*

Figure 4.2: Algorithm for the stepwise approach of treating hypertension without compelling indications

LoE:IIIb[46]

STEPWISE TREATMENT WITHOUT COMPELLING INDICATIONS

STEP 1: Lifestyle modification.

Entry to Step 1	Treatment	Target
» Diastolic BP 90–99 mmHg and/or systolic BP 140–159 mmHg without any existing disease. **AND** » No major risk factors.	» Lifestyle modification.	» BP control within 3 months to < 140/90 mmHg

STEP 2: Add hydrochlorothiazide.

Entry to Step 2	Treatment	Target
» Diastolic BP 90–99 mmHg and systolic BP 140–159 mmHg without any existing disease. **AND** » No major risk factors. **AND** » Failure of lifestyle modification alone to reduce BP after 3 months. **OR** » Mild hypertension with major risk factors or existing disease. **OR** » Moderate hypertension at diagnosis.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily. *LoE:IIIb*[47]	» BP control within 1 month to < 140/90 mmHg

STEP 3: Add a second antihypertensive medicine.

Entry to Step 3	Treatment	Target
» Failure to achieve targets in Step 2 after 1 month despite adherence to therapy. **OR** » Severe hypertension (See table).	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily. **ADD** ▪ Long-acting calcium channel blocker, e.g.: • Amlodipine, oral, 5 mg once daily. **OR** ▪ ACE-inhibitor. e.g.: • Enalapril, oral, 10 mg once daily. *LoE:IVb*[48]	» BP control within 1 month to < 140/90 mmHg

STEP 4: Increase the dose of the second antihypertensive medicine.

Entry to Step 4	Treatment	Target
» Failure of step 3 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily. **AND** Increase dose of antihypertensive started in Step 3:	» BP control within 1month to < 140/90 mmHg, with no adverse reactions.

	▪ Long-acting calcium channel blocker, e.g.: • Amlodipine, oral, increase to 10 mg once daily. **OR** ▪ ACE-inhibitor, e.g.: • Enalapril, oral, increase to 20 mg once daily.	

STEP 5: Add a third antihypertensive medicine

Entry to Step 5	Treatment	Target
» Failure of step 4 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily. **AND** ▪ ACE-inhibitor, e.g.: • Enalapril, oral: continue Step 4 dose, or if not started previously start at 10 mg once daily. **AND** ▪ Long-acting calcium channel blocker, e.g.: • Amlodipine, oral: continue Step 4 dose, or if not started previously start at 5 mg once daily.	» BP control within 1 month to < 140/90 mmHg with no adverse medicine reactions.

STEP 6: Increase the dose of the third antihypertensive medicine

Entry to Step 6	Treatment	Target
» Failure of step 5 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily **AND** ▪ ACE-inhibitor, e.g.: • Enalapril, oral, 20 mg once daily. **AND** ▪ Long-acting calcium channel blocker, e.g.: • Amlodipine, oral, 10 mg once daily.	» BP control within 1 month to < 140/90 mmHg with no adverse medicine reactions.

STEP 7: Increase the dose of HCTZ and add a fourth antihypertensive medicine

Entry to Step 7	Treatment	Target
» Failure of step 7 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 25 mg daily. **AND** ▪ ACE-inhibitor, e.g.: • Enalapril, 20 mg once daily **AND** ▪ Long-acting calcium channel blocker, e.g.: • Amlodipine, oral 10 mg once daily. **AND ADD** *LoE:Ia*[49] • Spironolactone, oral, 25 mg daily (Doctor initiated).	» BP control within 1 month to < 140/90 mmHg, with no adverse medicine reactions.

Table 4.4: Stepwise approach of treating hypertension without compelling indications

CAUTION

Spironolactone can cause severe hyperkalaemia and should only be used when serum potassium and renal function can be monitored. Check potassium levels within one month of starting therapy and thereafter, as per clinical need. Routine monitoring of potassium levels is essential if spironolactone is used with an ACE-inhibitor, other potassium sparing agents or in the elderly.

Do not use together with potassium supplements.

Avoid NSAIDs with spironolactone use.

Do not use in kidney failure (Do not use if eGFR < 30 mL/min).

If not controlled on step 7– refer. *LoE:IVb*[50]

Note:

» If lifestyle modification failed to achieve BP control: Counsel patient on the risk of major cardiovascular events associated with elevated BP; and initiate monotherapy.

» If BP control is suboptimal: Up titrate treatment (maximise dose of current antihypertensive and/or add additional medicine). Evidence suggests that treatment inertia contributes to suboptimal BP control with patients remaining on monotherapy and/or suboptimal doses. *LoE:IIIb*[51]

» Initiate combination medicine therapy in cases of severe hypertension and hypertension urgency (see Section 4.7.2: Hypertensive emergency).

TREATMENT OF HYPERTENSION WITH COMPELLING INDICATIONS

Compelling indications for specific medicines	Medicine therapeutic class
Angina	• Beta-blocker **OR** • Long-acting calcium channel blocker
Prior myocardial infarction	• Beta-blocker **AND** • ACE-inhibitor
Heart failure	• ACE-inhibitor **AND** • Carvedilol, oral **OR** • Spironolactone, oral For significant volume overload: • Loop diuretic
Left ventricular hypertrophy(confirmed by ECG)	• ACE-inhibitor
Stroke: secondary prevention	• Hydrochlorothiazide, oral **AND** • ACE-inhibitor
Diabetes type 1 and 2 with/without evidence of microalbuminuria/proteinuria	• ACE-inhibitor, usually in combination with diuretic
Chronic kidney disease	• ACE-inhibitor, usually in combination with diuretic
Isolated systolic hypertension	• Hydrochlorothiazide, oral **OR** • Long-acting calcium channel blocker
Pregnancy	• Methyldopa, oral

Table 4.5: Treatment of hypertension with compelling indications

Contraindications to individual medicines

Hydrochlorothiazide

- » gout, *LoE:IIIb*[52]
- » pregnancy,
- » severe liver impairment,
- » kidney impairment (eGFR < 30 mL/min),
- » use with caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

Calcium channel blockers

- » untreated heart failure.

Spironolactone

- » kidney impairment (eGFR < 30 mL/min), *LoE:IVb*[53]
- » pregnancy.

ACE-inhibitors

- » pregnancy,
- » bilateral renal artery stenosis or stenosis of an artery to a dominant/single kidney,
- » aortic valve stenosis,
- » history of angioedema,

» hyperkalaemia,
» severe renal impairment (eGFR < 30 mL/min), unless dose-adjusted usage is recommended by a specialist – See Section 8.1:Chronic kidney disease (CKD). *LoE:IVb*[54]

CAUTION
Advise all patients receiving ACE-inhibitors about the symptoms of ACE-induced angioedema.

REFERRAL
» Young adults (< 30 years of age).
» BP not controlled by 4 medicines and where there is no doctor available.
» Pregnancy.
» Signs of hypertension-mediated organ damage e.g. oedema, dyspnoea, proteinuria, angina etc.
» If severe adverse drug reactions develop.
» Hypertensive urgency and hypertensive emergency.
» Severe renal impairment (eGFR < 30 mL/min).

4.7.2 HYPERTENSIVE EMERGENCY
I10

DESCRIPTION
A markedly elevated BP: systolic BP > 180 mmHg and/or a diastolic BP > 130 mmHg **associated with** one or more of the following:
» unstable angina/chest pain,
» neurological signs, e.g. severe headache, visual disturbances, confusion, coma or seizures,
» pulmonary oedema,
» renal failure.

MEDICINE TREATMENT
- Amlodipine, oral, 10 mg immediately as a single dose.

<u>If pulmonary oedema:</u>
- Furosemide, IV, 40 mg as a single dose (See Section 21.2.8: Pulmonary oedema, acute).

CAUTION
A hypertensive emergency is life threatening and needs immediate referral to hospital.

REFERRAL
Urgent
All patients.

4.7.3 HYPERTENSION IN CHILDREN

I10

DESCRIPTION

Hypertension is defined as systolic and/or diastolic blood pressure ≥ the 95th percentile for gender, age, and height percentile on at least 3 consecutive occasions. Refer to table below.

The use of appropriate cuff size is important. Too small a cuff for the arm leads to false high BP. The cuff bladder must encircle at least 80% of the upper arm and should cover at least 75% of the distance between the acromion and the olecranon. It is better to use a cuff that is slightly too large than one that is too small. Large cuffs, if covered with linen-like material, can be folded to the appropriate size in smaller infants as long as the bladder encompasses the arm.

Infants and preschool-aged children are almost never diagnosed with essential hypertension and are most likely to have secondary forms of hypertension.

With age, the prevalence of essential hypertension increases, and after 10 years of age, it becomes the leading cause of elevated BP. Obesity currently is emerging as a common comorbidity of essential hypertension in paediatric patients, often manifesting during early childhood.

DIAGNOSIS

Age years	**95th BP percentiles for boys** mmHg	**95th BP percentiles for girls** mmHg
1	103/56	104/58
3	109/65	107/67
5	112/72	110/72
6	114/74	111/74
8	116/78	115/76
9	118/79	117/77
10	119/80	119/78
11	121/80	121/79
12	123/81	123/80

Table 4.6: Diagnosis of high blood pressure in children and adolescents

Adapted from U.S Department of Health and Human Services National Institutes of Health (National Heart, Lung, and Blood Institute): The 4th report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, May 2005 (using the 50th height percentile).

REFERRAL

All cases with BP above the 95th percentile.

4.8 PULMONARY OEDEMA, ACUTE

See Section 21.2.8: Pulmonary oedema, acute.

4.9 RHEUMATIC FEVER, ACUTE

I00/I01.0-2/I01.8-9

Note: notifiable condition.

DESCRIPTION

A condition in which the body develops antibodies against its own tissues, following a streptococcal throat infection. Effective treatment and prevention of recurrent of streptococcal pharyngitis can markedly reduce the occurrence and repeat episodes of rheumatic carditis.

Commonly occurs in children, 3–15 years of age.

Recurrences are frequent.

Clinical signs and symptoms include:

- » arthralgia or arthritis that may shift from one joint to another,
- » carditis, including cardiac failure,
- » heart murmurs,
- » subcutaneous nodules,
- » erythema marginatum,
- » chorea (involuntary movements of limbs or face),
- » other complaints indicating a systemic illness e.g. fever.

MEDICINE TREATMENT

Eradication of streptococci in throat:

Children: 18 months–11 years of age

- Phenoxymethylpenicillin, oral, 250 mg 12 hourly for 10 days.

Children > 11 years of age and adults

- Phenoxymethylpenicillin, oral, 500 mg 12 hourly for 10 days.

OR

Children

- Amoxicillin, oral, 50 mg/kg daily for 10 days.

Weight kg	Dose mg	Use one of the following				Age Months/years
		Susp		Capsule		
		125 mg/5mL	250 mg/5mL	250 mg	500 mg	
>2–2.5 kg	100 mg	4 mL	2 mL	–	–	>34–36 weeks
>2.5–3.5 kg	150 mg	6 mL	3 mL	–	–	>36 weeks–1 month
>3.5–5 kg	200 mg	8 mL	4 mL	–	–	>1–3 months
>5–7 kg	275 mg	11 mL	5.5 mL	–	–	>3–6 months
>7–11 kg	400 mg	–	8 mL	–	–	>6–18 months
>11–17.5 kg	575 mg	–	11.5 mL	–	–	>18 months–5 years
>17.5–25 kg	750 mg	–	15 mL	3	–	>5–7 years
>25–35 kg	1000 mg	–	20 mL	4	2	>7–11 years
>35 kg	2000 mg	–	–		4	>11years

LoE:IIb[55]

Adults

- Benzathine benzylpenicillin, IM, single dose.
  - Children < 30 kg: 600 000 IU.

- Children ≥ 30 kg and adults: 1.2 MU.
- Dissolve benzathine benzylpenicillin 1.2 MU in 3.2 mL lidocaine 1% without adrenaline (epinephrine) or 3 mL water for injection.

LoE:IIIb[56]

OR

- Amoxicillin, oral, 1 000 mg 12 hourly for 10 days.

LoE:IIb[57]

Severe penicillin allergy:
Z88.0

Children
- Macrolide, e.g.:
- Azithromycin, oral, 10 mg/kg daily for 3 days. See Section 23: Paediatric dosing tables.

Children > 35 kg and adults
- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days.

Prophylaxis for rheumatic fever: (Z29.2)

All patients with confirmed rheumatic fever and no persistent rheumatic valvular disease
» Treat for 10 years or until the age of 21 years, whichever is longer.

All patients with confirmed rheumatic fever and persistent rheumatic valvular disease
» Treat lifelong.

- Phenoxymethylpenicillin, oral, 12 hourly.
  - Children: 125 mg
  - Adults: 250 mg

OR

- Amoxicillin, oral, daily.
  - Children <30 kg: 125 mg
  - Children ≥30 kg and adults: 250 mg

LoE:IVb

OR

- Benzathine benzylpenicillin, IM, every 21–28 days (3–4 weeks).
  - Children < 30 kg: 600 000 IU
  - Children ≥ 30 kg and adults: 1.2 MU
  - For benzathine benzylpenicillin, IM injection, dissolve benzathine benzylpenicillin 1.2 MU in 3.2 mL lidocaine 1% without adrenaline (epinephrine) or 3 mL water for injection.

CAUTION
Avoid IM injections if patients are on warfarin.

Note: For guidance on warfarin management, see Adult Hospital Level STGs and EML, Appendix II.

Severe penicillin allergy:
Z88.0

Children < 11 years

LoE:IVb[58]

- Macrolide, e.g.:

- Azithromycin, oral, 10mg/kg/day, 3 times weekly. See Section 23: Paediatric dosing tables.

Children ≥ 11 years and adults

- Macrolide, e.g.:
- Azithromycin, oral, 250 mg daily. *LoE:IVb*[59]

REFERRAL

All patients for diagnosis and management.

4.10 VALVULAR HEART DISEASE AND CONGENITAL STRUCTURAL HEART DISEASE

I05.0-2/I05.8-9/I06.0-2/I06.8-9/I07.0-2/I07.8-9/I08.0-3/I08.8-9/I34.0-2/I34.8-9/I35.0-2/I35.8-9/I36.0-2/I36.8-9/I37.0-2/I37.8-9/Q22.0-6/Q22.8-9/Q23.0-4/Q23.8-9

DESCRIPTION

Damage to heart valves or chamber, or vessel wall anomalies caused by rheumatic fever or other causes, e.g. congenital heart defects, degenerative disease and ischaemic heart disease.

May be complicated by:

- » heart failure
- » infective endocarditis
- » pulmonary hypertension
- » atrial fibrillation
- » systemic embolism

GENERAL MEASURES

- » Advise all patients with a heart murmur regarding the need for prophylactic treatment prior to undergoing certain medical and dental procedures.
- » Advise patients to inform health care providers of the presence of the heart murmur when reporting for medical or dental treatment.

MEDICINE TREATMENT

Prophylactic antibiotic treatment for infective endocarditis:

- » Should be given prior to certain invasive diagnostic and therapeutic procedures e.g. tooth extraction, to prevent infective endocarditis.
- » Is essential for all children with congenital or rheumatic heart lesions needing dental extraction.

Dental extraction, if no anaesthetic is required:

Z29.2

- Amoxicillin, oral, 50 mg/kg (maximum dose: 2 g), 1 hour before the procedure.
  - Repeat dose 6 hours later.

Age	Dose
< 5 years	750 mg
5–10 years	1 500 mg
≥ 10 years	2 g

Severe penicillin allergy:

Z88.0

Refer.

If anaesthetic is required:
Refer.

Prophylaxis for rheumatic fever:
See Section 4.9: Rheumatic fever, acute.

REFERRAL

- » All patients with pathological heart murmurs for assessment.
- » All patients with heart murmurs not on a chronic management plan.
- » Development of cardiac signs and symptoms.
- » Worsening of clinical signs and symptoms of heart disease.
- » Any newly developing medical condition, e.g. persistent fever.
- » All patients with valvular heart disease for advice on prophylactic antibiotic treatment prior to any invasive diagnostic or therapeutic procedure.

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[59] Azithromycin, oral: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML, draft. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
PHC CHAPTER 4: CARDIOVASCULAR CONDITIONS
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

A: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
4.1 Ischaemic heart disease and atherosclerosis, prevention	Aspirin, oral	Not added
	Target BMI	Amended
	SCORE risk score	Not added
	BMI-based risk score	Replaced – added to Appendix III
	Framingham risk score	Retained – moved to Appendix III
	Treat-to-target approach	Not added
	Familial hypercholesterolemia management	Not added (referred to tertiary level)
	General measures- alcohol intake	Editorial amendment
- statin therapy	Simvastatin	Retained
	HMGCoA reductase inhibitors (statins)	Retained
- secondary prophylaxis	Statin therapy e.g., of therapeutic class	Amended
4.2 Angina pectoris, stable	Statin therapy	Aligned with section 4.1
	Isosorbide dinitrate -frequency of dosing	Retained
	Isosorbide dinitrate –dosing guidance	Editorial amendment
4.3 Angina pectoris, unstable / Non ST elevation myocardial infarction (NSTEMI) *and* **4.4 Myocardial infarction, acute (AMI)/ ST elevation myocardial infarction (STEMI)**	Aspirin	Dose not amended
	Oxygen	Caution added
	Oxygen requirements- effects of altitude	Not amended
	Streptokinase, parenteral	Directions for use not amended
	Cardio-selective beta-blocker	Therapeutic class retained
	Atenolol	Retained as example of class in STG
	Bisoprolol	Retained in therapeutic interchange database
	Statin therapy	Aligned with section 4.1
4.4 Myocardial infarction, acute (AMI)/ ST elevation myocardial infarction (STEMI)	Aspirin, oral	Loading dose not amended
	Statin therapy	Aligned with section 4.1
	Thrombolytic therapy – considerations for initiating thrombolytics	Guidance clarified
4.6.1 Cardiac failure, congestive (CCF), adults	Salt restriction	Retained
- Mild CCF (normal renal function)	Hydrochlorothiazide, oral	Retained
- STEP 2: After titration of ACE-inhibitor	Carvedilol, oral	Dosing amended
	Spironolactone	Caution box amended
4.7 Hypertension	Classification of hypertension	Not amended
	Target blood pressure	Not amended
	Urine dipstix screen	Amended
	Target BMI	Amended
	Prescribing of antihypertensive medication – timing of doses:	Amended
	Enalapril – once versus twice daily dosing	Retained
	General guidance on prescribing medicines	Editorial amendments

	Indapamide, oral	Not added (included in therapeutic interchange database)
	Hydrochlorothiazide, oral	Retained in the STG as example of therapeutic class
	Dual therapy	Directions for use not amended
	Amiloride, oral	Not added
	Hypertension algorithm	Amended
4.9 Rheumatic fever acute	Benzathine benzylpenicillin, IM	Retained
	Amoxicillin, oral dose	Retained
	Warfarin, oral	Cross-referenced to Adult Hospital Level STGs and EML
APPENDIX III: Cardiovascular risk assessment		New Appendix added

4.1 PREVENTION OF ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS

Aspirin, oral: *not added for primary prevention of ischaemic heart disease*

Refer to the evidence summary below on the use of aspirin for primary cardiovascular disease prevention[1]. A copy of the complete review may be found at the end of this document, or alternatively on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
	X				

Recommendation: The PHC/Adult Hospital Level Committee does not recommend the use of aspirin as primary prevention of IHD.

Rationale: Systematic review of RCTs (n = 164 225) found that the use of aspirin for primary cardiovascular disease prevention did not decrease all-cause cardiovascular mortality. Aspirin use decreased risk of cardiovascular events but increased major bleeding risk.

Level of Evidence: High certainty evidence

Review indicator: Long-term follow-up data of efficacy with lower harms

NEMLC RECOMMENDATION (24 FEBRUARY 2022):

- *Enteric-coated aspirin*: Query was raised if there would be a difference in bleeding if the enteric coated formulation was used. However, it was noted that a historic review by NEMLC had found that there was no difference with associated gastro-intestinal bleeds, despite the dosage formulation that is used[1]. Furthermore, absorption of enteric coated aspirin and effectiveness were not comparable to non-enteric coated aspirin[2].
- *Outcomes:* The balance between the composite outcomes versus risk associated with aspirin favoured that aspirin not be used for primary prevention (including amongst diabetics, or patients at low or high risk). However, more importantly no mortality benefit was seen with aspirin.

Recommendation: NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter.

Monitoring and evaluation considerations

Target BMI: *amended*

External comment received that target BMI should be amended to "18 to 25 kg/m^2" aligned with observational data[2] that informed the National Heart, Lung, and Blood Institute (NHLBI) guidelines[3].

Level of Evidence: Low certainty evidence

SCORE risk score: *not added*

BMI-based risk score: *replaced*

Reference to the online BMI-based risk calculator has been removed from the STG as the online tool is not functional via mobile phone application and therefore not pragmatic as not easily accessible for use at the PHC level of care. An alternative non-laboratory based tool has been included in the newly created Appendix III: Cardiovascular risk assessment, which has been adapted with permission from the Knowledge Translation Unit and authors of the 2023

[1] NDoH evidence review. Aspirin for primary cardiovascular disease prevention_11 February 2022_final

[2] McGee DL; Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol. 2005 Feb;15(2):87-97. https://pubmed.ncbi.nlm.nih.gov/15652713/

[3] National Heart, Lung, and Blood Institute in cooperation with The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, September 1998. Report No.: 98-4083. https://www.ncbi.nlm.nih.gov/books/NBK2003/

Adult Primary Care guideline. This paper-based tool is an adaptation of the WHO paper-based risk calculator for cardiovascular disease management in primary care[4]. While NEMLC acknowledged the limitations of the WHO based tool, the Committee recommended that the paper-based tool be included for CV risk assessment as an interim replacement, until a tool that is more suitable for the local population is available. A summary of the NEMLC deliberations pertaining to the inclusion of the WHO BMI-based risk tool is tabulated below:

Key limitations of the WHO risk charts[5] as acknowledged by the authors, include:

- Risk prediction models were derived from 85 cohorts which were primarily from high-income countries. Data from the GBD study[6] and the NCD-RisC[7], was used to inform the recalibration undertaken. These sources frequently do not have country-specific disease risk estimates as such data is often lacking.
- Data used for the external validation process may not be nationally representative i.e. epidemiology of CVD may not be representative of the population of interest.
- For primary prevention, the risk models may overestimate CVD risk as incidences from global regions may have included recurrent events.
- Underestimation of CVD risk is also possible as the underlying population data may have included patients already on preventative therapies.
- For the non-lab based risk charts, there is a significant underestimation of CVD risk in diabetic patients, as these charts do not accommodate for the greater CVD risk in this patient cohort.

Additional local considerations:

- The underestimation of risk in diabetic patients is not regarded as a significant concern as at PHC level of care, the tool will be used for a few diabetics under the age of 40 years with disease duration of less than 10 years. One suggestion, if the tool is included, would be to note that the BMI based tool should not be used for diabetics that do not qualify for statins automatically. At PHC level of care , the following patients are regarded as high risk and qualify for statin therapy:
  - Type 2 diabetes with age > 40 years.
  - Diabetes for > 10 years.
  - Diabetes with chronic kidney disease (eGFR < 60 mL/min).
- The WHO based risk charts have been included in the 2023 Adult Primary Care tool which is available at all PHC clinics.
- Local lab based costs (23/24 NHLS) [excludes cost of follow up visit for review of lab results, if we are solely reliant on Framingham]
  - All chronic patients have a baseline random cholesterol done, so those with TC above 7.5 can be referred to exclude familial hypercholesterolemia. This would not normally be repeated and costs R53.98.
  - HDL measurement needed for lab-based Framingham = R69.63.
  - Normally the risk assessment would be done at diagnosis and then 5-yearly if <20%.

Framingham risk score: *retained*

The SCORE chart included in the European Society of Cardiology Guideline is primarily for a European population. The Framingham Risk model[8] is used globally, and endorsed by the South African Lipid Guidelines.[9] This tool has been transferred to the newly created Appendix III: Cardiovascular risk assessment which may be accessed at the end of this document or alternatively on the NHI webpage.

