health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
ADULT HOSPITAL CHAPTER 3: CARDIOVASCULAR SYSTEM
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
3.1 Ischaemic heart disease and atherosclerosis, prevention	Target BMI	Amended
	Alcohol intake	Aligned
	Exercise	Guidance amended
	Aspirin, oral	Not added (for primary prevention)
	SCORE risk score	Not added
	BMI-based risk score	Replaced and now added to new Appendix VII
	Framingham risk score	Retained
	Treat-to-target approach	Not added
	Hypertriglyericeridemia management	Not added (referred to tertiary level)
	Familial hyerpcholesterolemia management	Not added (referred to tertiary level)
- *statin therapy*	Simvastatin	Retained
	HMGCoA reductase inhibitors (statins)	Retained
- *secondary prophylaxis*	Stain therapy e.g. of class	Amended
3.2.1 ST elevation myocardial infarction (STEMI)	Aspirin, oral	Loading dose not amended
	Oxygen	Directions for use not amended
	Clopidogrel, oral	Dose not amended
	Prasugrel, oral	Not added
	Ticagrelor, oral	Not added
	Streptokinase, parenteral	Directions for use not amended
	Alteplase, parenteral	Dosing amended
- *Thrombolytics*	Streptokinase	Retained as first-line option
	Thrombolytic therapy – considerations for initiating thrombolytics	Guidance clarified
	Alteplase	Retained as second-line option
	Tenecteplase	Added to the therapeutic interchange database
- *Adjunctive therapy*	Enoxaparin	Dosing not amended
	Enoxaparin (co-administered with streptokinase)	Not added
	Enoxaparin (co-administered with alteplase/tenecteplase)	Directions for use amended
- *For ongoing chest pain to control hypertension or to treat pulmonary oedema*	Glyceryl trinitrate (GTN), IV	Amended
- *Clinically stable*	Statin therapy	Aligned with section 3.1
- *LV dysfunction following myocardial infarction*	Angiotensin II receptor blocker	Directions for use amended
	Spironolactone	Not added
- *Referral*	Failed perfusion referral criterion	Amended
3.2.2 Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)	NSTEMI description	Amended
	Referral criteria	Amended to include cardiogenic shock
	Transfer for PCI	Not amended
	Clopidogrel, oral	Duration of therapy not amended
	Aspirin	Dose not amended

	Enoxaparin	Retained as first line option
	Unfractionated heparin	Not deleted and retained as second line option
	Statin therapy	Aligned with section 3.1
	Angiotensin II receptor blocker	Directions for use amended
- LV dysfunction following myocardial infarction	Spironolactone	Not added
3.2.3 Chronic management of STEMI/NSTEMI/UA	Clopidogrel	Not added
	Aspirin	Not added
	Statin (high dose)	Not added
	ACE-inhibitor	Not added
	Angiotensin II receptor blocker	Not added
	Beta-blocker	Not added
	Spironolactone	Not added
3.2.4 Angina pectoris, stable *and* **3.2.5 Atherosclerotic peripheral arterial disease**	Statin therapy	Aligned with section 3.1
	Isosorbide dinitrate- frequency of dosing:	Retained
3.3.1.1 Atrial fibrillation	Aspirin	Deleted
	Clopidogrel + warfarin	Not added
	CHA2DS2-VASc Score:	Directions for use not amended
	HAS-BLED score	Added
	Warfarin	Directions for use amended
	DOAC therapy	Not added
-Patients with severe symptoms	Amiodarone – concomitant use with digoxin:	Guidance amended
3.3.1.2 Atrial flutter	Description	Editorial amendment
- DC conversion	Midazolam, IV	Retained
- *Initial therapy - If vagal manoeuvres fail*	Adenosine, IV	Dosing and directions for use not amended
3.3.2.1 Regular wide QRS tachycardias	Amiodarone – concomitant use with digoxin:	Guidance amended
3.3.2.3 Non-sustained (<30 seconds) irregular wide QRS tachycardias	Amiodarone, oral – dosing guidance:	Amended
	Amiodarone – concomitant use with digoxin:	Guidance amended
	Lidocaine (Lignocaine), IV – dosing guidance:	Amended
3.4 Congestive cardiac failure (CCF)	Salt restriction	Retained
- *Mild CCF (normal renal function)*	Hydrochlorothiazide, oral: retained	Retained
- Renin-angiotensin-aldosterone system (RAAS) blockers	Angiotensin II receptor blocker	Directions for use amended
- Spironolactone	Spironolactone, oral	Directions for use not amended
	Potassium supplements	Directions for use not amended
-Beta-blockers	Carvedilol, oral	Dosing amended
3.5 ENDOCARDITIS, INFECTIVE	Vancomycin, IV	Dosing amended
- Empiric therapy – native valve	Benzylpenicillin (penicillin G), IV	Deleted
	Ampicillin, IV	Added
	Cloxacillin, IV	Added as first-line option to cefazolin
	Cefazolin, IV	Retained as second-line option to cefazolin
- Empiric therapy – prosthetic valve	Vancomycin, IV	Retained
	Rifampicin, IV	Retained
- Directed therapy (native valve) – streptococcal: fully/moderately resistant	Ampicillin, IV	Added
	Benzylpenicillin (penicillin G), IV	Retained
- Directed therapy (native valve) – enterococcal: susceptible to penicillin	Ampicillin, IV	Added
	Benzylpenicillin (penicillin G), IV	Retained
	Ceftriaxone, IV	Added
- Directed therapy (native valve) – staphylococcal	Cloxacillin, IV	Added as first-line option to cefazolin
	Cefazolin, IV	Retained as second-line option to cefazolin
	Gentamicin, IV	Deleted
3.6 Hypertension	Alcohol (lifestyle modifications)	Guidance amended
	Classification of hypertension	Not amended
	Target blood pressure	Not amended
	Target BMI	Amended

	Indapamide, oral	Not added to the STG, but listed in the therapeutic interchange database
	Hydrochlorothiazide, oral	Retained in the STG as example of therapeutic class
	Dual therapy	Directions for use not amended
	Enalapril, oral	Dosing not amended
	Angiotensin II receptor blocker	Directions for use amended
	Amiloride, oral	Not added
	Bisoprolol, oral	Not added to the STG, but listed in the therapeutic interchange database
	Atenolol, oral	Retained in the STG as example of therapeutic class
	Prescribing of antihypertensive medication – timing of doses	Amended
	Hypertension algorithm	Amended
3.6.1 Hypertension, asymptomatic severe	Anxiolytic agent	Not added
3.6.2 Hypertensive urgency	Management	Amended (specialist consult)
3.6.3 Hypertensive crisis, hypertensive emergency	Angiotensin II receptor blocker	Directions for use amended
APPENDIX II – Prescribing information for specific Medicines	Warfarin	Amended
APPENDIX VII – Cardiovascular risk assessment		New chapter added

3.1 ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS, PREVENTION

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[1] that informed the National Heart, Lung, and Blood Institute (NHLBI) guidelines[2].

Level of Evidence: Low certainty evidence

Alcohol intake**:** *aligned*

Guidance on reducing alcohol intake has been aligned to Section 3.6 Hypertension

Exercise: *guidance amended*

The STG was editorially amended as follows for clarity:

AMENDED FROM:

All persons should be encouraged to make the following lifestyle changes as appropriate:

» Smoking cessation.
» Weight reduction in overweight patients, i.e. BMI >25 kg/m^2.
» Maintain ideal weight, i.e. BMI <25 kg/m^2.
» Reduce alcohol intake to no more than 2 standard drinks/day
» Follow a prudent eating plan i.e. low saturated fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables.
» Moderate aerobic exercise, e.g. 40 minutes brisk walking at least 3 times a week.

AMENDED TO:

All persons should be encouraged to make the following lifestyle changes as appropriate (consult dietitian, if available):

» Smoking cessation.
» Weight reduction in overweight patients, i.e. maintain BMI 18.5 to 25 kg/m2.
» 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 saturated fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables.
» Moderate aerobic exercise, e.g. 30 minutes brisk walking 5-7 times/week (150 minutes/week).

[1] 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/

[2] 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/

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[3]. 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

Cardiovascular Risk Assessment

SCORE risk score: *not added*

BMI-based risk score: *replaced and now added to new Appendix VII*

Reference to the online BMI-based risk calculator in the PHC CV chapter, 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 VII: Cardiovascular risk assessment, which has been adapted with permission from the Knowledge Translation Unit and authors of the 2023 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.

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

[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

- 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 VII: 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.

Hypertriglyericeridemia management: *not added (referred to tertiary level)*

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

External comment received that management for hypertriglyericeridemia and 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.

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]

[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). S Afr Med J.

[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

3.2.1 ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

General: External comments received that generally related to percutaneous coronary intervention, noting that routine coronary intervention (pharmaco-invasive approach) for STEMIs is successfully lysed;[12] but locally the cardiologist-to- patient ratio and the lack of sufficient PCI facilities does not make this option universally feasible.

Thus, under the "Medicine Treatment" section, the following statement was included in the STG:

Note: The following guidance is not for primary percutaneous coronary intervention.

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[13] 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).

Oxygen: *directions for use not amended*

External stakeholder comment indicated that the South African Society of Cardiovascular Intervention (SASCI) recommended 90% as a cut-off,[14] for oxygen administration. The cut-off for oxygen administration was retained as 94% in the STG. Refer to the evidence summary on the use of oxygen therapy for ST elevated myocardial infarction (STEMI)[15] included below. The SPO_2 levels as included in the STG, are informed by the available evidence. 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

[12] Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England Journal of Medicine. 2013 Apr 11;368(15):1379-87.

[13] 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.

[14] DETO2X-SWEDEHEART STUDY. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. New England Journal of Medicine. 2017;377(13):1240-9.

[15] 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[16] 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.

Clopidogrel, oral: *dose not amended*

External comment received to add a loading dose for clopidogrel of 300mg, but 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):

Clopidogrel, oral: loading dose not added to treatment protocol for STEMI

The Adult Hospital Level Committee upheld the previous review cycle (2012-2015) recommendation not to include a loading dose of clopidogrel 300 mg to the treatment protocol for management of STEMI at secondary level of care.

Rationale: The COMMIT RCT[17] is generalisable to local practice as patients received 75 mg of clopidogrel daily with fibrinolytic therapy, mainly urokinase that is similar to streptokinase (54% of patients, n=24967, before or after randomisation).

In the CLARITY RCT[18], where patients were administered a loading dose of clopidogrel 300 mg followed by 75 mg daily, 99.7% patients received fibrinolytic agents; however the majority of patients underwent angiography.

A loading dose in STEMI is based on the assumption that patients will go for primary Percutaneous Coronary Intervention (PCI) and coronary stenting. As this is not possible at present in most public sector hospitals (secondary or tertiary) in South Africa, the closest generalizable evidence to our setting is the COMMIT RCT, where patients were administered clopidogrel at a dose of 75 mg, without a loading dose.

Loading dose of clopidogrel, 300 mg not be recommended due to associated risk of bleeding when co-administered with antiplatelet agents and streptokinase.

Level of Evidence: I COMMIT RCT

Prasugrel, oral: *not added*

Ticagrelor, oral: *not added*

External comment that prasugrel or ticagrelor can be used as an alternative for clopidogrel without supporting evidence. As the current review cycle is drawing to a close, consideration to be made to add these items to the project plan for the next review cycle.