Treat-to-target approach: *not added*

The PHC/Adult Hospital Level Committee proposed that a full costing analysis be done comparing the fire-and-forget vs treat-to-target approach for the primary and secondary prevention of ischaemic events. Commissioning of this economic analysis will be deferred when budget/funding is available.

Familial hypercholesterolemia management: *not added (referred to tertiary level)*

External comment received that management for familial hypercholesterolemia was omitted from the PHC and Adult Hospital Level STGs and EML. However, referral criteria include "random cholesterol >7.5mmol/L" and "triglycerides >10 mmol/L", as management occurs in lipid clinics generally accessible at tertiary level of care.

[4] Adopted with permission from the Knowledge Translation Unit and authors of the Adult Primary Care guideline (2023). This tool is based on the WHO cardiovascular disease non-laboratory-based Southern Sub-Saharan Africa. From: HEARTS technical package for cardiovascular disease management in primary healthcare risk based CVD management. World Health Organisation, Geneva, 2020.

[5] World Health Organisation. Hearts technical package for cardiovascular disease management in primary healthcare. Risk based CVD management. 2019 Update

[6] GBD Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1345–422.

[7] NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017

[8] D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.

[9] Klug E, Raal FJ, Marais AD, Smuts CM, Schamroth C, Jankelow D, et al. South African dyslipidaemia guideline consensus statement: 2018 update A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). SAfr Med J.

General measures – alcohol intake: *Editorial amendment*

Guidance on reducing alcohol intake has been aligned to the AH Chp 3 CV Section 3.6 Hypertension as tabulated below:

AMENDED FROM:

» Reduce alcohol intake to ≤ 2 standard drinks/day for men and ≤ 1 for women on no more than 5 out of 7 days per week (1 standard drink is equivalent to 25 mL of spirits, 125 mL of wine, 340 mL of beer or sorghum beer, or 60 mL of sherry).

AMENDED TO:

» Reduce alcohol intake to no more than 2 standard drinks per day for males and 1 for females. (1 standard drink = a can of beer = a glass of wine = a shot of spirits).

Statin therapy

Simvastatin: *retained*

HMGCoA reductase inhibitors (statins): *retained*

External comment was received that simvastatin high-dose is no longer appropriate as secondary prophylaxis. However, HMGCoA reductase inhibitors (statins) are recommended as a therapeutic class, ensuring accessibility of therapeutic equivalents. Inclusion in Provincial formularies will be determined by the budget impact of specific statins and whether the choice is affordable. Additionally, the STGs provide guidance if a patient experiences myalgia associated with high-dose statins.

Secondary prophylaxis

Statin therapy example of class: *amended*

The example of class of high-dose statin therapy as secondary prophylaxis was amended from "simvastatin 40 mg" to "rosuvastatin 10 mg", aligned with contract circular HP09-2021SD and the therapeutic interchange database that lists both agents as high-dose statin therapy, supported by Naci *et al.*[10] and the previous 2018 economic analysis.[11]

4.2 ANGINA PECTORIS, STABLE

Statin therapy: *aligned with section 4.1*

Aligned with section 4.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

Isosorbide dinitrate- frequency of dosing: *Retained*

Isosorbide dinitrate-dosing guidance: *Editorial amendment*

The dose of oral isosorbide dinitrate has been retained as 20-30mg twice daily rather than 10-20mg 6-8 hourly as included in the SAMF[12]. More frequent dosing of organic nitrates will not support the dose-free interval required to avoid tolerance associated with organic nitrates. Editorial amendments to the text have been made for improved clarity, as tabulated below:

AMENDED FROM:

Step 3

ADD

- Isosorbide mononitrate, oral, 10–20 mg twice daily.

OR

- Isosorbide dinitrate, oral, 20–30 mg twice daily.
  - Taken at 8:00 and 14:00 hours for both medicines in order to provide a nitrate free period to prevent tolerance.
  - Modify for night shift workers.

AMENDED TO:

Step 3

ADD

- Isosorbide mononitrate, oral, 10–20 mg twice daily.

OR

- Isosorbide dinitrate, oral, 20–30 mg twice daily.
  - Take either medicine at 8:00 and 14:00 in order to provide a nitrate-free period to prevent tolerance.
  - Modify for night shift workers.

[10] Naci H et al. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. Eur J Prev Cardiol. 2013 Aug;20(4):658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[11] Statins for Secondary Prevent Of CVD events cost-effectiveness analysis, 31 January 2018

[12] South African Medicines Formulary (SAMF). 15th Ed

4.3 ANGINA PECTORIS, UNSTABLE / NON ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI) *and* 4.4 MYOCARDIAL INFARCTION, ACUTE (AMI)/ ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

Aspirin: *dose not amended*

External motivation received that guidelines recommend a loading dose of aspirin, 300 mg, with specific reference to the 2020 ESC Guidelines.[13] However, the PHC/Adult Hospital Committee recommend that the loading dose of aspirin not be amended, erring on the side of caution and noting that the STG guidance provided, is in a non-PCI environment:

NEMLC REPORT FOR THE CARDIOVASCULAR CHAPTER (31 MARCH 2022): *Evidence from CURE RCT that suggested that dose-dependent increase in bleeding in patients receiving aspirin plus placebo[14]. (Incidence of major bleeding for aspirin dose groups ≤ 100 mg; 100-200mg and > 200 mg was 1.9%, 2.8% and 3.7% respectively, p=0.0001). Meta-analysis[15] that showed that aspirin at a daily dose of 75–325 mg reduced cardiovascular morbidity and mortality by 33% in patients with coronary artery disease.* ***Level of Evidence: I Meta-analysis, RCT, Expert opinion***
NEMLC MEETING OF 26 SEPTEMBER 2019: *Further deliberations were made by NEMLC at the meeting of 26 September 2019, noting that the current tender price of "100 mg" is more expensive than the "150 mg"[16].* ***Recommendation:** Aspirin be recommended as a daily dose of 150 mg throughout the STGs, until such time that there is price parity. Doses of 100 mg and 81 mg to be added to the Adult Hospital Level Therapeutic Interchange database.*

Oxygen: *Caution added*

The PHC/Adult Hospital Level Committee recommends conservative administration of oxygen therapy amongst the acutely ill. The SPO_2 levels as included in the STG, are informed by the available evidence. Refer to the evidence summary on the use of oxygen therapy for ST elevated myocardial infarction (STEMI)[17] included below. For a copy of the complete review, refer to the end of this report or alternatively, the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			
Recommendation: Based on this review, the PHC/Adult Hospital Level Committee recommends that the current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic. *Rationale:* Evidence suggests that acutely ill patients randomised to liberal oxygen therapy were more likely to die, without improving other patient outcomes. For pragmatic purposes the current recommendation of <94% be retained. **Level of Evidence: Moderate certainty evidence** **Review indicator: New evidence that will change the recommendation**					
NEMLC RECOMMENDATION (22 FEBRUARY 2022): • NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter. • The PHC/Adult Hospital Level ERC review the evidence of the impact of altitude on oxygen requirements, whilst the draft documents are circulated for external comment.					
Monitoring and evaluation considerations					
Research priorities					

[13] Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Rev Esp Cardiol (Engl Ed). 2021;74:544.

[14] Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. 2003 Oct 7;108(14):1682-7. https://www.ncbi.nlm.nih.gov/pubmed/14504182

[15] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86. Erratum in: BMJ 2002 Jan 19;324(7330):141. https://www.ncbi.nlm.nih.gov/pubmed/11786451

[16] Tender price – contract circular RT289-2019: Aspirin 100 mg single tablet = R 0.502; Weighted average price of aspirin 300 mg tablet = R0.211 [Accessed 8 October 2019]

[17] NDoH evidence review. Oxygen for ST elevated myocardial infarction_22 Feb 2022_final

Oxygen requirements - effect of altitude: *Not amended*

A brief review of the literature was undertaken to assess the impact of altitude on oxygen requirements, specifically with references to the need for local, province-specific guidance. No formal guidelines or documented RCTs were identified from a preliminary literature search, to support consideration of a differential approach to oxygen supplementation based on geography/altitude e.g. altitude at sea level (KZN province) versus land locked areas (e.g. Gauteng province). Guidance for initiating oxygen therapy is generally based on oxygen saturation levels in patients and no guidance could be identified to suggest that different thresholds are applicable based on geography and the likely impact of any differences in altitude. The Committee noted[18] that historical training at some medical schools made reference to a publication that looked at the oxygen dissociation curve at different altitudes. This was noted to be an old physiological study that has not translated into any meaningful clinical decision-making on patient management.

Amendments to the STG guidance are tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

Oxygen 40% via facemask, if saturation < 94% or if in distress.

AMENDED TO:

MEDICINE TREATMENT

Oxygen 40% via facemask, if saturation < 94% or if in distress.

CAUTION

Do not administer oxygen to acutely ill patients who are not hypoxic (SPO_2 ≥ 96%)

Streptokinase, parenteral: *directions for use not amended*

External comment received to amend the cut-off for the window period of administering streptokinase from "6 hours, followed by specialist consultation for an additional 6 hours" to "12 hours" routinely irrespective of prescriber level, and to "consult specialist beyond 12 hours, as there may be additional benefit. This was addressed in the previous review cycle - see NEMLC report of the 2019 Adult Hospital Level STGs and EML review below:

NEMLC REPORT FOR THE CARDIOVASCULAR CHAPTER (2017-2019 REVIEW):

Thrombolytic window: Comments to revise the thrombolytic time window to <12 hours were received, including a comment through the Western Cape (WC) Pharmaceutical and Therapeutics Committee (PTC).

Risk vs benefit and cost-benefit: In the previous review cycle (2012-2015), STEMI was recommended to be treated with lytic agents for up to 6 hours. There is available evidence for efficacy beyond 6 hours; however, the cost-benefit becomes rapidly unfavourable because of the small effect size. NEMLC had requested further information (in particular how cost-effectiveness and affordability were considered) from the WC PTC in order to determine if the STGs and EML needs amending to ensure consistent and equitable access to healthcare across Provinces. However, no further information was forthcoming.

Pragmatic implications: NEMLC was of the opinion that cases that present beyond 6 hours of the onset of STEMI requires specialist consultation for further guidance.

Rationale: Available evidence shows that the greatest benefit occurs in the first 1-2 hours, and the NNT starts to plateau before 6 hours (i.e. fibrinolytics are less effective when administered later). Despite there being evidence for efficacy beyond 6 hours, the cost-benefit becomes rapidly unfavourable because of the small effect size (with risk of haemorrhage consistent from 1 to 12 hours)[19]. However, where STEMI cases present beyond 6 hours of the onset of STEMI, specialist should be consulted for further management.

Level of Evidence: I RCTs[20], Expert opinion

It is proposed that the thrombotic window period be retained as is, noting the pragmatic implication that a 6-hour cut-off would prompt interaction with a specialist or cardiologist.

Cardio-selective beta-blocker: *therapeutic class retained*

Atenolol, oral: *retained in the STG as example of therapeutic class*

Bisoprolol, oral: *not added to the STG, but listed in the therapeutic interchange database*

[18] NDoH confidential records. PHC-AH ERC minutes 16 Mar 2023

[19] Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet. 1996 Sep 21;348(9030):771-5. http://www.ncbi.nlm.nih.gov/pubmed/8813982

[20] Squire IB, Lawley W, Fletcher S, Holme E, Hillis WS, Hewitt C, Woods KL. Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. Eur Heart J. 1999 Sep;20(17):1245-52. http://www.ncbi.nlm.nih.gov/pubmed/10454976

External comment received that there is no current evidence to suggest that any one of the beta-blockers hold a mortality benefit over another, and that a cardiac-specific beta-blocker (such as bisoprolol) should be available across the public sector in all provinces. As a key principle of the STGs and EML, though, is to ensure that the most affordable agent within a therapeutic class is recommended in the STG, atenolol has been retained for stable angina. Bisoprolol is listed in the therapeutic interchange database.

Statin therapy: *aligned with section 4.1*
Aligned with section 4.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

4.4 MYOCARDIAL INFARCTION, ACUTE (AMI)/ ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

Aspirin, oral: *loading dose not amended*
Dose retained as 150mg and not amended to 300 mg, as management is not in the setting of PCI service. STEMI guidelines[21] state 150 - 300mg, noting that dosage is dependent on the clinician's assessment of bleeding vs thrombotic balance. Guidance in this emergency acute STEMI setting is not specifically for cardiologists, but all clinicians (including primary care nurse prescribers at primary level of care).

Statin therapy: *aligned with section 4.1*
Aligned with section 4.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

Thrombolytic therapy – considerations for initiating thrombolytics: *Guidance clarified*
Guidance on the initiation of thrombolytics for acute MI with ST elevation or left bundle branch block has been editorially amended as detailed below:

AMENDED FROM:

Indications	Contra-indications
» For acute myocardial infarction with ST elevation or left bundle branch block: – maximal chest pain is ≤ 6 hours beyond 6 hours and chest pain, consult a specialist – > 6 hours and no chest pain, manage with anticoagulants (see section 4.3: NSTEMI) – if on-going ischaemic pain	» Absolute: – streptokinase used within the last year, – previous allergy, – CVA within the last 3 months, – history of recent major trauma, – bleeding within the last month, – aneurysms, – brain or spinal surgery or head injury within the preceding month, or recent (< 3 weeks) major surgery, – active bleeding or known bleeding disorder, – aortic dissection. » Relative (consult specialist): – refractory hypertension, – warfarin therapy, – recent retinal laser treatment, – subclavian central venous catheter, – pregnancy, – TIA in the preceding 6 months, – traumatic resuscitation.

Table 4.3: Streptokinase therapy
Note: Refer all suspected or diagnosed cases urgently.

AMENDED TO:

Considerations for initiating thrombolytics	Contra-indications
» For acute myocardial infarction with ST elevation or left bundle branch block: – maximal chest pain is ≤ 6 hours doctor to initiate treatment. – If beyond 6 hours and chest pain, consult a specialist – > 6 hours and no chest pain, thrombolytic not indicated. Manage as above and refer patient.	» Absolute: – streptokinase used within the last year, – previous allergy, – CVA within the last 3 months, – history of recent major trauma, – bleeding within the last month, – aneurysms, – brain or spinal surgery or head injury within the preceding month, or recent (< 3 weeks) major surgery, – active bleeding or known bleeding disorder, – aortic dissection.

[21] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2017;39(2):119-77.

	» Relative (consult specialist): – refractory hypertension, – warfarin therapy, – recent retinal laser treatment, – subclavian central venous catheter, – pregnancy, – TIA in the preceding 6 months, – traumatic resuscitation.

Table 4.3: Streptokinase therapy
Note: Refer all suspected or diagnosed cases urgently.

4.6.1 CARDIAC FAILURE, CONGESTIVE (CCF), ADULTS

General measures

Salt restriction: *retained*

External comment received to omit salt restriction in CCF. However, hypertension is the likely cause of CCF in South Africa, and 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure,[22] recommends salt restriction. The Guidelines were AGREE 2 -assessed by two reviewers to be of moderately good quality (overall score of 75%).

Level of Evidence: Guidelines

Mild CCF (normal renal function)

Hydrochlorothiazide, oral: *retained*

External comment received to remove hydrochlorothiazide as *"thiazide has no role except in synergy in diuretic resistance. Its loop diuretics as first line for all patients with congestion - just dosing and fluid restriction that needs determination as per physician discretion"*, citing the 2021 ESC CCF guidelines.[23] However, the setting in the STG is mild CCF and hydrochlorothiazide is provided as an option in the 2021 ESC CCF guidelines.

Level of Evidence: Guidelines

STEP 2 and STEP 3

Carvedilol, oral: *dosing amended*

Dosing for the elderly was added, aligned with the 2021 ESC CCF guidelines as follows:

AMENDED FROM:

- Carvedilol, oral (Doctor initiated).
  - Starting dose: 3.125 mg twice daily.
  - Increase dose at two-weekly intervals by doubling the daily dose until a maximum of 25 mg twice daily, if tolerated.
  - If not tolerated, i.e. worsening of cardiac failure manifestations, reduce the dose to the previously tolerated dose.
  - Up-titration can take several months.
  - Should treatment be discontinued for > 14 days, reinstate therapy as above.
  - Absolute contraindications include: (Refer to package insert)
    - cardiogenic shock, bradycardia, various forms of heart block
    - severe fluid overload
    - hypotension
    - asthma

AMENDED TO:

- Carvedilol, oral (Doctor initiated).
  - Starting dose: 3.125 mg twice daily.
  - Increase dose at two-weekly intervals by doubling the daily dose until a maximum of 25 mg twice daily, if tolerated.
  - If >85 kg and target heart rate has not been achieved, titrate to a maximum of 50 mg twice daily, if tolerated.
  - If not tolerated, i.e., worsening of cardiac failure manifestations, reduce the dose to the previously tolerated dose.
  - Up-titration may take several months.
  - Should treatment be discontinued for > 14 days, reinstate therapy as above.
  - Absolute contraindications include: (Refer to package insert)
    - cardiogenic shock, bradycardia, various forms of heart block
    - severe fluid overload
    - hypotension
    - asthma

Level of Evidence: Guidelines

[22] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. https://pubmed.ncbi.nlm.nih.gov/34447992/

[23] McDonagh TA, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Oct 14;: PMID: 34447992.

Spironolactone: *caution box amended*
Caution box was updated to guide on avoiding NSAIDs with spironolactone use, aligned with SAMF.[24]
Level of Evidence: Guidelines

4.7.1 HYPERTENSION IN ADULTS

Classification of hypertension: *not amended*
External comment received to update definitions and categories of hypertension. However, the EML definitions for hypertension is aligned with the SA Hypertension Society recommendations. [25]

Target blood pressure: *not amended*
External comment received to amend the target BP from "< 140/90 mmHg" to "≤ 130/80mmHg", as aligned with 2020 ISH Guidelines.[26] However, the ISH Guidelines recommend the lower BP target only for patients with evidence of organ damage, not isolated HPT without compelling indications.
Level of Evidence: Guidelines

Refer to the summary document for blood pressure targets in adults (July 2018)[27] on the NHI webpage or Knowledge Hub. A summary of the previous NEMLC recommendation is included below:

NEMLC REPORT FOR THE ADULT HOSPITAL LEVEL STGS AND EML REVIEW (2017-2019):
BP target of <140/90 mm Hg: not amended to <130/80 mmHg

***Recommendation:** Adoption of the new BP target of < 130/80 mmHg, as recommended by the ACC/AHA Guidelines (2017) is not recommended.*
Rationale: There is conflicting evidence in the literature with regards the benefit of BP control below the current standard.
There is also uncertainty as to which group of people benefit with lower blood pressures and evidence of possible harm. The patient cohorts in the RCTs may not be generalisable to the South African population, and the sub group analysis of SPRINT showed hetrogeneity in outcomes between groups.
The SPRINT trial protocol for measuring BP tried to reduce all external causes of a falsely elevated BP, unless BP is measured this way people with reactive elevated BP's would be inappropriately treated.
An additional factor that was considered was the affordability of intensive antihypertensive treatment, both to the health system and patients.
Level of Evidence: I Systematic reviews, RCT[28] [29] [30] [31] [32] [33], Expert Opinion

Monitoring
Urine dipstix screen: *Amended*
Guidance on urine dipstix screen has been amended i.e. serum creatinine and eGFR monitoring has been removed as these are included in the baseline screening for all patients. Amendments as tabulated below:

AMENDED FROM:

Baseline:
- Serum creatinine concentration (and eGFR) – see Section 8.1: Chronic Kidney Disease (CKD)
- Urine protein by dipstix to screen for secondary causes of hypertension.

[24] SAMF, 2022
[25] Cardiovascular Journal of Africa: Vol 30 No 3 (May/June 2019) (cvja.co.za)
[26] 2020 International Society of Hypertension Global hypertension Practice guidelines. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026Hypertension. 2020;75:1334–1357
[27] NDoH review. Blood pressure targets-adults_Summary_July2018_v4.0
[28] The SPRINT Research Group, A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103-16. https://www.ncbi.nlm.nih.gov/pubmed/26551272
[29] Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-967. https://www.ncbi.nlm.nih.gov/pubmed/26724178
[30] Brunström M, Carlberg B. Standardization according to blood pressure lowering in meta-analyses of antihypertensive trials: comparison of three methodological approaches. J Hypertens. 2018 Jan;36(1):4-15.https://www.ncbi.nlm.nih.gov/pubmed/28990987
[31] Filipovský J, Seidlerová J, Kratochvíl Z,K arnosová P, Hronová M, Mayer O Jr. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood Press.* 2016;25(4):228-234. https://www.ncbi.nlm.nih.gov/pubmed/26852625
[32] Brunstrom M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels A Systematic Review and Meta-analysis JAMA Intern Med. 2018;178(1):28-36. https://www.ncbi.nlm.nih.gov/pubmed/29131895
[33] Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387(10017):435-443. https://www.ncbi.nlm.nih.gov/pubmed/26559744

- If dipstix positive send blood for serum creatinine concentration (and eGFR) (See Section 8.2: Acute kidney injury).
- In patients with diabetes see Section 9.2: Type 2 diabetes mellitus.

AMENDED TO:

Baseline:

» Serum creatinine concentration (and eGFR) – see Section 8.1: Chronic Kidney Disease (CKD)

» Urine protein by dipstix to screen for secondary causes of hypertension.

- In patients with diabetes see Section 9.2: Type 2 diabetes mellitus.

General measures

Target BMI: *amended*

External comment received that target BMI should be amended to "18 to 25 kg/m^2" aligned with observational data[34] that informed the National Heart, Lung, and Blood Institute (NHLBI) guidelines[35].

Level of Evidence: Low certainty evidence

Medicine treatment

Prescribing of antihypertensive medication – timing of doses: *Amended*

In response to an external query on the nighttime dosing of antihypertensive medication, a brief review of the literature was undertaken which is included below along with the NEMLC recommendation. Reference to nighttime dosing of antihypertensive medication has been amended throughout the chapter in accordance with the NEMLC recommendation stated below:

Daytime versus night-time dosing

A Pubmed search on the 9th January 2024, identified 3 recently published SR on the effect of night–time dosing of antihypertensive medication.

Maqsood MH et al. Timing of Antihypertensive Drug Therapy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. 2023[36]

This SR involved a time limited search until 26 August 2022 and included 72 RCTs that compared the effect of morning versus evening dosing of antihypertensive medication on changes in ambulatory BP parameters (24/48-hour, night-time and day-time ambulatory systolic BP (SBP) and diastolic BP (DBP) and clinical outcomes (6 RCTs were evaluated for clinical outcomes and patients were followed up for a mean of 4.8 years). A subgroup analysis was also conducted based on Hermida versus non-Hermida et al due to the extensive data derived from a single centre supporting night time dosing which has met with some controversy in the literature.