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.

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

[17] Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005 Nov 5;366(9497):1607-21. http://www.ncbi.nlm.nih.gov/pubmed/16271642

[18] Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005 Mar 24;352(12):1179-89. http://www.ncbi.nlm.nih.gov/pubmed/15758000

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.

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 and consult a specialist - (see section 3.2.2: NSTEMI) - if on-going ischaemic pain	» Absolute: - streptokinase used within the last year, - previous allergy, - Confirmed 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.

AMENDED TO:

» For acute myocardial infarction with ST elevation or left bundle branch block: - maximal chest pain is ≤6 hours - if beyond 6 hours and ongoing chest pain - >6 hours and no chest pain, thrombolytic not indicated (see section 3.2.2: NSTEMI)	» Absolute: - streptokinase used within the last year, - previous allergy, - Confirmed 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 3.2: Indications and contraindications for streptokinase

Alteplase, parenteral: dosing amended
Dosing was aligned to SAMF 2022 guidance, using 65kg to tier the dosing for alteplase 3-hour infusion.
Level of Evidence: Very low certainty, conditional recommendation

[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

The STG text was amended as follows:

	Bolus	Next 30 minutes	Next 60 minutes
>~~67~~ 65 kg	15 mg	50 mg	35 mg
≤~~67~~ 65 kg	15 mg	0.75 mg/kg	0.5 mg/kg

If streptokinase is unavailable

Streptokinase: *retained as first-line option*

Alteplase: *retained as second-line option*

Despite alteplase being the preferred option, streptokinase is the more affordable option, with a cost differential per patient of R9823,40.[21]

Tenecteplase: *added to the therapeutic interchange database*

External motivation received that tenecteplase should be widely available as a single bolus dose and because of its ease of use. However, tenecteplase 40mg is unaffordable with an incremental cost of R7748,62 when 60% of SEP is compared to the tender price of streptokinase 1.5MU. Tenecteplase is thus, not listed in the STG, but listed as a therapeutic option in the therapeutic interchange database as tabulated below.

Indication	Therapeutic class	INN	Strength (mg)	formulation
Thrombolytic therapy in acute myocardial infarction	Thrombolytics	Streptokinase	1.5MIU	Injection
Thrombolytic therapy in acute myocardial infarction	Thrombolytics	Alteplase	50mg*	Injection
Thrombolytic therapy in acute myocardial infarction	Thrombolytics	Tenecteplase	40 or 50mg	Injection

***Dose requires 2X 50mg vials**

Adjunctive therapy

Enoxaparin: *dosing not amended*

External comment received that enoxaparin maintenance dosing option of 1.5mg/kg daily be deleted from the STG, as international guidelines only recommends the 1mg/kg 12 hourly dose. However, NEMLC ratified both dosing option based on a NEMLC-approved review of LMWH for venous thromboembolism and acute coronary syndrome in adults (April 2018)[22] and a systematic review.[23]

Enoxaparin (co-administered with streptokinase): *not added*

An external comment was received to consider heparin use after streptokinase and to amend the STG language from the contra-indication, "*Do not use heparin if streptokinase is given*". However, the previous NEMLC-approved recommendation was upheld – refer to the extract from the NEMLC report for the 2017-19 review of the cardiovascular chapter.[24]

Enoxaparin (co-administered with alteplase/tenecteplase[3]): *directions for use amended*

Duration for acute treatment for STEMI was recommended to a maximum of 8 days, guided by RCT protocols[4] cited in the European Society of Cardiology STEMI clinical guidelines[5]. The STG text was amended accordingly.

Level of Evidence: High certainty, strong recommendation

For ongoing chest pain to control hypertension or to treat pulmonary oedema – glyceryl trinitrate (GTN), IV: *Amended*

Guidance on the dilution and administration of GTN IV has been amended to accommodate for the different strengths of GTN IV formulations available which is now being procured through a Section 21 approval due to lack of a local supplier. Guidance has also been clarified as a step by step approach as tabulated below:

AMENDED FROM:
For ongoing chest pain, to control hypertension or treat pulmonary oedema:

[21] Contract circular HP06-2021SVP/01: Streptokinase 1.5MU= R4640.80; Alteplase 100mg = R14 464.20
13 SEP database, November 2022

[22] NDoH: LMWH for VTE and ACS - Adult review,_April2018

[23] Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074

[24] https://www.knowledgehub.org.za/elibrary/hospital-level-adults-nemlc-evidence-reports-2019.

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  - Start with 5 mcg/minute and increase by 5 mcg/minute every 5 minutes until response or until the rate is 20 mcg/minute.
  - No response after 20 mcg/minute, increase by 20 mcg/minute every 5 minutes until a pain response or medicine is no longer tolerated.
  - Flush the PVC tube before administering the medicine to patient.
  - Monitor BP carefully.

Dilution of Glyceryl trinitrate:

Volume of diluent	Glyceryl trinitrate 5mg/mL	Concentration of dilution
250 mL	5 mL (25 mg)	100 mcg/mL
	10 mL (50 mg)	200 mcg/mL
	20 mL (100 mg)	400 mcg/mL
500 mL	10 mL (50 mg)	100 mcg/mL
	20 mL (100 mg)	200 mcg/mL
	40 mL (200 mg)	400 mcg/mL

Solution Concentration (mcg/mL)	100 mcg/mL solution	200 mcg/mL solution	400 mcg/mL solution
Dose (mcg/min)	Flow rate (microdrops/min = mL/hour)		
5	3	—	—
10	6	3	—
15	9	—	—
20	12	6	3
30	18	9	—
40	24	12	6
60	36	18	9
80	48	24	12
100	60	30	15
120	72	36	18
160	96	48	24
200	–	60	30

AMENDED TO:

For ongoing chest pain, to control hypertension or treat pulmonary oedema:

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  - Guidance on preparation and administration included below.