Outcomes reported:

	Total	Hermida data	Non-Hermida data	Outcomes reported
BP parameters				
No. of RCTs	69	23	46	24/48 hour ambulatory BP Evening dosing led to greater reduction in 24/48-hour ambulatory SBP (MD=1.41 mmHg [95% CI, 0.48–2.34], I 2=82%; 53 trials) compared with morning dosing. Subgroup analysis based on Hermida versus non-Hermida trials (Pheterogeneity=0.01) showed significant BP lowering effect with evening dosing only in the trials by Hermida et al (MD=2.30 mmHg [95% CI, 0.90–3.70]; I 2=92%) but not in the non-Hermida trials (MD=0.16 mmHg [95% CI, −0.56 to 0.87], I2=0% Evening dosing led to greater reduction in 24/48-hour ambulatory DBP (MD=0.60 mmHg [95% CI, 0.12–1.08], I2=57%%; 54 trials) compared with morning dosing. Subgroup analysis of Hermida versus non-Hermida trials (Pheterogeneity=0.01) showed significant BP
No. of patients	29 265	25 734	3531	
No. of studies favouring PM dosing for 24/48 hr SBP*	11/53	10/21	1/32	

[34] McGee DL; Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol. 2005 Feb;15(2):87-97. https://pubmed.ncbi.nlm.nih.gov/15652713/

[35] National Heart, Lung, and Blood Institute in cooperation with The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, September 1998. Report No.: 98-4083. https://www.ncbi.nlm.nih.gov/books/NBK2003/

[36] Maqsood MH et al. Timing of Antihypertensive Drug Therapy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Hypertension. 2023 Jul;80(7):1544-1554. doi: 10.1161/HYPERTENSIONAHA.122.20862. Epub 2023 May 22. PMID: 37212152.

				lowering effect with evening dosing only in the trials by Hermida et al (MD=0.97 mmHg [95% CI, 0.30 to 1.64], I2=77%) but not in the non-Hermida trials. Night-time ambulatory BP Evening dosing led to greater reduction in night-time SBP (MD=4.09 mmHg [95% CI, 3.01–5.16], I2=86%; 65 trials) compared with morning dosing. Subgroup analysis showed no significant heterogeneity of treatment effect based on Hermida versus non-Hermida trials (Pheterogeneity=0.35) but the reduction in night-time SBP with evening dosing was smaller in the non-Hermida trials. Day-time ambulatory BP Evening dosing of antihypertensive drugs led to greater reduction in day-time SBP compared with morning dosing but the magnitude was small (MD=0.94 mmHg [95% CI, 0.01–1.87]; I2=81%; 66 trials.
Clinical outcomes				
No. of RCTs	6	3	3	Risk of MACE (OR=0.68 [95% CI, 0.46–1.01]; I2=96%; P=0.06; 6 trials; Figure 4A), cardiovascular mortality (OR=0.47 [95% CI, 0.21–1.04]; I2=92%; P=0.06; 4 trials; Figure 4B), all-cause mortality (OR=0.64 [95% CI, 0.37–1.08], I2=93%; P=0.10; 5 trials; Figure 4C), and heart failure (OR=0.54 [95% CI, 0.28–1.02], I2=91%; P=0.06; 4 trials; Figure 4D) were numerically lower with evening compared with morning dosing, and reached statistical significance in a sensitivity analysis, which excluded trials with different evening and morning antihypertensive drug doses. Subgroup analysis based on Hermida versus non-Hermida trials (P<0.001) showed significantly lower MACE, cardiovascular mortality, all-cause mortality, and heart failure with Hermida trials only with no significant difference in outcomes with non-Hermida trials.
No. of patients	59 976	22 016	37960	
No. of studies favouring PM dosing for MACE*	3	3	0	
*Taken from forest plot if null value is not within the 95% CI of mean value				

The review authors conclude that while dosing of antihypertensive drugs significantly reduced ambulatory BP parameters and lowered cardiovascular events, this effect was mainly driven by trials involving the Hermida group. The authors further conclude that antihypertensive drugs should be taken at a time of the day that is convenient and optimizes adherence and minmises undesirable effects, unless there is a specific intention to lower night-time BP.

Stergiou G et al. Bedtime dosing of antihypertensive medications: systematic review and consensus statement: International Society of Hypertension position paper endorsed by World Hypertension League and European Society of Hypertension. 2022[37]
Abstract ONLY available
*ABSTRACT: This Position Paper by the International Society of Hypertension reviewed the published evidence on the clinical relevance of the diurnal variation in BP and the timing of antihypertensive drug treatment, aiming to provide consensus recommendations for clinical practice. Eight published outcome hypertension studies involved bedtime dosing of antihypertensive drugs, and all had major methodological and/or other flaws and a high risk of bias in testing the impact of bedtime compared to morning treatment. Three ongoing, well designed, prospective, randomized controlled outcome trials (*The TIME study in UK and the BedMed and BedMedFrail in Canada)* are expected to provide high-quality data on the efficacy and safety of evening or bedtime versus morning drug dosing. Until that information is available, preferred use of bedtime drug dosing of antihypertensive drugs should not be routinely recommended in clinical practice. Complete 24-h control of BP should be targeted using readily available, long-acting antihypertensive medications as monotherapy or combinations administered in a single morning dose.*
**The TIME study was published in 2022 and has been included in the SR by Maqsood MH et al (detailed above). The BedMed due to be completed at the end of 2023 and BedMedFrail mid-2023 are yet to be published.*

Ho CLB et al. The effect of taking blood pressure lowering medication at night on cardiovascular disease risk. A systematic review. 2021[38]
Authors of this SR investigated the effect of taking antihypertensive treatment at night versus conventional morning treatment on the relative risk of major cardiovascular disease and all-cause mortality. Two RCTs (MAPEC [n=2156] and Hygia [n=19084] trials)

[37] Stergiou G, Brunström M, MacDonald T, Kyriakoulis KG, Bursztyn M, Khan N, Bakris G, Kollias A, Menti A, Muntner P, Orias M, Poulter N, Shimbo D, Williams B, Adeoye AM, Damasceno A, Korostovtseva L, Li Y, Muxfeldt E, Zhang Y, Mancia G, Kreutz R, Tomaszewski M. Bedtime dosing of antihypertensive medications: systematic review and consensus statement: International Society of Hypertension position paper endorsed by World Hypertension League and European Society of Hypertension. J Hypertens. 2022 Oct 1;40(10):1847-1858. doi: 10.1097/HJH.0000000000003240. Epub 2022 Aug 12. PMID: 35983870.
[38] Ho CLB, Chowdhury EK, Doust J, Nelson MR, Reid CM. The effect of taking blood pressure lowering medication at night on cardiovascular disease risk. A systematic review. J Hum Hypertens. 2021 Apr;35(4):308-314. doi: 10.1038/s41371-020-00469-1. Epub 2021 Jan 18. PMID: 33462391.

were identified for inclusion in their review. According to the review authors, both studies reported a reduction of ~50% in major CVD events and all-cause mortality with nighttime dosing and a reduction of 60% in CVD mortality, however they cautioned against interpretation of these results in view of ongoing discussion on the validity of the MAPEC and Hygia trials. Note that both MAPEC and Hygia trials were conducted by the Hermida group and as they have been included in the more recent SR by Maqsood MH et al (detailed above), we have not included a detailed analysis of the results of this SR.

NEMLC recommendation (March 2024):
Day-time versus night-time dosing of antihypertensive medication
NEMLC recommends that the STGs on hypertension in the PHC and AH CV chapters be amended from night time dosing to once daily dosing. The timing of the dose should be guided by the time of day that is most convenient for patients and that would optimize adherence and minimize side effects for individual patients.

Enalapril – once versus twice daily: R*etained*

In response to an external query on the recommendation for once versus twice daily administration of enalapril for the management of hypertension, a brief search of the literature was undertaken (details as tabulated below). Guidance on the dosing frequency of enalapril as a once daily dose has been retained based on review of the evidence.

Enalapril - once versus twice daily dosing for hypertension
Once daily versus twice daily administration of enalapril for the management of hypertension was previously reviewed by the ERC during the 2017-2019 review cycle. A Pubmed search was undertaken to assess for any recent publications. One publication by Fischer and Diec, published in 2021 was identified as detailed below.

Fischer K, Diec S. Once- Versus Twice-Daily Angiotensin-Converting Enzyme Inhibitors for Blood Pressure Control in Adult Patients With Hypertension. 2021[39]
This review involved a literature search from Jan 1980 to June 2020 to assess the efficacy and safety of once versus twice daily administration of ACE Inhibitors. Six studies were identified as relevant to the review, of which only one was specific to enalapril, a randomized single-blind cross over study involving 25 patients[40] (*this study was considered by NEMLC during the 2017-2019 review cycle*). Based on the overall review of the six included studies, the reviewers concluded that twice-daily dosing of ACE inhibitors (Lisinopril, enalapril, trandolapril, perindopril, captopril and ramipril) may be as effective as once daily dosing which they acknowledge as supported by weak evidence. The risks of poorer adherence would need to be balanced against any potential for added blood pressure lowering with a twice daily regimen. The authors acknowledge that current guidelines do not provide any recommendation for twice daily administration over once daily administration.

NEMLC recommendation (March 2024)
Dosing frequency of enalapril for the management of hypertension
NEMLC recommends that the previous recommendation be retained i.e.:

Enalapril, oral: dosing not amended
In clinical practice, enalapril is dosed as 12 hourly. Available evidence found better compliance with once daily dosing, but no significant difference in blood pressure[41, 42](but could not find evidence of superiority of the 12 hourly vs daily dosing of enalapril. Furthermore, enalapril 5 mg 12 hourly is more expensive than enalapril 10 mg daily (R6.00 vs R4.38, respectively for a 30 day treatment course[43]). ***Level of evidence: III Observational studies (low quality), Expert opinion***

General guidance on prescribing of medicines: *Editorial amendments*

Editorial amendments to the general prescribing guidance were made as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT
Initial medicine choices are dependent on the presence or absence of compelling indications for specific medicines.
Medicine treatment without compelling indications (see table below: Stepwise treatment without compelling indications, for a list of compelling indications and recommendations for specific medicines).

Advise patient to take medication regularly, including on the day of the clinic visit, but a single missed dose does not account for severe elevations in BP.

Note:
- » Check adherence to antihypertensive therapy by doing pill counts and questioning family members.
- » The use of fixed dose combination medication for control of hypertension provides greater adherence and such agents should be used when they are available.

[39] Fischer K, Diec S (August 20, 2021) Once- Versus Twice-Daily Angiotensin-Converting Enzyme Inhibitors for Blood Pressure Control in Adult Patients With Hypertension. Cureus 13(8): e17331.
[40] Girvin, Briegeen1,2; McDermott, Barbara J.1; Johnston, G Dennis1. A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood pressure lowering and patient compliance. Journal of Hypertension 17(11):p 1627-1631, November 1999.
[41]Girvin B, McDermott BJ, Johnston GD. A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood pressure lowering and patient compliance. J Hypertens. 1999 Nov;17(11):1627-31. https://www.ncbi.nlm.nih.gov/pubmed/10608477
[42] Davies RO, Gomez HJ, Irvin JD, Walker JF. An overview of the clinical pharmacology of enalapril. Br J ClinPharmacol. 1984;18Suppl 2:215S-229S. https://www.ncbi.nlm.nih.gov/pubmed/6099737
[43] Contract circular HP09-2016SD, average weighted prices used.

- » There is emerging evidence that taking the total daily dose of antihypertensive medication at bedtime rather than on awaking provides both better control of hypertension and a significant reduction in important cardiovascular events.
- » Monitor patients monthly and adjust therapy if necessary, until the BP is stable.
- » Check adherence to medication before escalating therapy.
- » After target BP is achieved, patients may be seen at 3–6 monthly intervals.

AMENDED TO:

MEDICINE TREATMENT

Initial medicine choices are dependent on the presence or absence of compelling indications for specific medicines. See Table 4.6: Treatment of hypertension with compelling indications, for a list of compelling indications and recommendations for specific medicines. In the absence of compelling indications, see Table 4.5: Stepwise approach of treating hypertension without compelling indications.

Advise patient to take medication regularly, including on the day of the clinic visit, but a single missed dose does not account for severe elevations in BP.

Note:

- » Check adherence to antihypertensive therapy by doing pill counts and questioning family members.
- » The use of fixed dose combination medication for control of hypertension results in greater adherence and such agents should be used when they are available.
- » The prescribing of antihypertensive medication should be guided by the time of day that is most convenient for patients and that would optimize adherence and minimize side effects for individual patients
- » Monitor patients monthly and adjust therapy if necessary, until the BP is stable.
- » Check adherence to medication before escalating therapy.
- » After target BP is achieved, patients may be seen at 3–6 monthly intervals.

Indapamide, oral: *not added to the STG, but listed in the therapeutic interchange database*

Hydrochlorothiazide, oral: *retained in the STG*

Refer to the evidence summary below[44]. A copy of the complete evidence review may be found at the end of this report, or alternatively on the NHI webpage.

[44] NDoH evidence review. Indapamide versus HCTZ as first line for uncomplicated primary hypertension_18 Aug 2022_v7.1 _final

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/ADULT Hospital Level Committee suggests that indapamide not be recommended for the first-line treatment of patients with uncomplicated hypertension.

Rationale: The clinical evidence supporting the use of indapamide over HCTZ is of low quality and uncertain. In addition, indapamide is more expensive than HCTZ and would have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. Indapamide may be considered for inclusion in the therapeutic interchange database as an alternative to HCTZ.

Level of Evidence: Systematic reviews of lower quality clinical trials and/or inconsistent findings.

Review indicator: Price reduction or new evidence of clinical benefit

NEMLC RECOMMENDATION (24 FEBRUARY 2022):

DISCUSSION

- *Metabolic effects:* It was queried if there would be a place for indapamide amongst diabetics, as approximately 15% of patients on thiazides develop diabetes (evidence not provided). However, the review states that: "Metabolic effects (electrolyte abnormalities, plasma glucose, cholesterol, uric acid levels) were reported in some of the studies included in the NICE 2011 evidence review (see Appendix F), but those outcomes were not reviewed or reported on. A critically low quality systematic review and meta-analysis[a] (with a very similar scope to the NICE 2011 evidence review) assessed the metabolic outcomes reported in the studies included in the NICE 2011 evidence review and reported no significant difference between indapamide and HCTZ on metabolic outcomes.[b]
- *Comparative costing analysis:* The reference for the source of the Indapamide price was omitted, but confirmed to be 100% of SEP. It was recommended that a sensitivity analysis be done for the analysis using 60% of SINGLE EXIT PRICE (SEP).

Recommendations:

- NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence review be circulated for external comment with the PHC cardiovascular chapter.
- A sensitivity analysis of the costing analysis using 60% of SEP be conducted, whilst the draft documents are circulated for external comment.

References:

a. This review was excluded at full-text screening stage due to its low quality and the significant overlap with the NICE 2011 evidence review (which is a higher quality review). See Appendix E for more detail.

b. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects. Hypertension. 2015;65:1041–6. https://pubmed.ncbi.nlm.nih.gov/25733245/

Monitoring and evaluation considerations

No changes to monitoring and evaluation required.

Continue with patient care and follow up guidance provided in STGs (1,2). This includes periodically assessing the level of blood pressure control in primary health care and adult hospital level of care.

Research priorities

1. To determine the level of blood pressure control in South Africa with the currently adopted therapeutic strategies
2. To determine the burden and cost implications of hypertension related complications in the public health sector.
3. To determine the implementation of the stepwise treatment algorithm in clinical practice and what factors contributes to non-implementation

Details of an external motivation received pertaining to the non-addition of indapamide to the STG and the Committee's response are detailed below:

External Motivation for indapamide

Comment A: *The substitution of HCTZ with Indapamide is supported for the following reasons:*

1. Metabolic neutrality.
2. True 24 hr blood pressure lowering effect.
3. Vasodilatory effect, as well as diuresis.

Comment b: Thiazides vs. Indapamide - Several articles written by eminent hypertension scholars question the role of HCTZ as first line treatment for hypertension and several major guidelines (ISH, NICE, AHA/ACC) suggest that thiazide -like diuretics (indapamide/chlorthalidone) should be preferred over HCTZ.

The arguments in favour of the preferred use of thiazide-like diuretics:[45] [46]

1. *HCTZ 12.50-25mg daily has less antihypertensive activity particularly compared to chlortalidone at similar dose. In particular night-time BP was lowered by chlothalidone to a greater degree strongly (7mmHg) suggesting a shorter duration of action.*
2. *Low dose HCTZ (12.5 – 25mg) data has no data showing in hard outcomes events in major studies. In contrast chlortalidone (ALLHAT, SHEP) and indapamide (HYVET, ADVANCE, PROGRESS) have shown strong outcome data*
3. *The ACCOMPLISH trial which was a direct comparison between ACEi/amlodipine vs ACEi/HCTZ showed superior CV outcome data*
4. *HCTZ is less well tolerated*

[45] Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: facts, fads, fiction, and follies. Am J Med. 2011 Oct;124(10):896-9.

[46] Kaplan NM. The choice of thiazide diuretics: why chlorthalidone may replace hydrochlorothiazide. Hypertension. 2009 Nov;54(5):951-

The argument against made by Spence et al is:[47]

1. *In a study conducted by them HCTZ showed equal BP lowering to indapamide had equal BP lowering with the same metabolic effects – increased uric acid, decreased potassium and increased triglycerides*
2. *Given the significant lower costs they suggested that HCTZ should be preferred to indapamide. However, there were baseline differences in BP favouring HCTZ in this trial.*

Commentator's expert opinion:

1. *All major guidelines recommend combination therapy with ACE-/ARB with CCB (amlodipine) as first line therapy and the argument related to monotherapy with HCTZ or indapamide are moot.*
2. *Both HCTZ and indapamide increase BP lowering in combination with other antihypertensives*
3. *HCTZ and thiazide-like diuretics are now 3rd line therapy and there are no trials addressing issues of BP efficacy and prevention of CV events*
4. *In the Creole study*[48] *performed in people of African descent Amlodipine/HCTZ was equally effective in lowering BP as amlodipine/ACEi including night-time BP. ACEi/HCTZ was less effective than the other arms. Question – would ACEi/indapamide have been more effective?*
5. *On the other hand, HCTZ is associated with skin cancer*[49] *and perhaps renal cell carcinoma*[50] *the former perhaps being less of an issue in our predominately African population*
6. *In my experience HCTZ causes more allergic reactions and indapamide could be a substitute*
7. *Undoubtedly indapamide has better outcome data than HCTZ in current doses.*

Recommendations:

- *If cost is not an issue on balance thiazide-like diuretics are the preferred option.*
- *However, the elephant in the room is the lack of single pill combinations especially triple combination in the public sector.*

Response from the PHC/Adult Hospital Level Committee to the external motivation

PHC/Adult Hospital Level Committee response to the external motivation for indapamide

Hydrochlorothiazide (HCTZ) is the first line (monotherapy) pharmacological treatment for uncomplicated hypertension recommended in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa. In the past HCTZ has been used successfully in the South African clinical landscape with minimal adverse metabolic effects in the majority of uncomplicated hypertensive patients.

When compared to indapamide, HCTZ is suggested to have limited efficacy. However, much of the available published data is suboptimal and does not compare these two agents on a head-to-head design with hard clinical outcomes. The current positions taken by some clinical guidelines to prefer thiazide-like diuretics over thiazide diuretics is largely based on the presumed improved BP lowering effect and favourable side effect profile, rather than on comparative efficacy. While other studies have investigated comparative efficacy of HCTZ and chlorthalidone, these have not been considered as chlorthalidone is not available in South Africa.

Due to the inconclusive evidence the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines do not state preference for either conventional thiazide or thiazide-like diuretics – instead these guidelines recommend two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada 2020 and the International Society of Hypertension guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.

Current evidence supporting the use of indapamide over HCTZ is of low quality with uncertain impact on important clinical outcomes. In addition, indapamide is almost four times more expensive than HCTZ and a large South African patient population would be eligible to receive the treatment each year. Including indapamide as a first-line treatment option will therefore have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. The Expert Review Committee therefore does not support the introduction of indapamide as a first line agent. Furthermore, with increasing awareness of the benefits of upfront combination therapy in appropriately risk stratified hypertensives, the case for changing first line monotherapy is now less compelling.

[47] Spence JD, Huff M, Barnett PA. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000 Spring;7(1):32-7.

[48] Ojji DB, Mayosi B, Francis V, Badri M, Cornelius V, Smythe W, et al.; CREOLE Study Investigators. Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans. N Engl J Med. 2019 Jun 20;380(25):2429-2439.
Ingabire PM, Ojji DB, Rayner B, Ogola E, Damasceno A, Jones E, Dzudie A, et al; CREOLE Study Investigators. High prevalence of non-dipping patterns among Black Africans with uncontrolled hypertension: a secondary analysis of the CREOLE trial. BMC Cardiovasc Disord. 2021 May 22;21(1):254.

[49] Garrido PM, Borges-Costa J. Hydrochlorothiazide treatment and risk of non-melanoma skin cancer: Review of the literature. Rev Port Cardiol (Engl Ed). 2020 Mar;39(3):163-170. English, Portuguese.

[50] Hiatt RA, Tolan K, Quesenberry CP Jr. Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA). Cancer Causes Control. 1994 Jul;5(4):319-25.

Furthermore, NEMLC had reviewed the CREOLE study previously in the context of a dual-therapy approach– see below:

NEMLC REPORT FOR THE ADULT HOSPITAL LEVEL STGS AND EML REVIEW (2017-2019):

DUAL THERAPY

Calcium channel blocker: listed as first-line option for add on therapy to HCTZ in step-up management of hypertension
ACE-inhibitor: listed as second-line option for add on therapy to HCTZ in step-up management of hypertension

Background: NDoH Non-Communicable Diseases (NCD) Directorate forwarded the NEJM article by Ojji, et al (2019), "Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans" for consideration.

Evidence review

- *NEJM article[51] was reviewed by the Adult Hospital Level Committee and following issues were raised:*
  - *Study hypothesis: Study compared three different 2-drug combinations for decreasing blood pressure amongst Black Africans. All hypertensive patients, irrespective of racial/ethnic profiling requires at least two agents to control blood pressure.*
  - *Study quality:*
    - *Underpowered study (n=728) that is probably hypothesis generating and lacks clinical inference.*
    - *Methodology for participant recruitment is unclear (from article and supplementary appendix).*
    - *The proportion of patients on "full dose" of anti-hypertensive medicines at the end of the study is unclear.*
    - *There are conflicting statistics regarding the number of participants who completed the study (107 vs 77).*
    - *Surrogate endpoint of lowered BP of 3 mmHg is not clinically meaningful.*
  - *Risk of bias: Study was industry funded, single-blinded (investigators were not aware of trial-group assignments) and study drug concealment was not adequate.*
- *Meta-analysis by Ettehad et al[52] showed that lowering BP by 10 mmHg resulted in a 20% risk of major cardiovascular events. Furthermore, the findings showed some significant differences among various drug classes in reducing the risk of specific clinical outcomes: diuretics more effective for heart failure whilst calcium channel blockers (CCB) are not; CCBs more effective for stroke prevention, but beta-blockers and ACE-inhibitors are not ideal. However, overall all the major drug classes had similar effects in reducing major adverse cardiovascular events (MACE) and mortality.*

Recommendations:

- *The algorithm for the step-wise treatment of hypertension without compelling indications to be retained in the STG - hydrochlorothiazide as first line therapy in the step-up treatment of hypertension without compelling indications*
- *The STG currently recommends initiation of dual therapy for moderate to severe hypertension. However, for the South African population, calcium channel blockers are preferred to ACE-inhibitors[53] – thus, calcium channel blockers to be recommended before ACE-inhibitors in the treatment protocol for hypertension.*

Rationale: There are intrinsic concerns of the study hypothesis by Ojji et al (very low quality, lack of external validity). However, the study merely confirms the current guidance in the current STG that recommends add-on therapy if non-responsive to a single agent. Meta-analysis showed that lowering BP by 10 mmHg resulted in a 20% risk of major cardiovascular events and despite various drug classes reducing specific clinical outcomes, overall all classes had similar effects in reducing MACE and mortality.
Level of Evidence: I Meta-analysis

Dual therapy: *directions for use not amended*

External motivation received that therapy should be initiated with two agents. However, the step-wise approach incorporates a risk assessment protocol to guide therapy (see amended stepwise algorithm below for managing hypertension without compelling indications).

Amiloride, oral*: not added*

External comment received to add amiloride to the EML, as an option to spironolactone was not accepted (no evidence was submitted). Consideration to be made to add amiloride to the project plan for the next review cycle (following market review of available agents.