Caution
Glyceryl trinitrate IV formulation must be diluted before infusion

STEP 1: Select the concentration as required for the individual patient
- For patients who are fluid congested or require higher doses for a clinical response, consider using a more concentrated solution e.g. 200 or 400 mcg/mL.

STEP 2: Select the volume of the diluent
- Patients who are likely to require treatment for a longer duration e.g. unstable angina prepare a larger volume e.g. 500mL.
- Compatible diluents include sodium chloride 0.9% or dextrose 5%.

STEP 3: Confirm the formulation of glyceryl trinitrate available and mix with diluent
- Confirm the strength of the GTN solution i.e. whether a 1mg/mL or 5mg/mL formulation is available.
- Depending on the formulation available, select the number of ampoules to be used based on the concentration and volume of the diluent as decided in Step 1 and 2 above.
- Ensure that the equivalent volume of diluent is removed from the bag before adding the total GTN volume e.g. if 100mLs of GTN is to be added, first remove 100mL of diluent from the bag before adding the GTN.

STEP 4: Set the flow rate for infusion
- Flush the PVC tube before administering to patient.
- Start with the lowest flow rate possible based on the concentration of the solution prepared.
- Increase by 5 mcg/minute every 5 minutes until response achieved or until the rate is 20 mcg/minute.
- If no response after 20 mcg/minute increase by 20 mcg/minute until response.
- Monitor blood pressure carefully.

E.g. To prepare a 200mcg/mL solution for a patient likely to require several hours of the GTN infusion:
Use 10 ampoules (100mL) of the 1mg/mL GTN formulation mixed with 400mL of diluent (100mL to be removed from a 500mL bag). Initiate the infusion at a flow rate 3mL/hr and titrate the infusion rate based on the patient's response.

STEP 1	STEP 2	STEP 3	
Concentration of dilution	Volume of diluent	Glyceryl trinitrate 1 mg/mL	Glyceryl trinitrate 5 mg/mL

		Volume (Dose)	Number of 10mL ampoules	Volume (Dose)	Number of 10mL ampoules
100 mcg/mL	250 mL	25 mL (25 mg)	2.5	5 mL (25 mg)	0.5
200 mcg/mL		50 mL (50 mg)	5	10 mL (50 mg)	1
400 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
100 mcg/mL	500 mL	50 mL (50 mg)	5	10 mL (50 mg)	1
200 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
400 mcg/mL		200 mL (200 mg)	20	40 mL (200 mg)	4

STEP 4	**Solution concentration (mcg/mL)**	**100 mcg/mL solution**	**200 mcg/mL solution**	**400 mcg/mL solution**
	Dose (mcg/min)	Flow rate (microdrops/min = mL/hr)		
	5	3	–	–
	10	6	3	–
	15	9	–	–
	20	12	6	3
	30	18	9	–
	40	24	12	6
	60	36	18	9
	80	48	24	12
	100	60	30	15
	120	72	36	18
	160	96	48	24
	200	–	60	30

Table 3.3: Dilution of glyceryl trinitrate

Clinically stable

Statin therapy: *aligned with section 3.1*

Aligned with section 3.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

LV dysfunction following myocardial infarction

Angiotensin II receptor blocker: *directions for use amended*

Indication amended to include angioedema, besides an intractable cough associated with ACE-inhibitors and aligned with the SAMF.[25]

Level of Evidence: Guidelines

The STG text was amended as follows:

If ACE-inhibitor intolerant, i.e. intractable cough or angio-oedema:

- Angiotensin receptor blocker (ARB), e.g.:
- Losartan, oral, 50–100 mg daily. Specialist initiated.

Spironolactone: *not added*

However, a cross-reference was added to section 3.4: Congestive cardiac failure

Institute other therapy for heart failure and LV dysfunction as described below – see section 3.4: Congestive cardiac failure.

Referral

Failed perfusion criteria: *amended*

Referral criteria amended to describe failed perfusion with streptokinase as well as alteplase, aligned with SAMF 2022, as follows:

» Failed reperfusion (<50% reduction in ST elevation at 90 minutes after initiation of streptokinase and 60 minutes after initiation of thrombolytics (e.g., alteplase) in leads showing greatest ST elevation, especially in anterior infarct or inferior infarct with right ventricular involvement).

[25] SAMF, 2022

3.2.2 NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AND UNSTABLE ANGINA (UA)

General: Similar to section 3.2.1: ST elevation myocardial infarction (STEMI), above, under the "Medicine Treatment" section, the following statement was included in the STG:

Note: The following guidance is not for primary percutaneous coronary intervention.

NSTEMI description: *amended*
Definition amended to include elevated cardiac biomarkers with a normal ECG, aligned with expert consensus document.[26]
Level of Evidence: Very low certainty, conditional recommendation

Referral criteria: *amended to include cardiogenic shock*
Cardiogenic shock was included as a referral criterion in this setting, aligned with clinical practice guidelines.[27]
Level of Evidence: Very low certainty, conditional recommendation

Transfer for PCI: *not amended*
External comment from SASCI[28] suggesting inclusion of STG text for patients with severe pain, unresponsive to nitrates was accepted: *"Discuss with a specialist for possible PCI transfer and then consider morphine".*
Furthermore, the issue regarding routine access to PCI in public sector facilities had been discussed extensively with the South African Heart Association during the previous review cycle – see below:

NEMLC report for 2017-19 review:
REFERRAL
External comment was received to refer all patients treated for STEMI as soon as possible for coronary angiography. However, this is currently not feasible or pragmatic in public sector as the current service delivery platform does not allow for this.
The following text was editorially amended for clarity purposes:
Contraindication to thrombolytic therapy (~~only if within the period for stenting~~) provided PCI facility available (confirm with cardiologist).