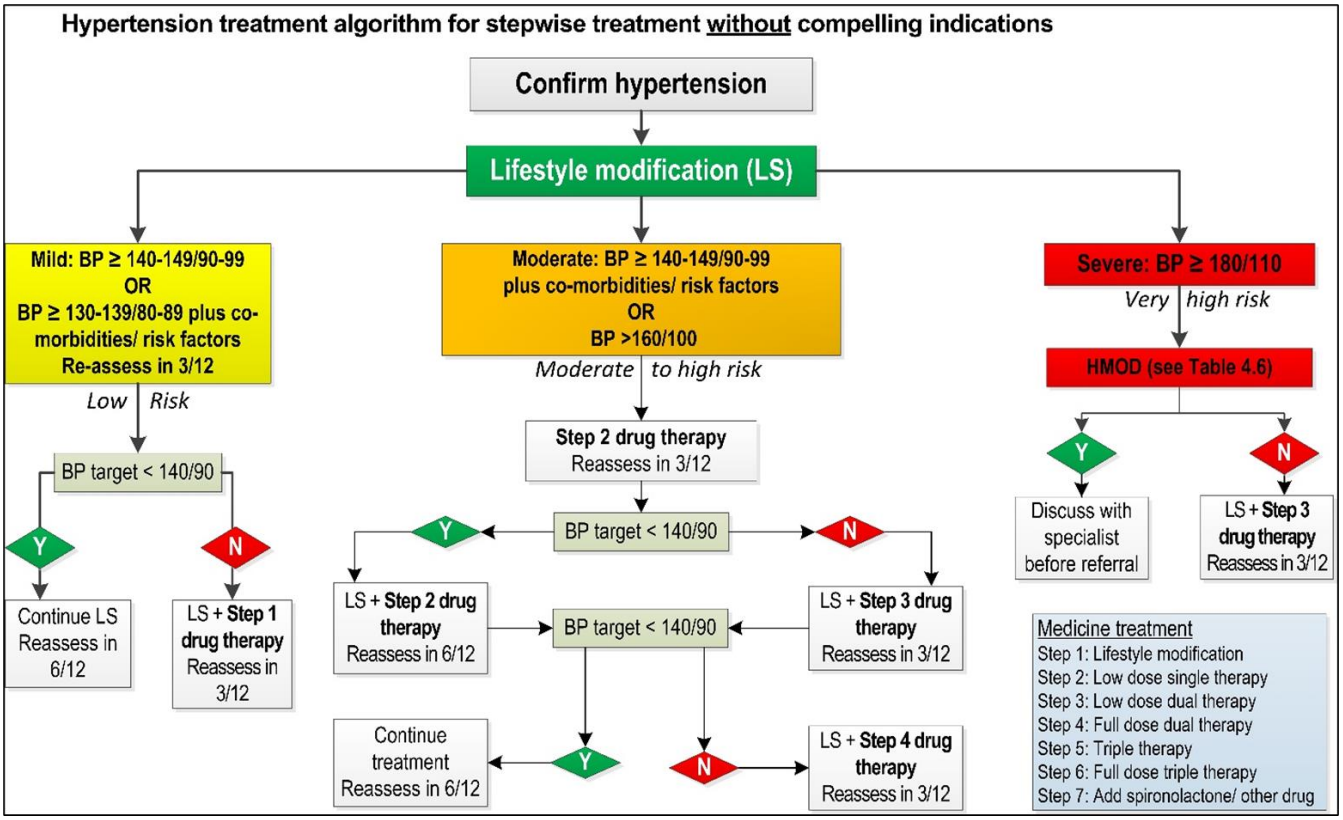
Hypertension algorithm: *amended*

The algorithm was amended for correctness, to align with the STG narrative. The updated algorithm follows:

[51] Ojji DB, Mayosi B, Francis V, Badri M, Cornelius V, Smythe W, Kramer N, Barasa F, Damasceno A, Dzudie A, Jones E, Mondo C, Ogah O, Ogola E, Sani MU, Shedul GL, Shedul G, Rayner B, Okpechi IG, Sliwa K, Poulter N; CREOLE Study Investigators. Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans. N Engl J Med. 2019 Mar 18. https://www.ncbi.nlm.nih.gov/pubmed/30883050

[52] Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016 Mar 5;387(10022):957-967. https://www.ncbi.nlm.nih.gov/pubmed/26724178

[53] Brewster LM, van Montfrans GA, Oehlers GP, Seedat YK. Systematic review: antihypertensive drug therapy in patients of African and South Asian ethnicity. Intern Emerg Med. 2016 Apr;11(3):355-74. https://www.ncbi.nlm.nih.gov/pubmed/27026378



4.9 RHEUMATIC FEVER, ACUTE

Eradication of streptococci in the throat

Benzathine benzylpenicillin, IM: *Retained*

As supply of benzathine benzylpenicillin has been restored (NDoH circular ref: 2024/30/EDP/01), benzathine benzylpenicillin, IM has been retained as the first line option for managing strep throat. Oral amoxicillin is also retained as an alternative in the event of further supply constraints.

Amoxicillin, oral dose: *Retained*

The dose of oral amoxicillin 1000mg 12 hourly for ten days has been retained in accordance with the NEMLC recommendation from a previous evidence review[54]. The maximum dose of 1 gram daily as recommended in the SAMF has therefore not been adopted.

Warfarin management

Warfarin, oral: *cross-referenced to Adult Hospital Level STGs and EML*

In response to the external comment, ""*INR <1.5 or >3.5, patient should ideally be managed by/ in consultation with a doctor*", and noting that guidance for warfarin management is not included in the PHC STGs and EML, a cross reference to the Adult Hospital Level STGs and EML, has been added:

Note: For guidance on warfarin management, see Adult Hospital Level STGs and EML, Appendix II.

APPENDIX III: CARDIOVASCULAR RISK ASSESSMENT

Appendix III – Cardiovascular risk assessment: *New chapter added to the PHC standard treatment guidelines*

Appendix III – Cardiovascular risk assessment may be accessed at the end of this report, or alternatively on the Knowledge Hub or NHI webpage. The Appendix includes both a non-laboratory BMI-based risk assessment tool as well as the cholesterol-based Framingham risk charts.

[54] NDoH evidence review. AmoxicillinVsPhenoxymethylpenicllin_Tonsolitis_Pharyngitis_Review_13Oct2016_v5.0

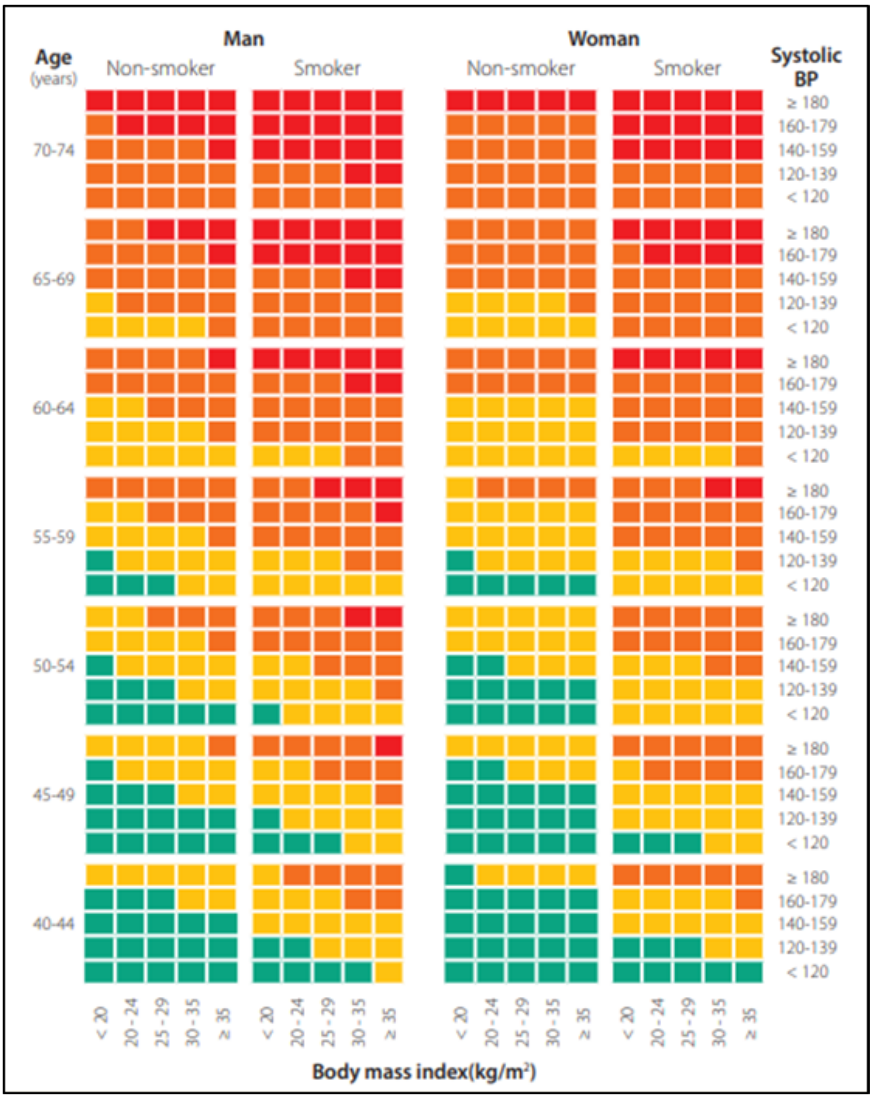
NON-LABORATORY BASED RISK SCREENING

BMI-BASED RISK ASSESSMENT

» Measure body mass index (BMI): BMI=weight (kg)/[height (m) x height (m)]
» Measure blood pressure.
» Calculate 10-year risk of a cardiovascular event using the BMI-based CVD risk tool below.
  - Use the patient's sex, age, BMI, systolic BP and smoking status to work out what colour block they fall into
  - Explain to the patient what his/her risk of heart attack or stroke might be over the next 10 years

Colour code	CVD risk
	CVD risk < 5%: there is less than a 1 in 20 chance of a heart attack or stroke over the next 10 years
	CVD risk 5-10%: there is between 1 in 10 and 1 in 20 chance of a heart attack or stroke over the next 10 years
	CVD risk 10-20%: there is between 1 in 5 and 1 in 10 chance of a heart attack or stroke over the next 10 years
	CVD risk > 20%: there is more than a 1 in 5 chance of a heart attack or stroke over the next 10 years

» Manage the risk as recommended in Section 4.1 Prevention of heart disease and atherosclerosis.



BMI-based risk assessment

Adopted with permission from the Knowledge Translation Unit and authors of the Adult Primary Care guideline (2023). This tool is based on the WHO cardiovascular disease non-laboratory-based Southern Sub-Saharan Africa. From: HEARTS technical package for cardiovascular disease management in primary healthcare risk based CVD management. World Health Organisation, Geneva, 2020.

LABORATORY BASED RISK SCREENING

FRAMINGHAM RISK SCORE (CHOLESTEROL-BASED)

» To derive the absolute risk as a percentage of patients who will have a cardiovascular event (i.e. death, myocardial infarction or stroke) over 10 years, add the points for each risk category (Section A). The risk associated with the total points is then derived from Section B.

» Calculation of CVD risk using the table:

- A risk of MI > 20% in 10 years equates to ≥ 15 points for men, and ≥ 18 points for women. It is important to score each patient individually, as there are many combinations of risk factors that can add up to those total points.
- For example:

  A male patient > 60 yrs old with systolic BP > 140 mmHg on treatment would score:
  - 11 points for his sex and age
  - 4 points for his on-treatment BP
  - Total: 15 points

  A male patient > 50 yrs old with systolic BP > 130 mmHg on treatment who is a smoker would score:
  - 8 points for his sex and age
  - 3 points for his on-treatment BP
  - 4 points for his smoking status
  - Total: 15 points

  A female patient > 70 yrs old with systolic BP > 160 mmHg on treatment would score:
  - 11 points for her sex and age
  - 7 points for her on-treatment BP
  - Total: 18 points

Calculation of risk of developing cardiovascular events over 10 years (in the absence of cardiovascular disease or genetic disorders such as familial hypercholesterolaemia)

SECTION A

Age (years)	**MEN**	**WOMEN**
30–34	0	0
35–39	2	2
40–44	5	4
45–49	6	5
50–54	8	7
55–59	10	8
60–64	11	9
65–69	12	10
70–74	14	11
75–79	15	12

Total cholesterol (mmol/L)	**MEN**	**WOMEN**
<4.1	0	0
4.1–5.19	1	1
5.2 – 6.19	2	3
6.2–7.2	3	4
>7.2	4	5

HDL cholesterol (mmol/L)	**MEN**	**WOMEN**
>1.5	–2	–2
1.3–1.49	–1	–1
1.2–1.29	0	0
0.9–1.119	1	1
<0.9	2	2

	MEN	**WOMEN**
Smoker	4	3
Diabetic*	3	4

*Type 2 diabetics > 40 years of age qualify for statin therapy irrespective of risk score.

	MEN		**WOMEN**	
Systolic BP (mmHg)	Untreated	Treated	Untreated	Treated
<120	–2	0	–3	–1
120–129	0	2	0	2
130–139	1	3	1	3
140–149	2	4	2	5
150–159	2	4	4	6
≥160	3	5	5	7

SECTION B

Total points

MEN	10-year risk %	WOMEN	10-year risk %
≤–3	<1	≤–2	<1
–2	1.1	–1	1.0
–1	1.4	0	1.2
0	1.6	1	1.5
1	1.9	2	1.7
2	2.3	3	2.0
3	2.8	4	2.4
4	3.3	5	2.8
5	3.9	6	3.3
6	4.7	7	3.9
7	5.6	8	4.5
8	6.7	9	5.3
9	7.9	10	6.3
10	9.4	11	7.3
11	11.2	12	8.6
12	13.2	13	10.0
13	15.6	14	11.7
14	18.4	15	13.7
15	21.6	16	15.9
16	25.3	17	18.5
17	29.4	18	21.5
≥18	>30	19	24.8

Framingham risk score assessment

EVIDENCE SUMMARY

Title: Evidence review of the use of aspirin for primary cardiovascular disease prevention.

Date: 11 February 2022

Reviewer: Nqoba Tsabedze, Trudy Leong

Affiliation and declaration of interests: NT (Division of Cardiology, Department of Medicine, Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand. NT has received honoraria for speaker and advisory board consulting fees relating to cardiovascular therapies from Acino Health Care Group, Boehringer – Ingelheim, Boston Scientific, Eli Lilly, Medtronic, Merck, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Phillips, Sanofi- Aventis, Servier and Takeda) and TL (National Department of Health, Essential Drugs Programme) have no interests to declare pertaining to aspirin.

Background:
Recently, several requests were received from healthcare professionals for the evidence review that informed the decision of not recommending aspirin for the primary prevention of cardiovascular disease and stroke. However, aspirin for primary prevention has historically ***not*** been included in the Standard Treatment Guidelines and Essential Medicine List since 2006.

There is a substantial body of evidence that collectively supports the use of aspirin for the secondary prevention of established cardiovascular disease.[1,2] However, current data on the role of aspirin in primary prevention of cardiovascular disease is conflicting and controversial with potential benefits limited by an increased bleeding risk. Early trials done before year 2000, evaluating aspirin for primary prevention, suggested reductions in myocardial infarction and stroke (although not mortality), and an increased risk of bleeding.[3-7] In order to balance the risks and benefits of aspirin on primary prevention of cardiovascular disease, the majority of international guidelines have recommended aspirin only when a significant 10-year risk of cardiovascular events exists.[8-11] This evidence summary will present the findings of the most recent systematic review and meta-analysis of RCTs evaluating the role for aspirin in cardiovascular primary prevention looking at potential benefits and possible harms from increased bleeding risk. This review has an AMSTAR rating of low to moderate quality (see Appendix 1).

Meta-Analysis of all the Aspirin in Primary Cardiovascular Disease Prevention Trails[12]

This meta-analysis included 13 RCTs (n=164 225) published until November 1, 2018, that enrolled at least 1000 participants with no known cardiovascular disease and a follow-up of at least 12 months (1 050 511 patient-years of follow up). Included RCTs comparing aspirin use with no aspirin (placebo or no treatment). Data were screened and extracted independently by both investigators. Bayesian and frequentist meta-analyses were performed.

The median age of trial participants was 62 years (range, 53 to 74), 77 501 (47%) were men, 30 361 (19%) had diabetes, and the median baseline 10-year risk for a primary cardiovascular outcome was 10.2% (range, 2.6 to 30.9%). Aspirin dose-range was 75 to 500mg daily, with 11 of the 13 RCTs investigating aspirin at a dose of 75-100mg daily.

Results:

Efficacy

- Composite primary endpoint of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke:
  - Aspirin use was associated with significant reductions in the composite cardiovascular outcome compared with no aspirin (60.2 per 10 000 participant-years with aspirin and 65.2 per 10 000 participant-years with no aspirin) - hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.84 to 0.94; absolute risk reduction (ARR) 0.41%, 95% CI, 0.23 to 0.59; number needed to treat (NNT) 241, 95% CI 169 to 435.

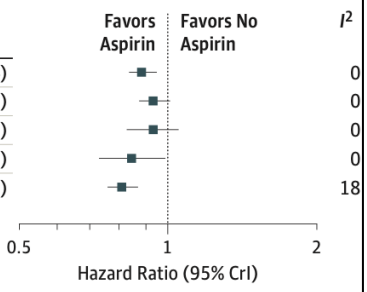
Safety

- The primary bleeding outcome was any major bleeding (defined by the individual studies).
  - Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin (23.1 per 10 000 participant-years with aspirin and 16.4 per 10 000 participant-years with no aspirin): HR 1.43, 95% CI 1.30 to 1.56; absolute risk increase 0.47% ,95% CI 0.34 to 0.62; number needed to harm (NNH) 210, 95% CI 161 to 294.

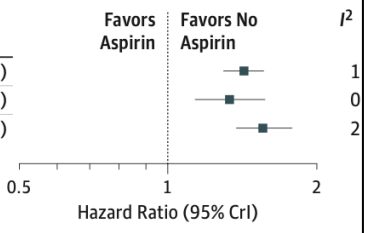
Therefore, the use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding.

Figure 1. Cardiovascular and Bleeding Outcomes in All Participants

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	13	2911	79717	3342	80057	0.41 (0.23 to 0.59)	0.89 (0.84-0.94)	0
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)	0
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)	0
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)	0
Ischemic stroke	10	831	65316	942	63752	0.19 (0.06 to 0.30)	0.81 (0.76-0.87)	18



Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)	1
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)	0
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)	2



The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Hazard ratios (HRs) and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis (eFigure 4 in Supplement 2). GI indicates gastrointestinal.

SUB GROUP ANALYSES:

Low CV risk subgroup

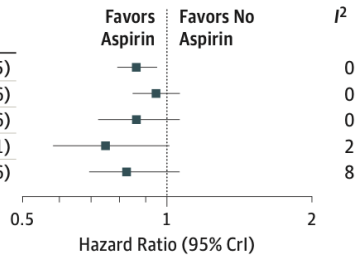
In studies where the primary 10-year risk for a cardiovascular outcome was low, heterogeneity was low for all outcomes in patients (I^2 range, 0%-11%).

- *Efficacy:* Aspirin use was associated with reductions in the primary composite cardiovascular outcome compared to no aspirin - HR 0.87 (95% CI 0.79 to 0.95); ARR 0.34% (95% CI 0.14 to 0.52); NNT 160 (95% CI 192 to 714).
- *Safety*: Aspirin use was associated with increased risk of major bleeding compared to no aspirin - HR 1.45 (95% CI 1.28 to 1.63); absolute risk increase 0.40% (95% CI 0.25 to 0.57); NNH 249 (95% CI 175 to 400). Intracranial bleeding (HR 1.41, 95% CI 1.16 to 1.71) major gastrointestinal bleeding (HR 1.58, 95% CI 1.34 to 1.87) were also more common with aspirin use compared to no aspirin.

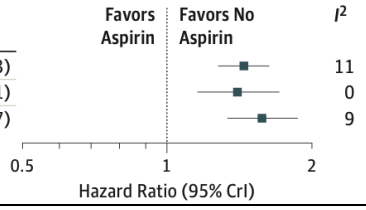
Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Patients at High and Low Risk for the Primary CV Outcome and With Diabetes

A Participants with low CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	6	1559	56212	1753	56354	0.34 (0.14 to 0.52)	0.87 (0.79-0.95)	0
All-cause mortality	6	1903	56212	1905	56354	0.01 (-0.27 to 0.27)	0.95 (0.85-1.06)	0
CV mortality	6	405	56212	448	56354	0.07 (-0.03 to 0.16)	0.87 (0.72-1.06)	0
Myocardial infarction	6	649	56212	793	56354	0.27 (0.00 to 0.49)	0.75 (0.58-1.01)	2
Ischemic stroke	5	508	49942	593	50078	0.16 (0.02 to 0.29)	0.83 (0.69-1.06)	8



Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	5	665	49942	465	50078	0.40 (0.25 to 0.57)	1.45 (1.28-1.63)	11
Intracranial bleeding	6	245	56212	175	56354	0.13 (0.05 to 0.22)	1.41 (1.16-1.71)	0
Major GI bleeding	5	359	48992	228	49110	0.27 (0.15 to 0.40)	1.58 (1.34-1.87)	9



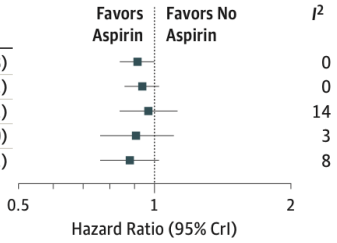
High CV risk subgroup

In studies where the primary 10-year risk of the cardiovascular outcome was high, heterogeneity was low for all outcomes in participants with high risk of the cardiovascular outcome (I^2 range, 0%-15%).

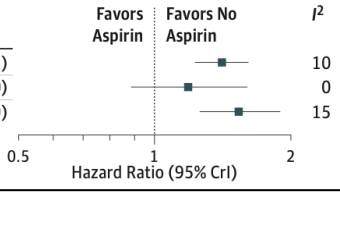
- *Efficacy:* Aspirin use was associated with reductions in the primary composite cardiovascular outcome compared with no aspirin - HR 0.91 (95% CI 0.84 to 0.98); ARR 0.63% (95% CI 0.18 to 1.03%); NNT 160 (95% CI 96 to 555).
- *Safety:* Aspirin use was associated with an increase in major bleeding compared to no bleeding - HR 1.41 (95% CI 1.23 to 1.61); absolute risk increase 0.64% (95% CI 0.35 to 0.97); NNH 152 (95% CI 103 to 286). Aspirin use was also associated with an increased risk of major gastrointestinal bleeding (HR 1.54, 95% CI 1.26 to 1.89) but not in intracranial bleeding (HR 1.19, 95% CI 0.89 to 1.60)

B Participants with high CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome[a]	8	1645	25411	1649	23703	0.63 (0.18 to 1.04)	0.91 (0.84-0.98)	0
All-cause mortality	7	1719	25411	1683	23703	0.43 (-0.02 to 0.84)	0.94 (0.86-1.02)	0
CV mortality	7	590	25411	549	23703	0.04 (-0.27 to 0.32)	0.97 (0.84-1.12)	14
Myocardial infarction[a]	8	820	25411	806	23703	0.32 (-0.16 to 0.74)	0.91 (0.76-1.10)	3
Ischemic stroke[a]	6	323	15374	350	13674	0.28 (-0.12 to 0.63)	0.88 (0.76-1.02)	8



Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	6	530	24773	369	23065	0.64 (0.35 to 0.97)	1.41 (1.23-1.61)	10
Intracranial bleeding	6	104	24773	82	23065	0.07 (-0.04 to 0.21)	1.19 (0.89-1.60)	0
Major GI bleeding	5	34	19452	30	19444	0.39 (0.16 to 0.69)	1.54 (1.26-1.89)	15



Diabetes subgroup

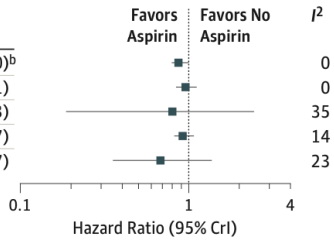
Data for participants with diabetes was reported in 10 studies, accounting for 30448 participants. There was evidence of moderate heterogeneity for cardiovascular mortality in patients with diabetes (I^2 = 35%). Heterogeneity was low for all other outcomes in patients with diabetes (I^2 range, 0%-23%).