Clopidogrel, oral: *duration of therapy not amended*
External comment was received to not restrict clopidogrel use to one-month but for chronic use of clopidogrel (no evidence submitted). Clopidogrel duration of therapy was retained as 3 months - refer to the NEMLC report that was disseminated for external comment:

NEMLC report for the cardiovascular chapter (31 March 2022):
Duration of therapy: Previously, the NEMLC recommended clopidogrel for a duration of 3 months for use at tertiary & quaternary level of care. This was based on data from an HTA[29] that suggests that there may be a 1.19% absolute risk reduction in the composite CVS outcome for use for the first month, another 0.83% for use from 1 to 3 months and thereafter a dramatic reduction to 0.06%.
Level of Evidence: I Health technology assessment

[26] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018 Nov 13;138(20):e618-e651. https://pubmed.ncbi.nlm.nih.gov/30571511
[27] Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2020;42(14):1289-367. https://pubmed.ncbi.nlm.nih.gov/32860058
[28] Duarte GS, Nunes-Ferreira A, Rodrigues FB, Pinto FJ, Ferreira JJ, Costa J, et al. Morphine in acute coronary syndrome: systematic review and meta-analysis. BMJ Open. 2019;9(3):e025232.
[29] Rogowski W, Burch J, Palmer S, Craigs C, Golder S, Woolacott N. The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis. Health Technol Assess. 2009 Jun;13(31):iii-iv, ix-xi, 1-77. https://www.ncbi.nlm.nih.gov/pubmed/19573471

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.[30] 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[31]. (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[32] 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"[33].

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.*

Enoxaparin: *retained as first line option*

Unfractionated heparin: *not deleted and retained as second line option*

External motivation received that LMWH is preferred over unfractionated heparin, due to ease of administration and as unfractionated heparin is currently available through Section 21, access is a concern. In the previous review cycle, enoxaparin was recommended as first-line option, and unfractionated heparin as second line option. Furthermore, heparin 5000 IU is readily available as a locally registered medicine.[34]

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

Anticoagulation

Enoxaparin, SC: retained – first line option

Unfractionated heparin, IV: retained as second line option

Fondaparinux, SC: not recommended as an alternative to LMWH/UFH

Treatment of Acute Coronary Syndrome (ACS) has been restricted to enoxaparin, aligned with European ACS Guidelines[35] as enoxaparin is the most studied LMWH and for which there is the most clinical experience (Refer to the LMWH medicine review, Appendix B).

The cost-effectiveness analysis (CEA) model of fondaparinux vs enoxaparin vs unfractionated heparin for the treatment of acute coronary syndromes suggests that management with enoxaparin is more cost-effective than unfractionated heparin (Refer to the NEMLC report for chapter 2: Blood and blood forming organs, 2017-2019[36]).

Statin therapy: *aligned with section 3.1*

Aligned with section 3.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

Angiotensin II receptor blocker: *directions for use amended*

Indication amended to include angioedema, besides an intractable cough associated with ACE-inhibitors and aligned with the SAMF.[37]

Level of Evidence: Guidelines

[30] 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.

[31] 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

[32] 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

[33] 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]

[34] Contract circular HP06-2021SVP/01

[35] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bet al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. G Ital Cardiol (Rome). 2016 Oct;17(10):831-872.

[36] NEMLC report for chapter 2: Blood and blood forming organs, 2017-2019. Available at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[37] SAMF, 2022

LV dysfunction following myocardial infarction
Spironolactone: *not added*
However, a cross-reference was added to section 3.4: Congestive cardiac failure

Institute other therapy for heart failure and LV dysfunction as described below – see section 3.4: Congestive cardiac failure.

3.2.3 CHRONIC MANAGEMENT OF STEMI / NSTEMI / UA

Clopidogrel: *not added*
Aspirin: *not added*
Statin (high dose): *not added*
ACE-inhibitor: *not added*
Angiotensin II receptor blocker: *not added*
Beta-blocker: *not added*
Spironolactone: *not added*

The specific medicines were not added to this section to avoid repetition but cross-reference to the relevant sections was included in the STG text as follows:

Continue oral therapy as above - see sections 3.2.1: ST elevation myocardial infarction (STEMI) and 3.2.2: Non-ST elevation myocardial infarction (NSTEMI) and Unstable angina (UA). If heart failure develops, replace atenolol with carvedilol. See section 3.4: Congestive cardiac failure.

3.2.4 ANGINA PECTORIS, STABLE *and* 3.2.5 ATHEROSCLEROTIC PERIPHERAL ARTERIAL DISEASE

Statin therapy: *aligned with section 3.1*
Aligned with section 3.1 Ischaemic heart disease and atherosclerosis, prevention – see above.

Isosorbide dinitrate- frequency of dosing: *Retained*
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[38]. 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.

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

3.3.1.1 ATRIAL FIBRILLATION

Aspirin: *deleted*

Deleted for patients <65 years with no heart disease or other risk factors, as there would be a low CHA_2DS_2-VASc Score (≤1) with a low propensity of stroke due to atrial fibrillation.

The following STG text was deleted:

~~Patients <65 years of age with no heart diseases or other risk factors should be managed with aspirin alone.~~

Rationale: There is no benefit of aspirin in stroke prevention, with a risk of bleeding – aligned with European guideline recommendation[39] and a retrospective observational study.[40]

Level of Evidence: Low certainty, conditional recommendation

Clopidogrel + warfarin*: not added*

Management for atrial fibrillation with acute coronary syndrome occurs at tertiary level of care.

CHA2DS2-VASc Score: *directions for use not amended*

External comment was received to provide guidance that Grown-Up Congenital Heart disease (GUCH) and Hypertrophic Cardiomyopathy (HCM) should receive anticoagulation regardless of CHA2DS2-VASc score. However, management would be at tertiary facilities.

HAS-BLED score: *added*

The tool included in STG text to provide practical guidance to assess individual bleeding risk of patients with atrial fibrillation to support clinical decision-making pertaining to the bleeding risks with antithrombotic therapy. Sourced from the European guidelines, based on the initial validation cohort from Pisters R[41], and accuracy assessed in a network meta-analysis.[42]

Level of Evidence: Moderate certainty, conditional recommendation

The following proposed STG text was accepted by NEMLC:

HAS-BLED Score:

The potential risk for bleeding needs to be assessed using the HAS-BLED score when initiating oral anticoagulation therapy.

	Risk factor and definitions	Score
H	Uncontrolled hypertension » SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** » Dialysis, transplant, serum creatinine >200mmol/L, cirrhosis, bilirubin >2xULN, AST/ALT/ALP >3xULN	1 point each
S	**Stroke** » Previous ischaemic or haemorrhagic stroke[a]	1
B	**Bleeding history or predisposition** » Previous major haemorrhagic, anaemia, severe thrombocytopenia	1
L	**Labile INR** » TTR ≤6o% in patient receiving warfarin	1
E	**Elderly** » Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol** » Concomitant use of antiplatelet or NSAID, excessive alcohol per week	1 point each
Maximum score		**9**

a: Haemorrhagic stroke would also score 1 point under the "B" criterion.
b: Only relevant if patient receiving warfarin or other vitamin K antagonists
c: Alcohol excess/abuse refers to a high intake (e.g. >14 units per week) where the clinician assesses there would be an impact on health or bleeding risk

Source: Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the

[39] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. https://pubmed.ncbi.nlm.nih.gov/32860505/. Erratum in: Eur Heart J. 2021 Feb 1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546-547. Erratum in: Eur Heart J. 2021 Oct 21;42(40):4194.

[40] Själander S, Själander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. Europace. 2014 May;16(5):631-8. https://pubmed.ncbi.nlm.nih.gov/24158253/

[41] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:10931100. https://pubmed.ncbi.nlm.nih.gov/20299623/

[42] Chang G, Xie Q, Ma L, Hu K, Zhang Z, Mu G, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: A network meta-analysis. J Thromb Haemost. 2020;18(4):791-801. https://pubmed.ncbi.nlm.nih.gov/31782613/

special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. https://pubmed.ncbi.nlm.nih.gov/32860505/

» The formal assessment of bleeding risk identifies modifiable bleeding risk factors that should be managed and patients should be assessed at every visit.
» The higher the score the greater the risk of bleeding.
» A high bleeding risk score should not lead to withholding oral anticoagulation therapy.

Warfarin: *directions for use amended*

Time in therapeutic range (TTR) > 65%

The STG guidance was amended, from keeping the "TTR > 60%" to a "TTR >65%", aligned with Connolly et al (2008), details as tabulated below:

Connolly (2008)[43]*:* The usual threshold for poor anticoagulation of TTR < 65% is backed by a commonly cited article by Connolly et al (2008). This analysis compared the incidence of vascular events in warfarin vs clopidogrel + aspirin, so relative effect of anticoagulation is smaller between groups in this analysis. TTR < 58-65% was associated with no added improvement.
ESC atrial fibrillation guidelines (2020)[44]*:* TTR > 70% is recommended[45], which is associated with reduced risk of stroke.[46]
RCTs: TTR > 70% bar is idealistic, and RCTs achieved lower median TTRs of 66.6% (ARISTOTLE[47]), 68.4% (ENGAGE AF[48]) and 58% (ROCKET AF[49]), and a mean TTR of 64% in RE-LY[50].
Real-world: TTRs are reported to be lower in clinical practice:

- Ebrahim et al, 2018[51]: 47% in Cape Town
- Sadhabiriss and Brown, 2021[52]: 45% in Durban
- Semakula et al, 2020[53]: 41% between Uganda and Cape Town sites
- Prinsloo et al, 2021[54]: 37% in Cape Town

INR monitoring – 2 monthly

The Rosendaal method to calculate TTR has been included in Appendix II: Prescribing information for specific medicines. However, it has been reported that the Rosendaal method is effective if the gap between INR monitoring in stable patients, is not more than 56 days.[55] [56] Thus, INR monitoring in stable patients the STG has been updated from "3-monthly" to "2-monthly".

The STG text has been amended as follows:

Initial therapy aimed at stroke reduction

[43] Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008 Nov 11;118(20):2029-37.
[44] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498.
[45] Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes 2008;1:84-91
[46] Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet. 2016 Aug 20;388(10046):806-17.
[47] Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation. 2015 Aug 25;132(8):624-32.
[48] Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010 Oct;160(4):635-41.
[49] Bansilal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR, et al; ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial). Am Heart J. 2015 Oct;170(4):675-682.e8.
[50] Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, Clemens A, Reilly PA, Connolly SJ, Yusuf S, Wallentin L. Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation. 2016 Aug 23;134(8):589-98.
[51] Ebrahim I, Bryer A, Cohen K, Mouton JP, Msemburi W, Blockman M. Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South Africa. S Afr Med J. 2018 May 25;108(6):490-494.
[52] Sadhabariss D, Brown SL. Warfarin: time in therapeutic range, a single centre study on patients using warfarin for stroke prevention in non-valvular atrial fibrillation and prosthetic heart valves. SA Heart Journal. 2021;18(1): 28-38.
[53] Semakula JR, Mouton JP, Jorgensen A, Hutchinson C, Allie S, Semakula L, et al. A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa. PLoS One. 2020 Jan 29;15(1):e0227458.
[54] Prinsloo DN, Gould TJ, Viljoen CA, Basera W, Ntsekhe M. International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa. S Afr Med J. 2021 Mar 31;111(4):355-360.
[55] Azar AJ, Cannegieter SC, Deckers JW, Briët E, van Bergen PF, Jonker JJ, Rosendaal FR. Optimal intensity of oral anticoagulant therapy after myocardial infarction. J Am Coll Cardiol. 1996 May;27(6):1349-55.
[56] Rose AJ, Miller DR, Ozonoff A, Berlowitz DR, Ash AS, Zhao S, Reisman JI, Hylek EM. Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence. Chest. 2013 Mar;143(3):751-757.