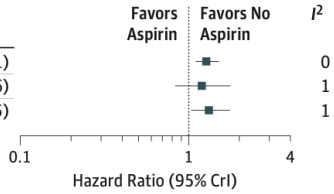
- Efficacy: Aspirin use was associated with reductions in the primary composite cardiovascular outcome – HR. 0.90 (95% CI 0.82 to 1.00); ARR 0.65% (95% CI 0.09 to 1.17); no difference shown.
- *Safety:* Aspirin use was associated with an increase in major bleeding compared to no bleeding - HR 1.29 (95% CI 1.11 to 1.51); absolute risk increase 0.80% (95% CI 0.29 to1.39); NNH 121 (95% CI 72 to 345). Aspirin use was also associated with an increased risk of major gastrointestinal bleeding (HR, 1.35, 95% CI 1.05 to 1.75) but not in intracranial bleeding (HR 1.21 95% CI 0.84 to 1.76).

C Participants with diabetes

Cardiovascular Outcomes	No. of Studies	Aspirin No. of Events	Aspirin No. of Participants	No Aspirin No. of Events	No Aspirin No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	8	977	14916	1072	14898	0.65 (0.09 to 1.17)	0.90 (0.82-1.00)[b]	0
All-cause mortality	5	1028	11938	1055	11946	0.24 (-0.49 to 0.91)	0.97 (0.85-1.11)	0
CV mortality	4	264	10159	279	10167	0.05 (-1.27 to 0.94)	0.82 (0.19-2.43)	35
Myocardial infarction	8	472	11788	490	11700	0.26 (-0.47 to 0.88)	0.94 (0.83-1.07)	14
Ischemic stroke	3	275	9535	317	9511	0.83 (-0.50 to 1.70)	0.70 (0.36-1.37)	23

Bleeding Outcomes	No. of Studies	Aspirin No. of Events	Aspirin No. of Participants	No Aspirin No. of Events	No Aspirin No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	3	370	10029	287	10047	0.80 (0.29 to 1.39)	1.29 (1.11-1.51)	0
Intracranial bleeding	2	63	9002	52	9017	0.12 (-0.09 to 0.43)	1.21 (0.84-1.76)	1
Major GI bleeding	2	142	9002	105	9017	0.41 (0.06 to 0.86)	1.35 (1.05-1.75)	1





Comparative table (aspirin vs no aspirin):

Study population	NNT (composite CV outcome)	NNH (Major bleeding)
All	241 (95% CI 169 to 435)	210 (95% CI 161 to 294)
Low CV risk	160 (95% CI 192 to 714)	249 (95% CI 175 to 400)
High CV risk	160 (95% CI 96 to 555)	152 (95% CI 103 to 286)
Diabetics	No difference shown	121 (95% CI 72 to 345)

Conclusions

This recently published systematic review of aspirin in primary cardiovascular disease prevention trial found that aspirin for primary prevention prevents cardiovascular events, but increases risk of major bleeds. NNT and NNH are similar. Aspirin did not reduce all cause or cardiovascular mortality. Aspirin for primary prevention reduces the risk of non-fatal ischaemic events but increases non-fatal bleeding events. This is observed in both high and low 10-year risk for cardiovascular events sub-groups as well as the diabetic subgroup.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
	X				

Recommendation: The PHC/Adult Hospital Level Committee does not recommend the use of aspirin as primary prevention of IHD.

Rationale: Systematic review of RCTs (n = 164 225) found that the use of aspirin for primary cardiovascular disease prevention did not decrease all-cause cardiovascular mortality. Aspirin use decreased risk of cardiovascular events but increased major bleeding risk.

Level of Evidence: High certainty evidence

Review indicator: Long-term follow-up data of efficacy with lower harms

NEMLC RECOMMENDATION (24 FEBRUARY 2022):

- *Enteric-coated aspirin*: Query was raised if there would be a difference in bleeding if the enteric coated formulation was used. However, it was noted that a historic review by NEMLC had found that there was no difference with associated gastro-intestinal bleeds, despite the dosage formulation that is used[1]. Furthermore, absorption of enteric coated aspirin and effectiveness were not comparable to non-enteric coated aspirin[2].
- *Outcomes:* The balance between the composite outcomes versus risk associated with aspirin favoured that aspirin not be used for primary prevention (including amongst diabetics, or patients at low or high risk). However, more importantly no mortality benefit was seen with aspirin.

Recommendation: NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter.

Monitoring and evaluation considerations

Refer to Appendix 2: Evidence to decision framework

[1] *Citation provided post-meeting:* Haastrup PF, Grønlykke T, Jarbøl DE. Enteric coating can lead to reduced antiplatelet effect of low-dose acetylsalicylic acid. Basic Clin Pharmacol Toxicol. 2015 Mar;116(3):212-5. doi: 10.1111/bcpt.12362.

[2] *Citation provided post-meeting*: Cox D, Maree AO, Dooley M, Conroy R, Byrne MF, Fitzgerald DJ. Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke. 2006 Aug;37(8):2153-8. https://pubmed.ncbi.nlm.nih.gov/16794200/

Appendix 1: Evaluating the methodological quality of the Zheng et al (2021)[3] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[4])

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	Explicitly described in the protocol
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	-
3	Review authors explained selection of the study designs for inclusion in the review	No	In the protocol they mention type of studies to be included. It is self-explanatory why they would have chosen RCTs, but not explicitly stated
4*	Review authors used a comprehensive literature search strategy	Partial yes	Search restricted to English language, but rationale not provided
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	No	PRISMA flow diagram summarises the excluded studies but no details were provided
8	Review authors described the included studies in adequate detail	Yes	-
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Cochrane Risk of Bias Assessment Tool (RoB 2)
10	Review authors reported on the sources of funding for the studies included in the review.	No	-
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	Sensitivity analysis conducted, excluding RCTs of high risk of bias (mostly open-label RCTs)
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	There was no significant heterogeneity in the results
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	The Egger test was used to identify asymmetry of funnel plots for publication bias
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	The authors have no conflicts of interest to disclose

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Low to moderate quality

Rationale: More than one non-critical weakness (# 3,10) with a critical flaw (#7)

[3] Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. JAMA. 2019 Jan 22;321(3):277-287. doi: 10.1001/jama.2018.20578. Erratum in: JAMA. 2019 Jun 11;321(22):2245. https://pubmed.ncbi.nlm.nih.gov/30667501/

[4] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Large, well-designed randomised controlled trials demonstrating conflicting results. Benefit may be subgroup dependent. However other strategies for primary prevention could be mitigating the magnitude of the benefit seen with aspirin. "9 of the 13 included RCTs were at low risk of bias and 4 were at high risk. There were 9 double-blind and 4 open-label studies. There was no evidence of publication bias for the primary outcome (Egger test: −0.47; p=0.57)"
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	*Aspirin vs no aspirin:* **Primary outcome:** Composite cardiovascular outcome (cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke): • 60.2 per 10 000 participant-years vs 65.2 per 10 000 participant-years with no aspirin • HR 0.89, 95% CI 0.84-0.94 • ARR 0.41%, 95% CI 0.23%-0.59% • NNT 241, 95% CI 169 to 435 Advances in other primary prevention strategies are proving more impactful and safer that aspirin.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [x] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Large, well-designed randomised controlled trials all consistently demonstrating significant harms.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	Moderately to large as the major bleeding risks are significant. *Aspirin vs no aspirin:* Increased risk of bleeding[15]: • Difference of 6.7 per10 000 participant-years • HR, 1.43, 95% CI, 1.30-1.56 • Absolute risk increase, 0.47%, 95% CI, 0.34%-0.62% • NNH 210, 95% CI 161 to 294
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [x] Intervention = Control *or* Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Aspirin is available as part of established cardiovascular disease secondary prevention strategies. However, the evidence does not support its use for primary prevention of IHD would be irrational.

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive ☐ Less intensive ☒ Uncertain ☐</td><td>Price of medicines/ month (28 days) – Aspirin up to 150mg/daily
<table><tr><th>Medicine</th><th>Price (ZAR)*</th></tr><tr><td>Aspirin 300mg tablet (14)*</td><td>4.37</td></tr><tr><td>Aspirin 80-81 mg tablet **</td><td>25.20</td></tr><tr><td>Aspirin 100mg tablet***</td><td>27.52</td></tr></table>* Contract circular HP09-2021SD, accessed 6 Sep 2021 – (average weighted price) www.health.gov.za
** SEP Database 26 November 2021: Asprin Teva 80®
*** SEP Database 26 November 2021: Myoprin® 100mg tablet</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor ☐ Major ☐ Uncertain ☒

Is the option acceptable to key stakeholders?
Yes ☒ No ☐ Uncertain ☐</td><td>No local survey data is available, but based on expert opinion there is uncertainty whether patients would value the option, but prescribers considers aspirin to be acceptable as primary prevention for ischaemic heart disease.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes ☐ No ☒ Uncertain ☐</td><td>No significant impact on equity in health for marginalized groups were identified.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	11 February 2022	NT, TL	Aspirin not recommended for primary prevention of IHD as aspirin associated with major bleeding risk and a small benefit of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke compared to no aspirin. Aspirin was also associated with a lower benefit compared to higher bleeding risk in populations with a low and high primary 10-year cardiovascular risk; and amongst diabetics.

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5. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet (London, England)* 1998; **351**(9098): 233-41.
6. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet (London, England)* 1998; **351**(9118): 1755-62.
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11. Fox CS, Golden SH, Anderson C, et al. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. *Circulation* 2015; **132**(8): 691-718.
12. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA* 2019; **321**(3): 277-87.

South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: CVS Chapters

EVIDENCE SUMMARY

Title: The appropriate use of oxygen therapy for ST elevation myocardial infarction (STEMI): evidence from a contemporary systematic reviews and meta-analysis

Date: 09th September 2021

Primary reviewer: Nqoba Tsabedze[a]
Secondary reviewer: Hanneke Brits[b]
Supported by: Trudy Leong[c]
Affiliation and declaration of interests:
a) NT: Division of Cardiology, Department of Medicine, Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand. NT has received honoraria for speaker and advisory board consulting fees relating to cardiovascular therapies from Acino Health Care Group, Boehringer – Ingelheim, Boston Scientific, Eli Lilly, Medtronic, Merck, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Phillips, Sanofi-Aventis, Servier and Takeda.
b) HB: Department of Family Medicine, University of the Free State. No conflict of interest to declare.
c) TL: Essential Drugs Programmer, National Department of Health, South Africa with no conflicts of interests to declare pertaining to oxygen therapy.

Background:

The current standard treatment guidelines (STG's) of STEMI, from the Adult Hospital Level Chapter 3: Cardiovascular conditions, recommends that oxygen therapy should only be started when the peripheral artery oxygen saturation is < 94%. This recommendation is based on the 2018 meta-analysis by Chu et al.[1] However, a recent external comment was received suggesting that a value < 90% in acute STEMI should be used, citing Hofmann et al (2017). [2] Thus, the evidence was reviewed, and an overview of the evidence follows on below:

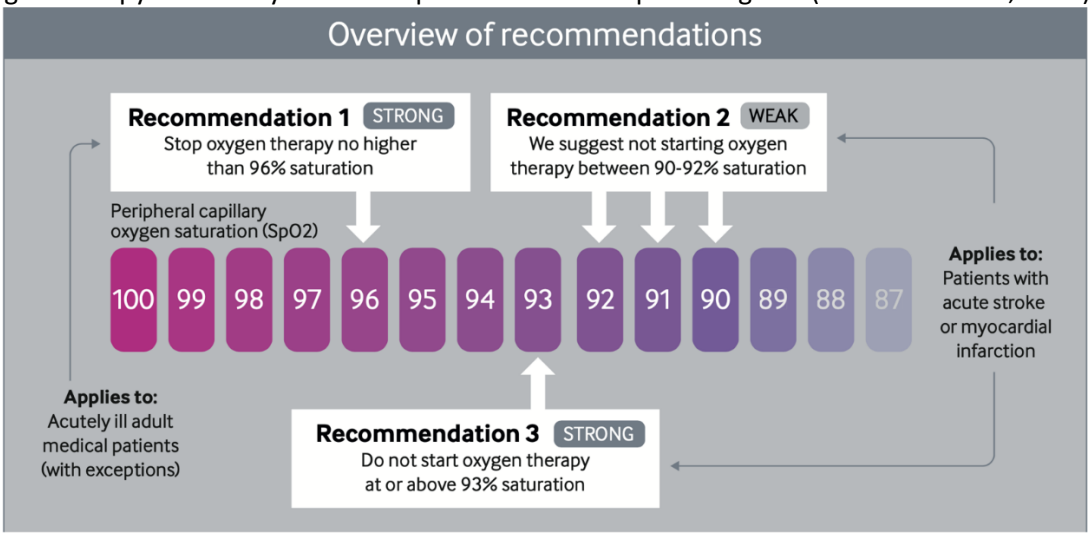
Guidelines:
A 2018 clinical guideline provided guidance based on the 2018 meta-analysis by Chu et al.

Table 1: Characteristics of guideline(s)

Citation (date published)	Recommendation (pg 1)	AGREE II appraisal
Siemieniuk RAC, Chu DK, Kim LH-Y, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ 2018;363:k4169 – Summary of the results from the Rapid Recommendation process	The panel suggested that for patients receiving oxygen therapy, aim for peripheral capillary oxygen saturation (SpO2) of ≤96% **(strong recommendation)**. For patients with acute myocardial infarction or stroke, do **not** initiate oxygen therapy in patients with SpO2 ≥90% (for ≥93% **strong recommendation**, for 90-92% (**weak recommendation**). A target SpO2 range of 90-94% seems reasonable for most patients and 88-92% for patients at risk of hypercapnic respiratory failure; use the minimum amount of oxygen necessary.	**6/7**

See appendix 1: AGREE 2 appraisal and figure 1 below.

Figure 1: Oxygen therapy for acutely ill medical patients: a clinical practice guide (Siemieniuk et al, 2018)[3]

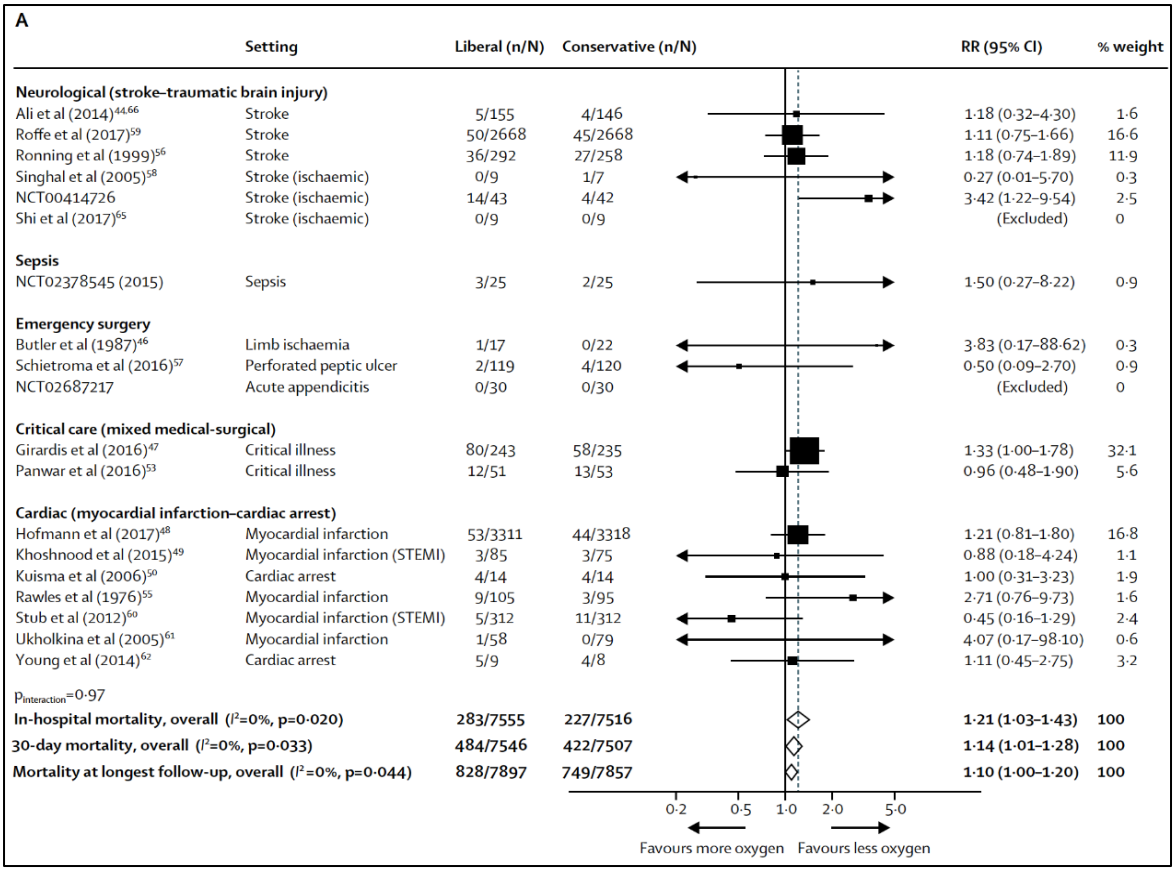


Systematic reviews and meta-analyses:

- *Chu et al (2018) systematic review and meta-analysis:*

The authors analysed 25 randomised controlled trials which enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. Compared with a conservative oxygen strategy, a liberal oxygen strategy (median baseline saturation of peripheral oxygen [SpO_2] across trials, 96% [range 94–99%, IQR 96–98]) increased mortality in-hospital (relative risk [RR] 1.21, 95% CI 1.03–1.43, I.=0%, high quality), at 30 days (RR 1.14, 95% CI 1.01–1.29, I.=0%, high quality), and at longest follow-up (RR 1.10, 95% CI 1.00–1.20, I.=0%, high quality). Morbidity outcomes were similar between groups. These findings were reported as robust to trial sequential, subgroup, and sensitivity analyses. The authors ultimately concluded that in acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO_2 range of 94–96%. These results support the conservative administration of oxygen therapy. See figure 1, below.

Figure 2: Forest plot of in-hospital mortality with at 30 days or longer follow-up (Chu et al, 2018)

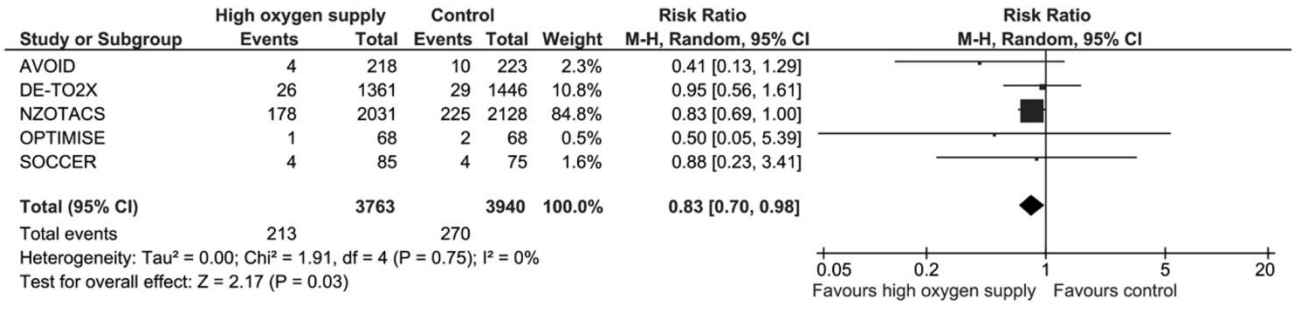


Furthermore, a search was conducted on PUBMED (search strategy – appendix 2), restricting to SRs of RCTs for oxygenation strategies in acute cardiovascular conditions to search for additional literature after 2018. Two SRs were retrieved, and a review of the most recently published SR (2021) follows below:

- *Alves et al (2021) systematic review and meta-analysis*[4]*:*

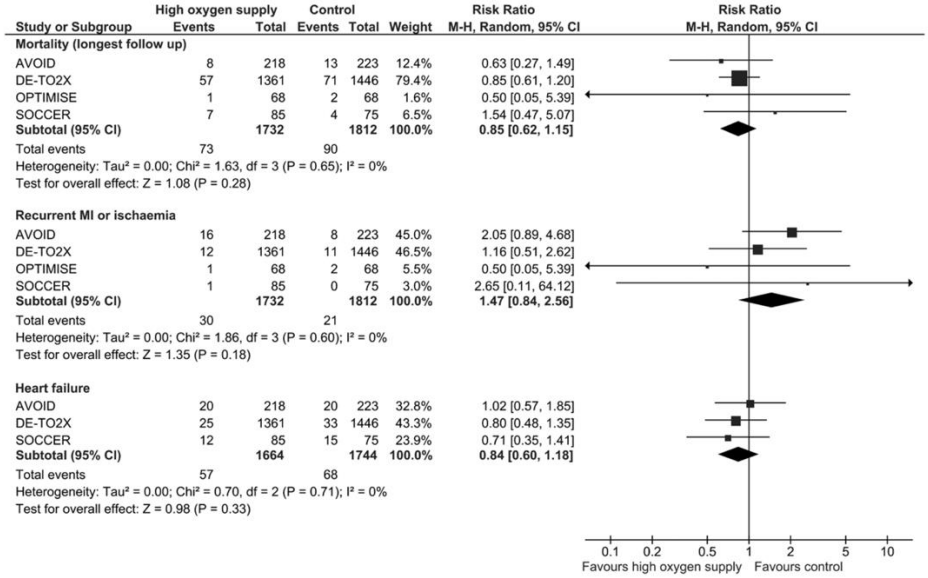
Alves *et al.* assessed the clinical effect of high oxygen supply in patients with STEMI using a systematic review of the available literature. All randomized controlled trials (RCTs) evaluating the systematic use of high oxygen (6 L/min or higher) versus room air or lower oxygen supply in STEMI patients were included. Systematic review with meta-analysis of trials retrieved in July 2020. Six databases were searched. Risk of bias was evaluated using the Cochrane risk of bias tool. There were five eligible RCTs (7703 patients). High oxygen supply was associated with a significant risk reduction of short-term mortality [risk ratio (RR) 0.83; 95% confidence interval (CI), 0.70–0.98; I^2 = 0%]. Mortality (longest follow-up) (RR 0.83; 95% CI, 0.71–0.97; I^2 = 0%) and heart failure (RR 0.84; 95% CI, 0.60–1.18; I^2 = 0%) did not present a risk reduction. Recurrent MI presented a contradictory result, favouring the lower oxygen protocol (RR 1.47; 95% CI, 0.84–2.56; I^2 = 0%). The GRADE analysis was very low, and the authors concluded that High oxygen supply may be associated with a decrease in short-term mortality in STEMI patients, but the pooled data are not robust enough to allow definitive conclusions. See figures 3 and 4 below.

Figure 3: Forest plot of short-term mortality (Alves et al, 2021)



Forest plot of short-term mortality (SOCCER data were provided by author). SOCCER, Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion.

Figure 4: Forest plot for secondary outcomes (Alves et al, 2021)



Forest plot for secondary outcomes – recurrent MI or ischemia, heart failure and mortality (longest follow-up) (SOCCER data on mortality were provided by author). SOCCER, Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion.

Table 2: Summary of findings according to GRADE (Alves et al, 2021)

		Anticipated absolute effects (95% CI)				
Outcome no. participants (studies)	Relative effect (95% CI)	Without high oxygen supply (%)	With high oxygen supply	Difference	Certainty	What happens
Short-term mortality no. participants: 7703 (5 RCTs)	RR 0.83 (0.70–0.98)	6.8	5.7% (4.8–6.7)	1.2% fewer (2 fewer to 0,1 fewer)	⨁◯◯◯ VERY LOW[a,b]	High oxygen therapy may reduce short-term mortality, but the evidence is very uncertain
Mortality (longest follow-up) no. participants: 7703 (5 RCTs)	RR 0.83 (0.71–0.97)	8.0	6.6% (5.7–7.2)	1.4% fewer (2,3 fewer to 1,2 fewer)	⨁◯◯◯ VERY LOW[a,b]	High oxygen therapy may reduce all-cause mortality but the evidence is very uncertain
Recurrent MI or ischemia no. participants: 3544 (4 RCTs)	RR 1.47 (0.84–2.56)	1.2	1.7% (1–3)	0.5% more (0,2 fewer to 1,8 more)	⨁◯◯◯ VERY LOW[a,b]	The evidence is very uncertain about the effect of high oxygen therapy on recurrent MI or ischemia
Heart failure no. participants: 3408 (3 RCTs)	RR 0.84 (0.60–1.18)	3.9	3.3% (2.3–4.6)	0.6% fewer (1,6 fewer to 0,7 more)	⨁◯◯◯ VERY LOW[a,b]	The evidence is very uncertain about the effect of high oxygen therapy on heart failure

CI, confidence interval; RR, risk ratio; RCT, randomized controlled trials.
[a]High risk of bias – open label design and selective reporting risk of bias.
[b]Insufficient/small sample size.

Conclusions

The main finding of the most recent SR and Meta-analysis was that high oxygen supply in patients with acute STEMI may be associated with a significant 17% risk reduction of short-term mortality (until 30 days). Despite this statistically significant difference in mortality, the trial sequential analysis showed that only 56.3% of the sample size required to assess the 17% risk reduction with a power 80% was reached, and the magnitude of the results were not large which precludes definite conclusions. This consideration and the high risk of bias of the included trials led to successive downgrading in the GRADE analysis of the confidence in the pooled data.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this review, the PHC/Adult Hospital Level Committee recommends that the current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic.

Rationale: Evidence suggests that acutely ill patients randomised to liberal oxygen therapy were more likely to die, without improving other patient outcomes. For pragmatic purposes the current recommendation of <94% be retained.

Level of Evidence: Moderate certainty evidence

Review indicator: New evidence that will change the recommendation

NEMLC RECOMMENDATION (22 FEBRUARY 2022):

- NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter.
- The PHC/Adult Hospital Level ERC review the evidence of the impact of altitude on oxygen requirements, whilst the draft documents are circulated for external comment.

Monitoring and evaluation considerations

Research priorities

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate [X] Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	High quality evidence not to initiate oxygen therapy in patients with acute myocardial infection or stroke, with SPO_2≥93% (Hofmann et al, 2017). However, uncertain whether this is applicable to patients requiring oxygen therapy that do not have these conditions. The BMJ Guideline panel down rated the evidence for indirectness.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small [x] None ☐	No impact on length of hospitalisation or risk of hospital acquired infections.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate [X] Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic review by Chu et al (2018)[1] graded the evidence for the outcome, increased mortality in-hospital at 30 days as high quality. The PHC/Adult Hospital Level Committee down rated evidence as uncertain whether applies to all medically ill patients.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small [X] None ☐	"Patients randomised to liberal oxygen therapy were more likely to die (RR 1.21 (95% confidence interval 1.03 to 1.43)). The increase in mortality was highest in the trials with the greatest increase in SpO_2; this suggests a dose-response relation and strengthens the inference that excessive oxygen is a cause of death. Providing supplemental oxygen above a SpO2 of 96% probably increases mortality by around 1%"

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [ ] Favours control: [X] Intervention = Control *or* Uncertain: [ ]	Guideline panel suggests a target SpO2 range of 90-94% so that "it does not require excessive attention" (Siemieniuk et al, 2018).
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [x] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [x] Uncertain: [ ]	
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [x] **Is the option acceptable to key stakeholders?** Yes: [x] No: [ ] Uncertain: [ ]	No local survey data is available, but the Committee was of the opinion that the option would be acceptable to prescribers.
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [x] Uncertain: [ ]	No significant impact on equity in health for marginalized groups were identified.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 September 2021	NT, HB	Current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic.

References:

1. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet (London, England)* 2018; **391**(10131): 1693-705.
2. Hofmann R, James SK, Jernberg T, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med* 2017; **377**(13): 1240-9.
3. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018; **363**: k4169.
4. Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. *Eur J Emerg Med* 2021; **28**(1): 11-8.

APPENDIX 1: AGREE II ASSESSMENT

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	94%	84%	94%	52%	92%	83%	Yes - 1, Yes with modifications - 1, No - 0

APPENDIX 2: Pubmed Search Strategy

Strategy: ((((Myocardial infarction [MeSH Terms]) OR(coronary artery disease[MeSH Terms])))) AND (Oxygen[MeSH Terms])) OR (oxygen inhalation therapy[Other Term])

#	Searches
1	Myocardial infarction
2	Coronary artery disease
3	1 or 2
4	Oxygen
5	Oxygen inhalation therapy
6	4 or 5
7	Systematic review
8	Meta-analysis
9	7 or 8
10	Exp animals/not humans
11	Not 10
12	3 and 6 and 9
13	Remove duplicates from 12

Systematic Reviews and Meta-analysis Retrieved: In Chronological order.

Restricted to publications after 2018.

1. Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. *Eur J Emerg Med* 2021; **28**(1): 11-8.
2. Khan AR, Abdulhak AB, Luni FK, et al. Oxygen Administration Does Not Influence the Prognosis of Acute Myocardial Infarction: A Meta-Analysis. *Am J Ther* 2019; **26**(1): e151-e60.

South African National Essential Medicine List
Primary and Adult Hospital Level of Care Medication Review Process
Component: Cardiovascular conditions – Hypertension in Adults

MEDICINE REVIEW

TITLE: Indapamide as first-line therapy for uncomplicated primary hypertension compared to HCTZ

DATE: 16 July 2021

Key findings

- Hydrochlorothiazide (HCTZ) is currently the first-line pharmacological treatment for hypertension recommended in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa. Indapamide is not currently listed on the EML and is not on national tender. Some clinical guideline recommendations and local clinicians state a preference for thiazide-like diuretics (indapamide, chlorthalidone) over conventional thiazide diuretics (hydrochlorothiazide [HCTZ], chlorothiazide, bendroflumethiazide) for the management of essential hypertension.
- We conducted a review of systematic reviews and clinical practice guidelines that reported on or provided recommendations on first-line use of thiazide diuretics.
- We identified two relevant systematic reviews and three clinical practice guidelines.
- Findings from systematic reviews: There were no direct comparisons between the different diuretics regarding long-term clinical outcomes. Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. This makes it difficult to be certain regarding the comparative efficacy of HCTZ vs indapamide for blood pressure lowering. According to one of the systematic reviews, indapamide reduce left ventricular mass (LVM) 2-fold more than HCTZ in hypertensive patients, but the authors found no difference between the diuretics reviewed and HCTZ for systolic or diastolic blood pressure. Therefore, changes in blood pressure failed to explain the superiority of indapamide in reducing LVM.
- Findings from clinical practice guidelines: The National Institute for Health and Care Excellence (NICE) 2011 guideline recommendation that use of thiazide-like diuretics (e.g. indapamide) are preferred over conventional thiazides (e.g. HCTZ) is based on lack of evidence supporting use of conventional thiazide diuretics, not comparative efficacy. The European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guideline doesn't state preference for either conventional thiazide or thiazide-like diuretics – instead it recommends two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada 2020 guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.
- Estimated pharmaceutical costs (annual cost for estimated patient population likely to start first-line treatment): Indapamide 2.5mg: R28 732 586, Indapamide SR 1.5mg: R203 012 207, HCTZ 25mg: R7 536 416
- The review found that the evidence supporting the use of indapamide over HCTZ is of low quality with uncertain impact on important clinical outcomes. In addition, indapamide is almost four times more expensive than HCTZ and a large patient population will be eligible to receive the treatment each year. Including indapamide as a first-line treatment option will therefore have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/ADULT Hospital Level Committee suggests that indapamide not be recommended for the first-line treatment of patients with uncomplicated hypertension.

Rationale: The clinical evidence supporting the use of indapamide over HCTZ is of low quality and uncertain. In addition, indapamide is more expensive than HCTZ and would have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. Indapamide may be considered for inclusion in the therapeutic interchange database as an alternative to HCTZ.

Level of Evidence: Systematic reviews of lower quality clinical trials and/or inconsistent findings.

Review indicator: Price reduction or new evidence of clinical benefit

NEMLC RECOMMENDATION (24 FEBRUARY 2022):

DISCUSSION

- *Metabolic effects:* It was queried if there would be a place for indapamide amongst diabetics, as approximately 15% of patients on thiazides develop diabetes (evidence not provided). However, the review states that: "Metabolic effects (electrolyte abnormalities, plasma glucose, cholesterol, uric acid levels) were reported in some of the studies included in the NICE 2011 evidence review (see Appendix F), but those outcomes were not reviewed or reported on. A critically low quality systematic review and meta-analysis[a] (with a very similar scope to the NICE 2011 evidence review) assessed the metabolic outcomes reported in the studies included in the NICE 2011 evidence review and reported no significant difference between indapamide and HCTZ on metabolic outcomes.[b]
- *Comparative costing analysis:* The reference for the source of the Indapamide price was omitted, but confirmed to be 100% of SEP. It was recommended that a sensitivity analysis be done for the analysis using 60% of SINGLE EXIT PRICE (SEP).

Recommendations:

- NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence review be circulated for external comment with the PHC cardiovascular chapter.
- A sensitivity analysis of the costing analysis using 60% of SEP be conducted, whilst the draft documents are circulated for external comment.

References:

a. This review was excluded at full-text screening stage due to its low quality and the significant overlap with the NICE 2011 evidence review (which is a higher quality review). See Appendix E for more detail.

b. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects. Hypertension. 2015;65:1041–6. https://pubmed.ncbi.nlm.nih.gov/25733245/

Monitoring and evaluation considerations

No changes to monitoring and evaluation required.

Continue with patient care and follow up guidance provided in STGs (1,2). This includes periodically assessing the level of blood pressure control in primary health care and adult hospital level of care.

Research priorities

1. To determine the level of blood pressure control in South Africa with the currently adopted therapeutic strategies
2. To determine the burden and cost implications of hypertension related complications in the public health sector.
3. To determine the implementation of the stepwise treatment algorithm in clinical practice and what factors contributes to non-implementation

(Refer to the evidence-to-decision framework)

1. EXECUTIVE SUMMARY

Date: 16 July 2021
Medicine (INN): Indapamide
Medicine (ATC): C03BA11
Indication (ICD10 code): I10 – Essential (primary) hypertension
Patient population: Adults aged 18 years or older with uncomplicated primary hypertension
Prevalence of condition: 46% of women and 44% of men aged 15 years and older (SADHS 2016 (3))
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse practitioner, Medical Doctor, Specialist
Current standard of Care: Hydrochlorothiazide (HCTZ)
Efficacy estimates: Blood pressure: Uncertain effect potentially favouring indapamide. Left ventricular hypertrophy: Indapamide is superior to HCTZ by reducing left ventricular mass by -7.5% (-12.7, -2.3).
Budget estimates (annual cost for estimated patient population likely to start first-line treatment):
Indapamide 2.5mg: R28 732 586, Indapamide SR 1.5mg: R203 012 207, HCTZ 25mg: R7 536 416
Motivator/reviewer name(s): Nqoba Tsabedze, Maryke Wilkinson, Trudy Leong, Tamara Kredo

2. NAME OF AUTHORS

Nqoba Tsabedze, Maryke Wilkinson, Trudy Leong, Tamara Kredo

3. AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

- Dr. N Tsabedze: University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital.
- Mrs. Maryke Wilkinson: Cochrane South Africa, South African Medical Research Council and Better Health Programme South Africa.
- Ms. Trudy Leong: Essential Drugs Programme, National Department of Health, South Africa.
- Dr. Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, Stellenbosch University.

NT, MW, TL, TK have no conflicts of interest to declare pertaining to Indapamide.

4. ACKNOWLEDGEMENTS

- Mrs. Joy Oliver (Cochrane SA, SA Medical Research Council) for developing and implementing the search strategy.
- Dr. Leah Ferguson (Red Cross Children's Hospital) for assisting with AGREE II assessments.

5. INTRODUCTION/ BACKGROUND

Description of the condition

In South Africa, the probability of premature mortality between the ages of 30 and 70 due to non-communicable diseases (NCDs) is 34% for males and 24% for females (total 29%). Most of these NCD-related deaths are due to cardiovascular disease (CVD), followed by cancer, diabetes and chronic respiratory disease (4). Hypertension is a major risk factor for cardiovascular diseases such as stroke and ischaemic heart disease.

The South Africa Demographic and Health Survey (SADHS) showed that 46% of women and 44% of men aged 15 years and older have essential hypertension. Since 1998, national prevalence of hypertension has nearly doubled[1], from 25% to 46% among women and from 23% to 44% among men (3).

The national incidence of hypertension expressed as the number of newly diagnosed cases per annum per 1000 population aged 40 years and older, was 18.9 in 2016/2017 (5).

[1] Note: different instruments were used to measure blood pressure in the two surveys (Omron M1 in 1998 and Omron 1300 in 2016).

Description of the interventions
An overview of the intervention under review is provided in Table 1.

Table 1. Description of the intervention

Information Field	Details	Reference
Name of the technology	International Nonproprietary Name((INN): Indapamide Proprietary names: Multiple (see Appendix A)	SAHPRA (6)
Licensing status	SAHPRA registered	SAHPRA (6)
Reimbursement status	Not currently approved for use on EML for any level of care, and not on national tender.	Master Health Product List (7)
ATC classification	C03BA11	
Mechanism of action	Indapamide exhibits an antihypertensive action. The antihypertensive effect of indapamide is due to the reduction in the total peripheral and arterial vascular resistance and possibly involves both renal and extra-renal effects.	Indapamide package insert (8)
Indication relevant to this review	Management of mild to moderate hypertension.	Indapamide package insert (8)
Dosage form and strength(s)	Indapamide 2,5mg tablet (30 tablet pack) Indapamide 1,5mg sustained-release tablet (30 tablet pack)	SAHPRA (6)
Route of administration	Oral	SAHPRA (6)
Dosage regimen	Once daily (morning)	Indapamide package insert (8)
Setting	Primary and hospital level	
Additional tests or investigations required to administer technology	No additional requirements in addition to those required when prescribing hydrochlorothiazide	
Anticipated place in therapy	First-line pharmacological treatment for essential hypertension	
Comparator(s)/ Standard of Care	Hydrochlorothiazide – 12,5mg and 25mg (28 tablet packs) (see Appendix B)	

ATC - Anatomical Therapeutic Chemical, EML - Essential Medicines List , SAHPRA - South African Health Products Regulatory Authority

Hydrochlorothiazide (HCTZ) is currently the first-line pharmacological treatment for hypertension recommended in the Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for South Africa - Primary Healthcare Level (2020 Edition) (1) as well as the Adult Hospital Level STG and EML (2). HCTZ has a once-daily dosing regimen, and is available in doses of 12,5mg, 25mg and 50mg per tablet. The 50mg HCTZ tablet is not recommended for use in the STGs. Contraindications for HCTZ are gout, pregnancy, severe liver impairment, and kidney impairment (eGFR < 30 mL/min), and it should be used with caution in patients with a history or family history of skin cancer. All patients on HCTZ must be counselled on sun avoidance and sun protection (1).

Indapamide is not currently listed on the EML and is not on national tender. Indapamide has a once-daily dosing regimen, and is available in doses of 2,5mg (tablet) and 1,5mg (sustained-release tablet). A larger dose than 2.5mg indapamide daily is not recommended. Contraindications for indapamide are renal impairment (eGFR < 30 mL/min), hepatic encephalopathy or severe impairment of liver function, and hypokalaemia. Safety in pregnancy and lactation has not been established.

Why it is important to do this review
Some clinical guideline recommendations state a preference for thiazide-like diuretics (indapamide, chlorthalidone) over conventional thiazide diuretics (HCTZ, chlorothiazide, bendroflumethiazide) for the management of essential hypertension.

“The thiazide-like diuretics retain the main action of thiazide diuretics, i.e. inhibition of the sodium chloride co- transporter in the distal nephrons of the kidney. However, the thiazide and thiazide-like drugs have differential effects on other enzyme effects in the kidney, e.g. carbonic anhydrase inhibition, which can differ by up to 10,000-fold. Differential effects

on platelet aggregation and regulation of angiogenesis have also been reported. The relevance of these actions beyond the characteristic thiazide action of inhibition of the sodium chloride cotransporter with regard to blood pressure control and the prevention of clinical outcomes is unknown." [NICE 2011 evidence review (9)] Furthermore, these potential benefits may only be realised after chronic use and not immediately realised.

This review aims to investigate the relative clinical efficacy of indapamide versus HCTZ, and present how clinical guideline panels interpreted the evidence when they developed recommendations regarding first-line use of thiazide diuretics. The relative costs of indapamide and HCTZ and pharmaceutical budget impact is also presented for consideration in addition to the evidence and discussion of the relative clinical effect.

6. PURPOSE/OBJECTIVE

Review question: Should indapamide be used for first-line therapy for uncomplicated primary hypertension, compared to HCTZ?

Table 2. Scope of the technical review

Population	Adults aged 18 years or older with uncomplicated primary hypertension - No congestive cardiac failure (Loop diuretics preferred) - No resistant hypertension (Patients should be on a diuretic and add-on spironolactone is preferred)
Intervention/s and comparisons	Intervention: Indapamide (immediate- and slow-release formulations) Comparator: Hydrochlorothiazide
Outcomes	**Primary outcomes:** - Blood pressure reduction (in mmHg) - Systolic and diastolic BP (in mmHg) - Major adverse cardiovascular effects: stroke, myocardial infarction **Secondary outcomes:** - Asymptomatic target organ damage - Microalbuminuria - Chronic kidney disease (CKD) - Retinopathy - Left ventricular hypertrophy - Metabolic effects: ▪ Dyslipidaemia ▪ Glucose control (HBA1c changes) ▪ Electrolyte abnormalities: Hypokalaemia, hyponatremia **Clinical Effects:** - Hypotension (postural)
Study designs	Systematic reviews of trials Clinical practice guidelines

7. METHODS

We conducted a review of the evidence including systematic searching on two electronic databases: PubMed and the Cochrane Library. The search strategies for the systematic literature searchers in PubMed and the Cochrane Library are shown in Appendix C. Title and abstract and full-text screening for systematic reviews were done in duplicate using COVIDENCE software. One reviewer summarised the included systematic reviews; a second reviewer checked the results. The AMSTAR (A MeaSurement Tool to Assess systematic Reviews) instrument was used to appraise the methodical quality of the systematic reviews selected for inclusion. AMSTAR assessments were done in duplicate, with disagreements resolved through discussion.

In addition, a search for relevant clinical practice guidelines was completed using the following databases: World Health Organization (WHO), Guidelines International Network (GIN), National Institute for Health Care Excellence (NICE), and the

Scottish Intercollegiate Guidelines Network (SIGN). One reviewer used simple, broad search terms, including 'hypertension' and 'cardiovascular' in the electronic searches for clinical guidelines. One reviewer extracted the relevant recommendations from the clinical guidelines, and this was checked by a second reviewer. AGREE II (Appraisal of Guidelines, for Research, and Evaluation) assessments was carried in duplicate of clinical guidelines selected for inclusion to evaluate the process of guideline development and quality of reporting.

8. FINDINGS

Systematic reviews

Two electronic databases (PubMed and the Cochrane Library) were searched on 29 April 2021 and sixty systematic reviews were identified. Two additional systematic reviews were identified through checking reference lists of eligible reviews and clinical guidelines. After title and abstract screening, six systematic reviews were selected for full-text screening, from which two eligible systematic reviews were selected (9,10) for inclusion, and AMSTAR II assessments were completed for both the reviews (see Appendix D). The four systematic reviews excluded at full text screening (and the reason for their exclusion) are presented in Appendix E. The Prisma flow diagram for the search output is shown below (figure 1).

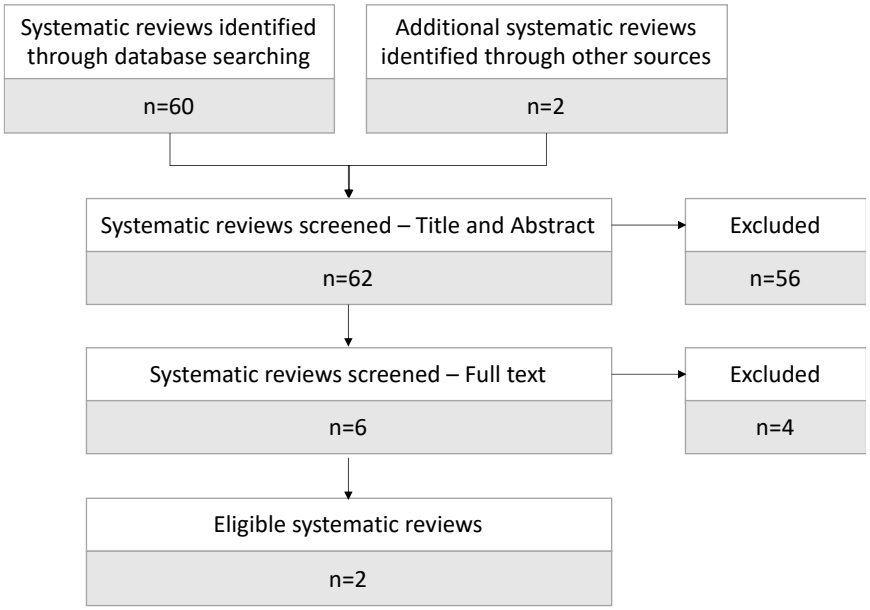


Figure 1. Prisma flow diagram of search results: systemic reviews

The evidence review that most closely corresponded to our review question and had the highest AMSTAR II score was commissioned by NICE (conducted by the Royal College of Physicians, published in August 2011 (9)) to inform *NICE Clinical Guideline 127: The clinical management of primary hypertension in adults.* One of the thirteen review questions selected for systematic review as part of the update of NICE CG 127 was: *In adults with primary hypertension, which is the most clinically and cost-effective thiazide diuretic (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment, and does this vary with age and ethnicity?*(9)

The other systematic review selected for inclusion was conducted by Roush et al in 2018 (10). Roush et al 2018 tested the hypothesis that "CHIP" diuretics (CHlorthalidone, Indapamide, and Potassium-sparing diuretic/hydrochlorothiazide [PSD/HCTZ]) are superior to HCTZ for reducing left ventricular mass (LVM) in hypertensive patients (10).

A summary of the methods and findings from the two included systematic reviews are presented below.

A. <u>NICE 2011 evidence review</u> (9) – ***AMSTAR II assessment: Moderate quality review***

- The analysis examined data for the four most commonly used thiazide-type diuretics:
  i) conventional thiazide diuretics (e.g. bendroflumethiazide and HCTZ), and
  ii) thiazide-like diuretics (e.g. chlorthalidone and indapamide).
- The review included studies that compared hypertensive patients taking one of the four diuretics as first-line therapy with each other. Patients that were exclusively diabetic or had CKD were excluded, and outcomes of interest were BP measurements.
- A total of 15 RCTs were found that fulfilled the inclusion criteria, of which six RCTs compared indapamide with HCTZ (11–16) and one compared indapamide with placebo (17). See characteristics of included studies in Appendix F.
- Head-to-head comparisons were usually based on blood pressure changes as the main outcome.
- There were no direct comparisons between the different diuretics with regard to clinical outcomes.
- HCTZ–indapamide comparison evidence of systolic blood pressure (SBP) and diastolic blood pressure (DBP):
  - Table 3 summarises the quality of the evidence and outcome data for the studies included in the review.
  - The studies were often of short duration (did not allow for hard outcomes evaluation) and the NICE guideline development group considered all of them to be underpowered to detect a significant blood pressure difference between diuretic treatments. A sample size of N > 500 is required in order to detect a 5 mmHg difference in the two arms. Furthermore, there was considerable variation in the doses of diuretics used in the various studies.
  - The results of the meta-analyses are presented in Table 4.
  - "The results of the meta-analyses comparing indapamide and HCTZ for SBP and DBP (supine and upright) should be interpreted with extreme caution due to the observed significant heterogeneity. This appears to be attributed to one of the RCTs (11) which reports an effect size in the opposite direction to the other studies and because it has much smaller standard deviations than the other trials, it has therefore been weighted more highly. If this trial is removed from the meta-analysis then heterogeneity is reduced to more acceptable levels of 0% and the effect becomes not significant. Removing the two lower quality trials (12,13) from the analysis did not result in removing the observed heterogeneity. If a random effects model is applied to the pooled estimate, then the effect size also becomes not significant."(9)
- Metabolic effects (electrolyte abnormalities, plasma glucose, cholesterol, uric acid levels) were reported in some of the studies included in the NICE 2011 evidence review (see Appendix F), but those outcomes were not reviewed or reported on. A critically low quality systematic review and meta-analysis[2] (with a very similar scope to the NICE 2011 evidence review) assessed the metabolic outcomes reported in the studies included in the NICE 2011 evidence review and reported no significant difference between indapamide and HCTZ on metabolic outcomes (18).