Anticoagulate with warfarin:

- Warfarin, oral, 5 mg daily.
  - INR should be done after 48 hours, then every 1 to 2 days until within the therapeutic range of 2 to 3 (refer to initiation dosing tables in Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to Maintenance dosing tables in Appendix II).
  - Every effort should be made to keep the time in therapeutic range (TTR) > ~~60%~~ 65%. If TTR ≤ ~~60%~~ 65% there is less benefit of warfarin therapy and a greater risk of stroke and haemorrhage.
  - See Appendix II for guidance on calculating TTR for management with warfarin.

Long-term therapy

Continue warfarin anticoagulation long-term, unless contra-indicated:

- Warfarin, oral, 5 mg daily.
  - Control with INR to therapeutic range:
    - INR between 2–3 and patient stable: monitor every ~~3~~ 2 months.
    - INR <1.5 or >3.5: monitor monthly.

DOAC therapy: *not added*

The initial medicine review and supporting economic analysis was done with consideration of the generic formulations of rivaroxaban. However, at the time of undertaking the review, it was noted that the generic formulations were removed from the market due to a patent court ruling that judged the generics unlawful i.e. the patent of the originator rivaroxaban formulation was still valid. Refer to the evidence summary on the clinical benefits and harms of Direct Oral Anticoagulants (DOACs) compared to warfarin for adult patients with chronic non-valvular atrial fibrillation (AF) (March 2022)[57] and the updated economic analysis (December 2022)[58]. A copy of the complete evidence review and/or budget impact analysis may be found at the end of this report 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 suggests that DOACs not be used for anticoagulation in atrial fibrillation. *Rationale:* Direct oral anticoagulants (DOACs) have similar efficacy to warfarin in preventing ischaemic stroke and systemic embolism. They are associated with reduced mortality and lower rates of intracranial haemorrhage and major bleeding events. Despite these benefits, DOACs are not currently affordable. A rivaroxaban price reduction of at least 35% would be required for rivaroxaban to be considered as cost-effective using an ICER threshold of R100,000/QALY, while a price reduction of 75% would be required for cost-neutrality (Approximately R153.00 per patient per month). **Level of Evidence: High certainty evidence** **Review indicator: Price reduction**					
NEMLC RECOMMENDATION (MEETING OF 31 MARCH 2022): The medicine review and supporting economic analysis was done with consideration of the generic formulations of rivaroxaban. As the patent of the originator rivaroxaban formulation is currently still valid, the evidence review and economic analysis needs to be updated and re-tabled at the next NEMLC meeting. • *Medicine review – key findings:* It was recommended that the AMSTAR assessment of the critically low evidence to be added to the key findings. **NEMLC RECOMMENDATION (MEETING OF 8 DECEMBER 2022):** The Committee ratified the review and related costing analyses for DOACS for the management of AF for publication, pending editorial amendments to the costing analysis.					
Monitoring and evaluation considerations					
Research priorities					

BIA – CONCLUSION

Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, there is still considerable uncertainty around the long-term outcomes and clinical benefits in a mixed population, real-world setting.

In this model, the only variable that could be changed sufficiently to reduce the incremental cost-effectiveness ratio (ICER) to below R250 000/QALY was to reduce the price of the currently available rivaroxaban produce (Ixarola®) by 50% and this is unlikely to be considered cost-effective. A more sophisticated model (with probabilistic sensitivity analysis and more health states) may have the outcome of further reducing the ICER but at the current model outcome of R462 544/QALY it is unlikely to reduce the ICER to a point which could be considered cost-effective in the public health setting.

Furthermore, the budget impact needs to be considered. The prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be. This will be very dependent on uptake and utilization.

Other factors need to be considered;

- How to define warfarin failure or true warfarin intolerance in order to be eligible for DOACs
- The baseline risk of patients in the current healthcare setting compared to the clinical trial setting
- How to improve warfarin control and monitoring (TTR) as an alternative strategy

[57] NDoH review. DOACs for chronic non-valvular atrial fibrillation_8 December 2022_final

[58] NDoH BIA. Rivaroxaban_AF_HealthEconomicsReport_Update_8 December 2022_v3.0_final

Patients with severe symptoms

Amiodarone – concomitant use with digoxin: *Guidance amended*

Guidance to avoid the concomitant use of amiodarone and digoxin has been amended to allow for concomitant use which may be clinically appropriate for select patients. These patients will require close monitoring of their heart rate. Amendments to the STG are as tabulated below:

AMENDED FROM:

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Avoid concomitant digoxin.
- Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months

AMENDED TO:

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Monitor heart rate closely when patient is on concomitant digoxin.
- Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months

3.3.1.2. ATRIAL FLUTTER

Description: *Editorial amendment*

An editorial amendment to the description was made as tabulated below:

AMENDED FROM:

Synchronised direct current (DC) cardioversion is occasionally necessary in haemodynamic instability.

AMENDED TO:

Synchronised direct current (DC) cardioversion may be necessary in haemodynamic instability.