[2] This review was excluded at full-text screening stage due to its low quality and the significant overlap with the NICE 2011 evidence review (which is a higher quality review). See Appendix E for more detail.

Table 3: Evidence Thiazide-like diuretics vs Thiazide diuretics (Indapamide versus hydrochlorothiazide) [Table 72 in NICE 2011 evidence review (9)]

Quality assessment						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Indapamide vs HCTZ**	**Control**	**Relative**	**Absolute**	
SBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
5 (11–14,17)	RCTs	Serious[1]	very serious[2]	no serious indirectness	no serious imprecision	77	74	-	MD 8.36 lower (10.92 to 5.8 lower)	VERY LOW
DBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
5 (11–14,17)	RCTs	very serious[1]	Serious[3]	no serious indirectness	no serious imprecision	77	74	-	MD 4.2 lower (5.48 to 2.92 lower)	VERY LOW
SBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
4 (11,12,14,17)	RCTs	no serious limitations	very serious[4]	no serious indirectness	no serious imprecision	54	55	-	MD 8.74 lower (11.75 to 5.73 lower)	LOW
DBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
4 (11,12,14,17)	RCTs	no serious limitations	very serious[5]	no serious indirectness	no serious imprecision	54	55	-	MD 3.85 lower (5.41 to 2.28 lower)	LOW
SBP supine (change from baseline) (follow-up 3-6 months; measured with: mmHg; Better indicated by lower values)										
2 (14,16)	RCTs	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	196	192	-	MD 3.95 lower (7.03 to 0.87 lower)	MODERATE
DBP supine (change from baseline) (follow-up mean 3-6 months; measured with: mmHg; Better indicated by lower values)										
2 (14,16)	RCTs	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	196	192	-	MD 0.76 lower (2.5 lower to 0.98 higher)	MODERATE
SBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)										
1 (14)	RCTs	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	18	21	-	MD 12.55 lower (17.11 to 7.99 lower)	HIGH
DBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)										
1 (14)	RCTs	no serious limitations	no serious inconsistency	no serious indirectness	Serious[7]	18	21	-	MD 2.07 lower (7.2 lower to 3.06 higher)	MODERATE
SBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 5.5 higher (0 to 0 higher)[9]	MODERATE
DBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 5.9 higher (0 to 0 higher)[9]	MODERATE

Quality assessment						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Indapamide versus HCTZ**	**Control**	**Relative**	**Absolute**	
SBP: 24 hour ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 7.5 higher (0 to 0 higher)[9]	MODERATE
DBP: 24h ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 2.0 higher (0 to 0 higher)[9]	MODERATE

ABPM – Ambulatory Blood Pressure Monitoring, DBP – diastolic blood pressure, HCTZ- hydrochlorothiazide, MD – mean difference, RCTs – randomised controlled trial(s), SBP – systolic blood pressure

[1] There were inadequate methodological information in two of the three trials

[2] Heterogeneity was 78%

[3] Heterogeneity was 76%

[4] Heterogeneity was 72%

[5] Heterogeneity 68%

[6] 1/2 studies unclear for allocation concealment

[7] 95% CI includes no effect and appreciable harm or benefit

[8] unclear allocation concealment

[9] There was NS difference between groups

Table 4. Results of studies / meta-analysis [Table 76 in NICE 2011 evidence review (9)**]**

Diuretic name (intervention)	Diuretic name (comparator)	Outcome measure and statistical significance (arm favoured)														Ref
		Change from baseline								End of follow-up				Absolute change		
		Supine		Upright		Seated		24h ABPM		Supine		Upright		Unclear method		
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	SBP	SBP	SBP	
Thiazide-like diuretic vs Thiazide diuretic																
CTD	HCTZ					NS	NS	NS								
IND	**HCTZ**	**SS (IND)**	**NS**	**SS (IND)**	**NS**	**NS**	**NS**	**NS**	**NS**	**SS* (IND)**	**SS* (IND)**	**SS* (IND)**	**SS* (IND)**			(11–17)
IND	BDZ									NS	NS	NS	NS	NS	NS	
Thiazide-like diuretic vs Thiazide-like diuretic																
IND	CTD	NS	NS							NS	NS					
Thiazide diuretic vs Thiazide diuretic																
HCTZ	BDZ	NS	NS	NS	NS											

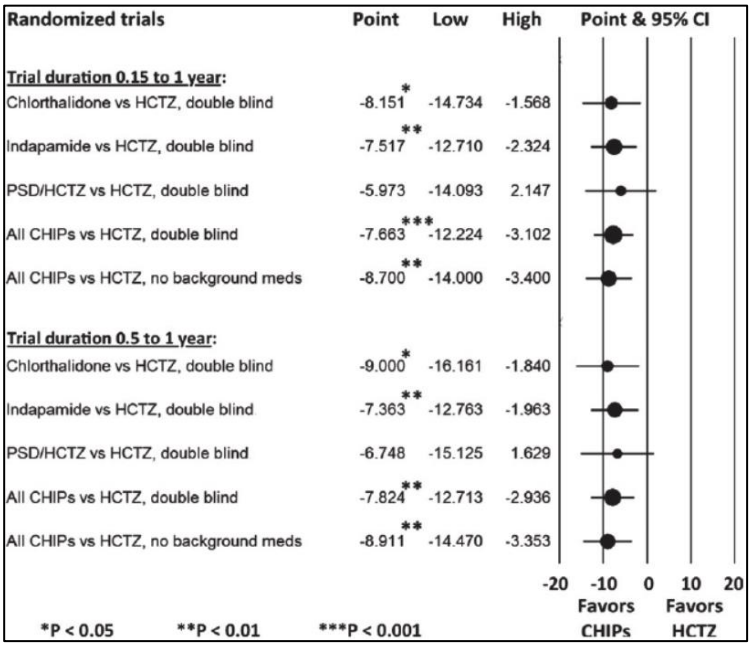
ABPM – Ambulatory Blood Pressure Monitoring, BDZ – bendroflumethiazide, CTD – chlorthalidone, DBP – diastolic blood pressure, HCTZ- hydrochlorothiazide, IND – indapamide, NS – not significant, SS – statistically significant, SBP – systolic blood pressure

*significant heterogeneity. Heterogeneity is removed if the Plante trial (11) is excluded from the analysis, and the overall effect becomes not significant. If a random effects model is applied to the pooled estimate, then the effect size also becomes not significant

B. <u>Roush et al 2018</u> (10) – ***AMSTAR II assessment: Moderate quality review***

- The analysis examined data for HCTZ, chlorthalidone, indapamide, triamterene/HCTZ, amiloride/HCTZ, spironolactone/HCTZ, spironolactone, eplerenone, or canrenone compared with another diuretic or one of the nondiuretic classes commonly used to treat hypertension. The study hypothesis was that 'CHIP' diuretics (CHlorthalidone, Indapamide, and Potassium-sparing diuretic/ HCTZ [PSD/HCTZ]) would reduce left ventricular mass (LVM) more than HCTZ. Left ventricular hypertrophy (LVH) is found in 36% - 41% of patients with hypertension and predicts cardiovascular events and total mortality independently of traditional risk. Among hypertensive patients, LVH contributes to about 30% of all deaths, 25% of cardiovascular events, and 75% of chronic heart failure (10).
- The review included studies with hypertensive patients with change in LVM or change in LVM indexed to height or to body surface area as outcomes.
- Thirty-eight RCTs were identified, with one RCT comparing indapamide with HCTZ and 37 comparing diuretics with non-diuretics (total of 2299 patients). The characteristics of the included studies are not reported in the review or its supplementary documents.
- Among the 38 RCTs, a 1% reduction in systolic blood pressure (SBP) predicted a 1% reduction in LVM, P = 0.00001.
- *HCTZ–indapamide comparisons of LVM reduction* (meta-analysis):
  - The difference between CHIP diuretics and HCTZ in reducing LVM varied substantially across trials (n=38) (heterogeneity), making interpretation uncertain. Double-blind trials (n=28) and trials with no background antihypertensive medications had no detectable heterogeneity, so analyses were limited to these trials. Among double-blind trials, there was no detectable publication bias.
  - Among the 28 double-blind trials, HCTZ reduced LVM (percent reduction [95% CI]) by -7.3 (-10.4, -4.2), P < 0.0001. Indapamide were superior to HCTZ by -7.5 (-12.7, -2.3), P=0.005. See figure 3.
  - The results indicate that indapamide reduce LVM 2-fold more than HCTZ among hypertensive patients.
  - The strength of evidence that CHIP diuretics surpass HCTZ for reducing LVM was high (GRADE criteria).
- *HCTZ–indapamide comparisons of reducing SBP and DBP* (meta-analysis):
  - There was no difference between CHIP diuretics and HCTZ: SBP -0.3 (-5.0, +4.3), DBP -1.6 (-5.6, +2.4)
  - There was some evidence of heterogeneity for the SBP and DBP comparisons for double-blind trials, but this did not achieve statistical significance.
  - Authors concluded that although blood pressure is generally related to LVM, it fails to explain the superiority of CHIP diuretics for reducing LVM.

Figure 2. Percent reduction in left ventricular mass from CHIP diuretics relative to HCTZ among trials where there was no detectable heterogeneity



Guidelines

Four relevant guidelines on the management of hypertension (with recommendations that include first-line use of thiazide diuretics) were identified. These guidelines were produced by Hypertension Canada, the National Insitute of Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the European Society of Cardiology and the European Society of Hypertension (ESC/ESH).

Three clinical guidelines (Hypertension Canada 2020, NICE 2011, ESC/ESH 2018) were appraised using the AGREE II tool (see Appendix G), and were found to have good quality of reporting. The references for these three guidelines, the relevant recommendations and selected items from the AGREE II appraisal outcome are presented in Table 5. Relevant recommendations made in the SIGN guideline [SIGN 149: Risk estimation and the prevention of cardiocascuar disease] are based on the NICE guideline presented in Table 5, so recommendations from SIGN 149 are not reported in this report.

Table 5. Clinical guideline quality assessments and recommendations

Citation	Recommendation	Strength of evidence	AGREE II*
Hypertension Canada. Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2020;36:596–624. (19)	*VIII. Choice of therapy for adults with hypertension without compelling indications for specific agents.* *A - Indications for drug therapy for adults with diastolic hypertension with or without systolic hypertension* Recommendations: - Initial therapy should be with either monotherapy or single-pill combination (SPC). - **Recommended monotherapy choices are: a) a thiazide/thiazide-like diuretic (Grade A), with longer-acting diuretics preferred (Grade B)**; b) a β-blocker (in patients younger than 60 years; Grade B); c) an ACE inhibitor (in non-black patients; Grade B); d) an ARB (Grade B); or e) a long-acting CCB (Grade B). - **Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).**	Grade A Grade B Grade C	Rigour of development: 72% Overall score: 92%
National Institute of Health and Care Excellence. Hypertension in adults: diagnosis and management (CG127). London; 2011 (20)	*1.6 Choosing antihypertensive drug treatment* *Step 1 treatment* Recommendations: - Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB. - Do not combine an ACE inhibitor with an ARB to treat hypertension. - Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. **If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.** - **If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.** - **For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide.** - Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly: those with an intolerance or contraindication to ACE inhibitors and angiotensin II receptor antagonists or women of child-bearing potential or people with evidence of increased sympathetic drive. - If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes.		Rigour of development: 96% Overall score: 92%
Citation	**Recommendation**	**Strength of evidence**	**AGREE II***

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. (21)	*7.5.3 Drug treatment strategy for hypertension* Recommendations - Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CBs, and diuretics (thiazides and thiazide-like drugs such a chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. - Combination treatment is recommended for most hypertensive patients as initial therapy.	Class 1 Level A Class 1 Level A	Rigour of development: 79% Overall score: 67%

*AGREE II assessments are presented in Appendix G

A summary of the deliberations and recommendations from the three included clinical guidelines are presented below.

A. Hypertension Canada: Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020) (19)

- Detailed information on the link from evidence to recommendations not provided
- Thiazides and thiazide-like diuretics recommended as monotherapy options (recommendation based on GRADE A evidence: RCTs or systematic reviews with high levels of internal validity and statistical precision), with preference stated for longer-acting diuretics, e.g. indapamide SR preparation (recommendation based on GRADE B evidence: RCTs, systematic reviews or prespecified subgroup analyses of RCTs that have lower precision or there is a need to extrapolate from studies).

B. NICE: Hypertension in adults: diagnosis and management (2004, updated 2006, 2011 and 2019) (20)

- During the 2011 update of the guideline, NICE changed its recommendations regarding the use of thiazides/thiazide-like diuretics as Step 1 therapy options. These recommendations remained unchanged in the 2019 guideline update.
- The guideline recommendations are stratified according to age and ethnicity (people aged under 55 years, people aged over 55 years and to black people of African or Caribbean family origin of any age), and it recommends that people be offered an angiotensin-converting enzyme (ACE) inhibitor, a low-cost angiotensin-II receptor blocker (ARB) or a calcium-channel blocker (CCB) under specified conditions, with thiazide-like diuretics only offered if a CCB is not suitable.
- The recommendations state a preference for thiazide-like diuretics, such as chlortalidone or indapamide, to conventional thiazide diuretics such as bendroflumethiazide or HCTZ, but include a statement that people who are already being treated with bendroflumethiazide or HCTZ and whose blood pressure is stable and well controlled should continue treatment with bendroflumethiazide or HCTZ.
- The guideline development group (GDG) used the NICE 2011 evidence review data presented above (see systematic reviews section), as well as the findings from another meta-analysis conducted as part of the guideline update [review question 8 (9)] , and made the following statements:
  - There were no direct comparisons between the different diuretics with regard to clinical outcomes.
  - Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. The guideline development group (GDG) found it difficult to reach firm conclusions regarding the comparative efficacy of different thiazide-type diuretics with regard to blood pressure lowering.
  - The GDG reviewed the clinical outcome studies with thiazide-type diuretics and found no direct comparator studies between different diuretics. Interpretation of data from head-to-head trials comparing diuretics with placebo or other antihypertensive drugs was complicated by the markedly different diuretic doses used across studies. The GDG noted that there was limited evidence confirming benefit of initial therapy on clinical outcomes with low doses of HCTZ (12.5-25mg o.d).
  - The evidence for the thiazide-like diuretics showed benefits of low dose indapamide or low dose chlorthalidone on a range of clinical outcomes. The evidence was derived from more contemporary studies that had more consistently used lower doses across studies (e.g. indapamide 1.5mg SR or 2.5mg o.d.) The GDG concluded that the consistency of the data suggested that the SR formulation was unlikely to have influenced the clinical outcomes in studies with indapamide.
  - Considering the data, the GDG found it difficult to recommend treatment with low dose thiazide-type diuretics, (e.g. bendroflumethiazide or HCTZ) for which there was no evidence of a benefit on clinical outcomes.
  - Consequently, the GDG recommended that when thiazide-type diuretics are used for the treatment for primary hypertension, thiazide-like diuretics should be preferred to conventional thiazide diuretics. The GDG did not consider it necessary to recommend that those people already treated with low dose thiazides and in whom blood pressure is controlled, should be switched to chlorthalidone or indapamide. However, when new diuretic therapy was to be initiated, then chlorthalidone or indapamide should be preferred.

C. ESC/ESH Guidelines for the management of arterial hypertension (2018) (21)

1. A new concept introduced in this version of the guideline is the preference for the use of two-drug combination therapy for the initial treatment of most people with hypertension, with a single-pill treatment strategy preferred. The use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic is proposed as the core treatment strategy for most patients, with beta-blockers used for specific indications.
2. No preference is stated for either thiazide or thiazide-like diuretics
3. The following statements relating to first-line therapy and thiazides are made in the guideline (21) and supplementary chapters (22):

   Combination therapy

   - A large number of randomized trials confirm that the main benefits of antihypertensive therapy are due to lowering of BP per se, largely independently of the drugs used to lower BP, but also that specific drug classes may differ in some effect or in special groups of patients (22).
   - "It can therefore be concluded that the major classes of antihypertensive agents—diuretics, beta blockers, calcium antagonists, ACE inhibitors, and ARBs—are suitable for the initiation and maintenance of antihypertensive therapy..." "Emphasis on identifying the first class of drugs to be used is probably outdated by the awareness that two or more drugs in combination are necessary in the majority of patients, particularly those with higher initial BPs or subclinical organ damage or associated diseases, in order to achieve target BP."(22)

   Conventional thiazides and thiazide-like diuretics

   - The lack of head-to-head RCTs testing the superiority of thiazide-like diuretics to conventional thiazide diuretics is noted.
   - The availability of studies showing cardiovascular benefits of thiazide-like diuretics is also discussed, noting that these agents are potentially more potent in lowering BP, have a longer duration of action compared with HCTZ, and lack evidence of greater incidence of side effects (18)
   - There is also more RCT evidence supporting the use of low dose thiazide-like diuretics compared to low dose conventional thiazide diuretics.
   - A recent meta-analysis of placebo-controlled studies based on thiazides, chlorthalidone and indapamide reported similar effects on CV outcomes for the three types of diuretics (18)
   - Therefore, in the absence of evidence from direct comparator trials and recognizing that many of the approved single-pill combinations (SPC) are based on HCTZ, the GDG recommended that thiazides, chlorthalidone, and indapamide can all be considered suitable antihypertensive agents.
4. Gaps in the evidence and need for further studies identified includes 'Outcome-based comparison between treatments based on thiazides vs thiazide-like diuretics'.

Summary of the clinical evidence

There were no direct comparisons between the different diuretics with regard to clinical outcomes. Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies (9). Another systematic review found that indapamide reduce left ventricular mass (LVM) 2-fold more than HCTZ in hypertensive patients, but it found no difference between the diuretics reviewed and HCTZ for systolic or diastolic blood pressure. Therefore, changes in blood pressure failed to explain the superiority of indapamide in reducing LVM.

The NICE 2011 guideline recommendation that thiazide-like diuretics are preferred over conventional thiazide diuretics is based on lack of evidence supporting use of conventional thiazide diuretics, not comparative efficacy. ESC/ESH guideline doesn't state preference for either conventional thiazide or thiazide-like diuretics - it recommends two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.

9. ALTERNATIVE AGENTS

Thiazide diuretics can be grouped into conventional thiazide diuretics (e.g. bendroflumethiazide and HCTZ), and thiazide-like diuretics (e.g. chlorthalidone and indapamide), so some of the evidence presented above included references to these medicines.

5. Bendroflumethiazide is not approved for use in South Africa.
6. Chlorthalidone is registered for use with SAHPRA, but only the 50mg tablet has a listed single exit price (SEP). Hygroton (chlortalidone 50mg) medicine SEP = R361.82 per 30 tablets (acquisition cost for one dosing unit = R12.06)

10. PHARMACEUTICAL COSTING AND BUDGET IMPACT DATA

Table 6. Pharmaceutical costs

	Intervention: Indapamide	**Intervention: Indapamide (SR)**	**Comparator: Hydrochlorothiazide (HCTZ)**
Pharmaceutical formulation	Tablet (standard)	Tablet (sustained release)	Tablet (standard)
Method of administration	Oral	Oral	Oral
Average dose/s and dosing schedule/s	One 2.5mg tablet once a day	One 1.5mg SR tablet once a day	One 25mg tablet once a day~
Average daily dose	1 x 2.5mg tablet	1 x 1.5mg tablet	1 x 25mg tablet
Dosing unit	1 tablet	1 tablet	1 tablet
Acquisition cost for one dosing unit (tablet)	R0,61	R4,31	R0,16
Total cost of treatment per month (30 days)	R18,30*	R129,30*	R4,80*
Total cost of treatment per year	R222,65	R1 573,15	R58,40
Estimated pharmaceutical acquisition costs for patient population newly initiated on thiazide diuretics (first-line therapy) in Year 1	R28 732 586	R203 012 207	R7 536 416
Additional annual acquisition costs compared to HCTZ *	R21 196 170	R195 475 791	-

~ 25mg HCTZ was selected as the most appropriate comparator for 2.5mg indapamide (dose equivalence)
*Annual cost assuming 100% market share for each intervention respectively - SEP database, 28 December 2020 (100% of SEP)

Budget impact analysis

Based on the following assumptions, the estimated budget impact of selecting indapamide 2,5mg for inclusion to the EML in the next five years will incur an additional annual cost of R10 598 085 in year 1 rising to R16 983 251 in year 5:

a) **Indapamide 2.5mg market share will be 50% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter.**
b) Only patients initiating first-line antihypertensive treatment are included (incidence only).
c) Only patients accessing public health care services are included.
d) Only 50% of the eligible population (newly diagnosed with essential hypertension) will seek treatment/be treated for hypertension.
e) HCTZ will not be appropriate for 5% of newly diagnosed hypertension patients (CCF, CKD, resistant hypertension, contra-indications).
f) Manufacturer price increases were not taken into account as tenders prices remain unchanged for 3+ years.

g) HCTZ 25mg is considered the most relevant comparator, as this is the technology most likely to be displaced by indapamide 2,5mg and is considered dose equivalent.
h) Health care resource use and adverse event costs have not been considered as they are assumed to be similar for indapamide (intervention) and HCTZ (comparator).

If only the first assumption (a) is changed (rest of the assumptions stay the same) to suggest that 100% of new patients initiated on antihypertensives are given indapamide 2.5mg as first-line treatment (instead of HCTZ), the additional annual pharmaceutical cost incurred will be R21 196 170 in year 1 rising to R23 199 916 in year 5.

See Appendix H for more detailed information about the budget impact analysis.

11.EQUITY CONSIDERATIONS

No significant impact on equity in health for marginalized groups were identified.

12.ACCEPTABILITY CONSIDERATIONS

There is variation in practice and preferences amongst health care professionals. Some clinicians have stated preference for indapamide over HCTZ, evidenced by prescribing patterns in the private health sector. There is a perception amongst clinicians that indapamide is more effective at controlling blood pressure, its pharmacokinetic properties allow for a better 24-hour therapeutic effect compared to HCTZ, and it's less likely to cause metabolic side-effects. Evidence supporting these theories are limited, but this might be due to the lack of high-quality studies investigating the long-term impact of thiazides. In the absence of evidence, clinicians rely on their practical observations, experience and recommendations from international guidelines and professional societies in treating patients with uncomplicated primary hypertension.

13.IMPLEMENTATION CONSIDERATIONS

No significant implementation considerations were identified.

14.EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty based on the NICE 2011 evidence review and report of blood pressure effects. Studies mainly report on the surrogate outcome, blood pressure. The studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. Very limited data on long-term outcomes available.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ x None ☐	Blood pressure: Uncertain benefit potentially favouring indapamide with small, possibly not clinical meaningful, decreases in blood pressure (9,18) Left ventricular hypertrophy: Indapamide may reduce left ventricular mass 2-fold more than HCTZ among hypertensive patients, but the relation between this finding and blood pressure reduction is unclear (18).
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	One systematic review and network meta-analysis reported on metabolic outcomes for indapamide, HCTZ and chlorthalidone. The review was excluded as it was considered a critically low quality review.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☒ x	Indapamide and HCTZ were not detectably different in their effects on serum potassium, sodium, creatinine, glucose, cholesterol or uric acid (18).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ x	Uncertain desirable effect, no detectable difference in undesirable effects. On balance the evidence does not favour either the intervention or the comparison.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	Chlorthalidone discontinued from the South African market.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ x No ☐ Uncertain ☐	No significant implementation considerations were identified.
RESOURCE USE	**How large are the resource requirements?** More intensive ☒ x Less intensive ☐ Uncertain ☐	**Approximately 4-fold relative increase in costs for 1 year if the intervention were introduced.** **Price of medicines** - See detailed information above. **Estimated pharmaceutical cost for 1 year:** • Indapamide 2.5mg: R28 732 586,18

		• Indapamide SR 1.5mg: R203 012 207,29 • HCTZ 25mg: R7 536 416,05
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [x] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Some health care professionals have stated their preference for indapamide over HCTZ, evidenced by prescribing patterns in the private health sector. Education about the evidence based will be needed to improve evidence based prescribing patterns.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	No significant impact on equity in health for marginalized groups were identified.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	16 July 2021	NT, MW, TL, TK	Indapamide not be recommended as first-line treatment of patients with uncomplicated hypertension. Indapamide is unaffordable, but may be considered for inclusion in the therapeutic interchange database as an alternative to HCTZ.
7.1	18 Aug 2022	NT, TL	Response to external comments

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APPENDIX A: REGISTERED INDAPAMIDE PREPARATIONS AVAILABLE IN SOUTH AFRICA [SAHPRA (6)]

Registration number	Registered	Proprietary name	Dosage form	Manufacturer	Ingredients	Pack size	Single Exit Price (ZAR)	
							Pack	Unit
32/7.1.3/0406	2/7/2001	Catexan	Tablet	Biogaran South Africa (PTY) LTD	Indapamide 2,5 mg	30 tablets	18,30	0,61
G/7.1/65	7/26/1974	Natrilix*	Tablet	Servier Laboratories SA (PTY) LTD	Indapamide 2,5 mg	30 tablets	18,84	0,63
30/7.1/0092	2/8/1996	Adco-dapamax	Tablet	Adcock Ingram LIMITED	Indapamide 2,5 mg	30 tablets	18,90	0,63
						600 tablets	378,00	0,63
31/7.1/0099	2/21/1997	Daptril	Tablet	FDC SA (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,29	0,64
						600 tablets	385,98	0,64
29/7.1/0590	12/20/2002	Mylan indapamide 2,5	Tablet	Mylan (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,47	0,65
31/7.1/0097	6/28/1997	Cipla-indapamide	Tablet	Cipla Medpro (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,69	0,66
Z/7.1/203	10/11/1993	Sandoz indapamide 2,5	Tablet	Zimbili Pharma CC, RSA	Indapamide 2,5 mg	30 tablets	26,04	0,87
29/7.1/0266	4/1/1996	Hydro-less	Tablet	Litha Pharma (PTY) LTD	Indapamide 2,5 mg	30 tablets	22,74	0,76
						600 tablets	345,36	0,58
31/7.1/0670	4/14/1998	Indalix	Tablet	Pharmacare LIMITED	Indapamide 2,5 mg	30 tablets	36,65	1,22
						600 tablets	411,98	0,69
31/7.1/0098	6/28/1997	Rilix	Tablet	Xeragen Laboratories (PTY) LTD	Indapamide 2,5 mg	Not available		
35/7.1/0179	11/25/2005	Dinatrix	Tablet	Pharmacare LIMITED	Indapamide 2,5 mg	Not available		
31/7.1/0166	5/2/1997	Natrilix SR	Tablet	Servier Laboratories SA (PTY) LTD	Indapamide 1,5 mg	30 tablets	129.28	4,31

APPENDIX B: REGISTERED HYDROCHLOROTHIAZIDE PREPARATIONS AVAILABLE ON TENDER [MASTER HEALTH PRODUCT LIST – MAY 2021]

Registration number	Registered	Proprietary name	Dosage form	Manufacturer	Ingredients	Pack size	Tender Price (ZAR)	
							Pack	Unit
A39/18.1/0399	9/23/2005	Ridaq Tab 12.5mg 28's	Tablet	Pharmacare Limited	Hydrochlorothiazide 12,5mg	28 tablets	4,1	0,15
M/18.1/35	1/28/1981	Ridaq Tabs 25mg 28's BB	Tablet	Pharmacare Limited	Hydrochlorothiazide 25mg	28 tablets	4,35	0,16
To find		Hydrochlorothiazide 25 Ascendis	Tablet	Dezzo Trading 392 (Pty) Ltd	Hydrochlorothiazide 25mg	28 tablets	4,61	0,16
To find		Gulf Hydrochlorothiazide 25	Tablet	Gulf Drug Company (Pty) Ltd	Hydrochlorothiazide 25mg	28 tablets	4,58	0,16

APPENDIX C: SEARCH STRATEGY

Title: Thiazide – Like Diuretics Compared to Thiazide Diuretics in Patients with Essential Hypertension
Database: CENTRAL (Issue 3 of 12, March 2021) & CLIB (Issue 4 of 12, April 2021)
Date: 29 April 2021

ID	Search	Hits
#1	[mh hypertension] or hypertens*:ti,ab (Word variations have been searched)	58898
#2	(high or rais* or rising OR increas* or elevat* or lower) near/3 ("blood pressure" or "diastolic pressure" or "systolic pressure" or "arterial pressure"):ti,ab (Word variations have been searched)	16172
#3	(high or rais* or rising OR increas* or elevat* or lower) near/4 (bp or dbp or hbp or sbp):ti,ab (Word variations have been searched)	6233
#4	#1 or #2 or #3	68974
#5	[mh indapamide] or indapamide:ti,ab,kw or metindamide:ti,ab,kw or lozol:ti,ab,kw (Word variations have been searched)	664
#6	[mh Hydrochlorothiazide] or Hydrochlorothiazide:ti,ab,kw or microzide:ti,ab,kw or esidrix:ti,ab,kw or maxzide:ti,ab,kw or dichlothiazide:ti,ab,kw or oretic:ti,ab,kw or esidrex:ti,ab,kw OR hypothiazide:ti,ab,kw (Word variations have been searched)	3984
#7	#4 and #5 and #6	75
#8	("thiazide-like" or thiazide) near/3 diuretic*:ti,ab,kw	937
#9	#4 and #8	724
#10	#7 or #9 in Cochrane Reviews	14
#11	#7 or #9 in Trials	770

Title: Thiazide – Like Diuretics Compared to Thiazide Diuretics in Patients with Essential Hypertension
Database: PubMed
Date: 29 April 2021

Search	Query	Results
#12	Search: (#7 OR #9) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review Sort by: Most Recent	46
#10	Search: #7 OR #9 Sort by: Most Recent	2,428
#9	Search: #4 AND #8 Sort by: Most Recent	2,322
#8	Search: ("Thiazide-like"[tiab] OR thiazide[tiab]) AND diuretic*[tiab] Sort by: Most Recent	3,547
#7	Search: #4 AND #5 AND #6 Sort by: Most Recent	170
#6	Search: Hydrochlorothiazide[mh] OR Hydrochlorothiazide*[tiab] OR microzide[tiab] OR esidrix[tiab] OR maxzide[tiab] OR dichlothiazide[tiab] OR oretic[tiab] OR esidrex[tiab] OR hypothiazide[tiab] Sort by: Most Recent	9,190
#5	Search: indapamide[mh] OR indapamide*[tiab] OR metindamide*[tiab] OR lozol[tiab] Sort by: Most Recent	1,399
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	731,354
#3	Search: (High[tiab] OR rais*[tiab] OR rising[tiab] OR increas*[tiab] OR elevat*[tiab] OR lower[tiab]) AND (bp[tiab] OR dbp[tiab] OR hbp[tiab] OR sbp[tiab]) Sort by: Most Recent	99,280
#2	Search: (High[tiab] OR rais*[tiab] OR rising[tiab] OR increas*[tiab] OR elevat*[tiab] OR lower[tiab]) AND (blood pressure[tiab] OR diastolic pressure[tiab] OR systolic pressure[tiab] OR arterial pressure[tiab]) Sort by: Most Recent	261,076
#1	Search: Hypertension[mh] OR hypertens*[tiab] Sort by: Most Recent	521,426

APPENDIX D: EVALUATING THE METHODOLOGICAL QUALITY OF SYSTEMATIC REVIEWS - AMSTAR 2 TOOL

	NICE 2011 evidence review (9) – **Moderate quality review**	Yes/ Partial Yes/ No
No.	**Criteria**	**Consensus**
1	Did the research questions and inclusion criteria for the review include the components of PICO?	**Yes**
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**Partial Yes**
3	Did the review authors explain their selection of the study designs for inclusion in the review?	**Yes**
4	Did the review authors use a comprehensive literature search strategy?	**Partial Yes**
5	Did the review authors perform study selection in duplicate?	**Yes**
6	Did the review authors perform data extraction in duplicate?	**Yes**
7	Did the review authors provide a list of excluded studies and justify the exclusions?	**No**
8	Did the review authors describe the included studies in adequate detail?	**Yes**
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	**Partial Yes**
10	Did the review authors report on the sources of funding for the studies included in the review?	**No**
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	**Yes**
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	**Yes**
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	**Yes**
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	**Yes**
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	**No**
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Yes**

	ROUSH 2018 (10) – Moderate quality review	Yes/ Partial Yes/ No
No.	**Criteria**	**Consensus**
1	Did the research questions and inclusion criteria for the review include the components of PICO?	**Yes**
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**Yes**
3	Did the review authors explain their selection of the study designs for inclusion in the review?	**Yes**
4	Did the review authors use a comprehensive literature search strategy?	**Yes**
5	Did the review authors perform study selection in duplicate?	**Yes**
6	Did the review authors perform data extraction in duplicate?	**Yes**
7	Did the review authors provide a list of excluded studies and justify the exclusions?	**No**
8	Did the review authors describe the included studies in adequate detail?	**No**
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	**Partial Yes**
10	Did the review authors report on the sources of funding for the studies included in the review?	**No**
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	**Yes**
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	**Yes**
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	**Yes**
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	**Yes**
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	**Yes**
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Yes**

APPENDIX E: SYSTEMATIC REVIEWS EXCLUDED AFTER FULL TEXT SCREENING

Author, date	Type of study	Reason for exclusion
Roush 2015 (18)	Systematic review	The systematic review and meta-analysis of head-to-head randomized controlled trials investigated how HCTZ compares with indapamide in terms of antihypertensive and metabolic effects. The review had a similar scope to the NICE 2011 evidence review (findings included in this medicine review), but included some additional studies excluded from the NICE 2011 evidence review. These additional studies were focused on more restrictive populations [diabetic patients (23), chronic kidney disease (24), excluded insulin-dependent patients (25)], had different outcome measures [metabolic changes (26)], or included patients receiving concomitant baseline treatments [enalapril at baseline (27)]. Findings from Roush 2015 are not presented in this medicine review after AMSTAR assessment indicated it to be of critically low quality and seeing that its scope significantly overlaps with NICE 2011 evidence review (which was assessed to be a review of moderate quality). Roush 2015 provided some information on metabolic outcomes (no significant difference between indapamide and HCTZ).
Zhang 2016 (28)	Systematic review	The review aimed to assess to the effects of thiazide-type diuretics on glycaemic metabolism in hypertensive patients. Studies included in the review included monotherapy and combination therapy regimes.
Olde Engberink 2015 (29)	Systematic review	The review investigated the effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality. Studies included in the review included monotherapy and combination therapy regimes. HCTZ were mostly given as part of combination therapy.
Liang 2017 (30)	Systematic review	The authors summarized the existing evidence on the two types of drugs and conducted a meta-analysis on their efficacy in lowering blood pressure and effects on blood electrolyte, glucose, and total cholesterol. Studies included in the review included monotherapy and combination therapy regimes.

APPENDIX F: CHARACTERISTICS OF HEAD-TO-HEAD RCTS (INDAPAMIDE/HCTZ COMPARISON ONLY) INCLUDED IN NICE 2011 EVIDENCE REVIEW

Authors (year)	N	Population	Intervention	Comparator	Design	Outcomes measured	Results
Kreeft, 1984 (12)	17	Patients 34-66 years in age with uncomplicated essential hypertension	Indapamide 2.5mg/day	HCTZ (50mg/day)	Randomized, placebo-controlled, double-blind cross-over study 2 months placebo run-in, 12 weeks thiazide diuretic drug, 2 months placebo washout, 12 weeks alternate thiazide diuretic drug	Standing systolic/diastolic pressure Orthostatic changes in mean pressure and heart rate Serum potassium, serum uric acid and cholesterol.	No significant difference in blood pressure between groups. Similar changes in serum potassium, serum uric acid and cholesterol.
Plante, 1988 (13)	47	Elderly hypertensive patients (ages 65 to 91)	Indapamide 2.5mg/day	HCTZ (50mg/day)	Randomized 6-week placebo-treatment period, followed by 48 weeks active therapy	Blood pressure and serum chemistry	Indapamide better for reduced blood pressure (no P value reported) and was less likely to be associated with hyponatremia and hypokalaemia.
Plante, 1983 (11)	24	Patients with mild arterial hypertension	Indapamide 2.5mg/day	HCTZ (50mg/day)	Double-blind, controlled 4-6 week washout placebo period, followed by 12 weeks active therapy.	Blood pressure and pulse rate in the recumbent and upright positions. Laboratory measurements of plasma electrolytes, other biochemical and haematological parameters.	Indapamide better for reduction in diastolic blood pressure in the recumbent position. Some significant changes in plasma electrolytes (both groups) and serum uric acid (HCTZ group) but none of clinical importance
Spence, 2000 (14)	39	Patients with mild to moderate hypertension	Indapamide 2.5mg/day	HCTZ (25mg/day)	Randomized, double-blind 6 months	Blood pressure Potassium and chloride Plasma total cholesterol, high density lipoprotein, apolipoprotein A1, apolipoprotein B, triglycerides. Plasma glucose	No significant difference in blood pressure between groups No significant differences in the reduction of potassium and chloride Neither drug was associated with a significant change in plasma total cholesterol, high density lipoprotein, apolipoprotein A1, apolipoprotein B or the ratio of total cholesterol to HDL levels. Triglyceride levels increased significantly more with indapamide than with HCTZ (P=0.02). Neither drug affected plasma glucose.

Authors (year)	N	Population	Intervention	Comparator	Design	Outcomes measured	Results
Brandao, 2010 (15)	94	Patients recently diagnosed hypertension on stage 1, with no other risk factors, and naive of antihypertensive medication	Indapamide 1.5mg/day (SR)	HCTZ (25mg/day)	Randomized 12 weeks. Addition of ACE inhibitor at 6 weeks if target BP not met.	Antioxidized low-density lipoprotein antibodies Office-based and 24-h ambulatory blood pressure measurements	No significant difference in blood pressure (office or 24-h ambulatory blood pressure) between groups
Emeriau, 2001 (16)	524	Elderly hypertensive patients (mean age: 72.4 years)	Indapamide 1.5mg/day (SR)	HCTZ (25mg/day) Amlodipine (5 mg/day)	Randomized, double-blind, controlled 4-week washout placebo period; 12 weeks treatment	Clinic systolic and diastolic blood pressure variations	Similar reduction in blood pressure between groups (equivalence test)
Elliot, 1991 (17)	11	Hypertensive patients with serum uric acid concentrations greater than 8.0 mg/dL while receiving previous therapy with thiazides	Indapamide 2.5mg/day or HCTZ (25 mg/day)	Placebo (lactose)	Double-blind, randomized, placebo-controlled, double-crossover 28 days	Supine and standing blood pressures, weight, pulse rates and sera	No significant difference in blood pressure between groups. Urate concentration with indapamide was significantly lower than that with HCTZ ($p<0.02$), but the magnitude of the difference was small.

APPENDIX G: EVALUATING THE METHODOLOGICAL QUALITY OF CLINICAL GUIDELINES – AGREE II

Hypertension Canada: 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children

AGREE II assessment scores																								
Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	6	7	6	5	6	7	6	2	6	6	6	5	6	7	6	6	7	7	4	6	7	7	7
Appraiser 2	7	7	7	7	4	7	5	6	3	7	5	1	7	7	7	4	7	5	3	3	5	7	7	6
Item total	14	13	14	13	9	13	12	12	5	13	11	7	12	13	14	10	13	12	10	7	11	14	14	13
Domain total	41			35			85								37			40				28		13
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**97**			**81**			**72**								**86**			**67**				**100**		**92**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{axumim possible score - minimum possible sco}} \times 100$$

NICE: Hypertension - The clinical management of primary hypertension in adults (CG127)

AGREE II assessment scores																								
Hypertension: The clinical management of primary hypertension in adults (CG127)																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	6	7	7	6	7	6	7	7	6	7	6	7	7	6	7	7	7	7	7	7
Appraiser 2	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	4	5	7	5	6	6	6
Item total	14	14	14	14	13	14	14	13	14	13	14	14	12	14	13	14	14	10	12	14	12	13	13	13
Domain total	42			41			108								41			48				26		13
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**100**			**97**			**96**								**97**			**83**				**92**		**92**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{laxumim possible score - minimum possible sco}} \times 100$$

2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension

AGREE II assessment scores																							
2018 ESC/ESH Guidelines for the management of arterial hypertension																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	6	7	4	1	7	4	4	4	5	5	5	4	6	7	7	7	6	7	1	3	4	5	4
Appraiser 2	7	7	6	7	3	6	7	7	6	7	7	7	7	7	7	7	7	4	7	3	7	7	7	6
Item total	14	13	13	11	4	13	11	11	10	12	12	12	11	13	14	14	14	10	14	4	10	11	12	10
Domain total	40			28			92								42			38				23		10
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**94**			**61**			**79**								**100**			**63**				**79**		**67**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{maxumim possible score - minimum possible sco}} \times 100$$

APPENDIX H: PHARMACEUTICAL BUDGET IMPACT ANALYSIS

This budget impact analysis presents the relative acquisition costs of indapamide and HCTZ for consideration in addition to the evidence of the relative clinical effect.

Technology under review: Indapamide

Description		**Source**
Acquisition cost per annum	R222.65	Single exit price for lowest indapamide 2.5mg tablet (Catexan)
Method of administration	Oral	Prescribing information
Dosage	2.5mg once a day	Prescribing information
Average length of a course of treatment	Ongoing (chronic)	Prescribing information
Dose adjustments	Not applicable	Prescribing information

Table adapted from the NICE budget impact analysis template

HCTZ 25mg is considered the most relevant comparator, as this is the technology most likely to be displaced by Indapamide and is considered dose equivalent.

Uptake and market share

Five-year estimates for the following implementation scenarios are provided:

1. Status Quo: No change with all eligible patients receiving HCTZ
2. Rapid adoption of indapamide: Indapamide 2.5mg market share will be 50% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter
3. Slow adoption of indapamide: Indapamide 2.5mg market share will be 25% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter

Market share for indapamide and HCTZ for all eligible patients receiving first line antihypertensive treatment each year

Scenario	**Treatment**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Status Quo: existing treatment(s) only	Indapamide	0%	0%	0%	0%	0%
	HCTZ	100%	100%	100%	100%	100%
Rapid Adoption Scenario	Indapamide	50,00%	55,00%	60,50%	66,55%	73,21%
	HCTZ	50,00%	45,00%	39,50%	33,45%	26,80%
Slow Adoption Scenario	Indapamide	25,00%	27,50%	30,25%	33,28%	36,60%
	HCTZ	75,00%	72,50%	69,75%	66,73%	63,40%

Eligible population

The eligible patient population has been calculated under the following assumptions:

- Only patients newly initiated on first-line antihypertensive treatment are included (incidence only).
- Only patients accessing public health care services are included (84% of SA population).
- Only 50% of the eligible population (newly diagnosed with essential hypertension) will seek treatment for hypertension.
- HCTZ will not be appropriate for 5% of newly diagnosed hypertension patients (CCF, CKD, resistant hypertension, contra-indications).

Resources

Health care resource use and adverse event costs have not been considered in this budget impact analysis as they are assumed to be the similar for indapamide (intervention) and HCTZ (comparator).

Drug acquisition costs for indapamide and HCTZ

Cost type	Cost (ZAR)*	Unit
Indapamide 2.5mg	R222.65	Per person for one year
Indapamide 1.25mg	R1 573.15	Per person for one year
HCTZ 25mg	R58.40	Per person for one year

*SEP database, 28 December 2020 (100% of SEP)

Manufacturer price increases were not considered in this budget impact analysis.

Estimates of annual budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Rapid adoption implementation scenario					
Indapamide acquisition costs	R14 366 293	R16 163 272	R18 185 407	R20 460 958	R23 021 741
HCTZ acquisition costs	R3 768 208	R3 468 720	R3 114 260	R2 697 517	R2 210 249
Total acquisition costs	*R18 134 501*	*R19 631 992*	*R21 299 667*	*R23 158 475*	*R25 231 990*
Slow adoption implementation scenario					
Indapamide acquisition costs	R7 183 146	R8 081 636	R9 092 703	R10 230 479	R11 510 870
HCTZ acquisition costs	R5 652 312	R5 588 493	R5 499 231	R5 380 921	R5 229 494
Total acquisition costs	*R12 835 458*	*R13 670 129*	*R14 591 935*	*R15 611 400,*	*R16 740 364*
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with rapid adoption of the new technology	R10 598 085	R11 923 725	R13 415 464	R15 094 150	R16 983 251
> In a market with slow adoption of the new technology	R5 299 042	R5 961 862	R6 707 732	R7 547 075	R8 491 625

Additional analyses

1. Change in market share assumptions: all eligible patients are switched to indapamide in year 1

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Complete switch to indapamide implementation scenario					
Indapamide acquisition costs	R28 732 586	R29 387 768	R30 058 524	R30 745 242	R31 448 317
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with complete switch from HCTZ to Indapamide	R21 196 170	R21 679 501	R22 174 321	R22 680 916	R23 199 578

2. Variation in cost of indapamide (acquisition cost of indapamide is reduced by 40%)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Rapid adoption implementation scenario					
Indapamide acquisition costs	R8 619 775	R9 697 963	R10 911 244	R12 276 575	R13 813 044
HCTZ acquisition costs	R3 768 208	R3 468 720	R3 114 260	R2 697 517	R2 210 249
Total acquisition costs	*R12 387 983*	*R13 166 683*	*R14 025 504*	*R14 974 092*	*R16 023 294*
Slow adoption implementation scenario					
Indapamide acquisition costs	R4 309 887	R4 848 981	R5 455 622	R6 138 287	R6 906 522
HCTZ acquisition costs	R5 652 312	R5 588 493	R5 499 231	R5 380 921	R5 229 494
Total acquisition costs	*R9 962 199*	*R10 437 475*	*R10 954 854*	*R11 519 209*	*R12 136 016*
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with rapid adoption of the new technology	R4 851 567	R5 458 416	R6 141 301	R6 909 766	R7 774 555
> In a market with slow adoption of the new technology	R2 425 783	R2 729 208	R3 070 650	R3 454 883	R3 887 277

Date: 21 July 2022

Response to external comments on the HCTZ vs indapamide review

Hydrochlorothiazide (HCTZ) is the first line (monotherapy) pharmacological treatment for uncomplicated hypertension recommended in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa. In the past HCTZ has been used successfully in the South African clinical landscape with minimal adverse metabolic effects in the majority of uncomplicated hypertensive patients.

When compared to indapamide, HCTZ is suggested to have limited efficacy. However, much of the available published data is suboptimal and does not compare these two agents on a head-to-head design with hard clinical outcomes. The current positions taken by some clinical guidelines to prefer thiazide-like diuretics over thiazide diuretics is largely based on the presumed improved BP lowering effect and favourable side effect profile, rather than on comparative efficacy. While other studies have investigated comparative efficacy of HCTZ and chlorthalidone, these have not been considered as chlorthalidone is not available in South Africa.

Due to the inconclusive evidence the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines do not state preference for either conventional thiazide or thiazide-like diuretics – instead these guidelines recommend two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada 2020 and the International Society of Hypertension guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.

Current evidence supporting the use of indapamide over HCTZ is of low quality with uncertain impact on important clinical outcomes. In addition, indapamide is almost four times more expensive than HCTZ and a large South African patient population would be eligible to receive the treatment each year. Including indapamide as a first-line treatment option will therefore have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. The Expert Review Committee therefore does not support the introduction of indapamide as a first line agent. Furthermore, with increasing awareness of the benefits of upfront combination therapy in appropriately risk stratified hypertensives, the case for changing first line monotherapy is now less compelling.