DC Conversion

Midazolam, IV: *retained*

External comment was received that midazolam, IV should not be used for flutter. However, DC cardioversion is the most effective therapy and midazolam, IV is used as adjunct therapy. The STG was editorially amended for clarity purposes as follows:

DC cardioversion is the most effective therapy and administer midazolam as adjunct therapy:

- Midazolam IV, 1–2.5 mg, administered over 2-3 minutes.

Initial therapy - If vagal manoeuvres fail

Adenosine, IV: *dosing and directions for use not amended*

Adenosine dosing and directions for use was not amended, as aligned with the SAMF.[59]

3.3.2.1 REGULAR WIDE QRS TACHYCARDIAS

Amiodarone – concomitant use with digoxin: *Guidance amended*

Guidance to avoid the concomitant use of amiodarone and digoxin has been amended to allow for concomitant use which may be clinically appropriate for select patients. These patients will require close monitoring of their heart rate. Amendments to the STG are as tabulated below:

AMENDED FROM:

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Avoid concomitant digoxin.
- Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months

[59] SAMF, 2022.

AMENDED TO:

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Monitor heart rate closely when patient is on concomitant digoxin.
- Monitor thyroid function every 6 months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months

3.3.2.3 NON-SUSTAINED (<30 SECONDS) IRREGULAR WIDE QRS TACHYCARDIAS

Amiodarone, oral – dosing guidance: *Amended*

Dosing guidance for the use of amiodarone, oral has been amended to align with the registered professional information leaflet[60].

Amiodarone – concomitant use with digoxin: *Guidance amended*

Guidance to avoid the concomitant use of amiodarone and digoxin has been amended to allow for concomitant use which may be clinically appropriate for select patients. These patients will require close monitoring of their heart rate.

AMENDED FROM:

MEDICINE TREATMENT

- Amiodarone, IV, 5 mg/kg infused over 30 minutes.

Follow with:

- Amiodarone, oral, 800 mg daily for 7 days.
  - Then 600 mg daily for 3 days.
  - Follow with a maintenance dose of 200–400 mg daily, depending upon clinical judgement. Consult specialist before instituting long-term (>1 week) therapy

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Avoid concomitant digoxin.
- Monitor thyroid function every 6months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months.

AMENDED TO:

MEDICINE TREATMENT

- Amiodarone, IV, 5 mg/kg infused over 30 minutes.

Follow with:

- Amiodarone, oral, 200 mg three times a day for 7 days.
  - Then 200 mg 12 hourly for 7 days.
  - Follow with a maintenance dose of 200–400 mg daily, depending upon clinical judgement. Consult specialist before instituting long-term (>1 week) therapy.

Precautions:

- If on warfarin, halve the dose of warfarin and monitor INR closely, until INR is stable.
- Monitor heart rate closely when patient is on concomitant digoxin.
- Monitor thyroid function every 6months as thyroid abnormalities may develop.
- Ophthalmological examination every 6 months.

Lidocaine (Lignocaine), IV – dosing guidance: *Amended*

The rate of IV administration of lignocaine has been aligned to guidance included in the SAMF[61] and professional information leaflet[62] as tabulated below:

AMENDED FROM:

Only in haemodynamically stable patients:

- Lidocaine (lignocaine), IV, 50–100 mg (1–2 mg/kg) initially and at 5 minute intervals if required to a total of 200–300 mg.

[60] Professional Information Leaflet. Amiodarone hydrochloride 200mg tablets. Biotech Laboratories (Pty) Ltd. Date of first authorization/renewal of authorization: 24 January 2003.

[61] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[62] Lignocaine slow IV injection: professional Information Leaflet. Lignocaine HCl Fresenius 10 % (Ampoules) solution for injection. Fresenius Kabi Manufacturing SA (Pty) Ltd. Date of revision of text: 2 September 2020.

AMENDED TO:

- Lidocaine (lignocaine), IV, 50–100 mg (1–2 mg/kg) initially as a slow IV injection over 2 minutes.
  - Repeat at 5 minute intervals if required to a total of 200–300 mg.

3.4 CONGESTIVE CARDIAC FAILURE (CCF)

General measures

Salt restriction (dietitian guided where possible): *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,[63] 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. It's 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. However, the setting is mild CCF and hydrochlorothiazide is provided as an option in the 2021 ESC CCF guidelines.

Level of Evidence: Guidelines

Renin-angiotensin-aldosterone system (RAAS) blockers

Angiotensin II receptor blocker: *directions for use amended*

Indication amended to include angioedema, besides an intractable cough associated with ACE-inhibitors and aligned with the SAMF.[64]

Level of Evidence: Guidelines

Spironolactone

Spironolactone, oral: *directions for use not amended*

Potassium supplements: *directions for use not amended*

External comment received that spironolactone should be used in all CCF patients with routine potassium supplementation (no evidence submitted). However, the STG stepwise approach with monitoring of potassium levels, with supplementation only as needed was considered a more pragmatic option.

Level of Evidence: Expert opinion

Beta-blockers

Carvedilol, oral: *dosing amended*

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

- Carvedilol, oral.
  - Initial dose: 3.125 mg 12 hourly.
  - Increase at 2-weekly intervals by doubling the daily dose until a maximum of 25 mg 12 hourly, if tolerated.
  - If not tolerated, i.e. worsening of cardiac failure symptoms, reduce the dose to the previously tolerated dose.
  - Up-titration should take several weeks or months.
  - If > 85 kg: maximum of 50 mg 12 hourly.

Level of Evidence: Guidelines

[63] 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/

[64] SAMF, 2022

3.5 ENDOCARDITIS, INFECTIVE

Vancomycin, IV: *dosing amended*
Aligned with the SAMF[65], as follows:

- Vancomycin, IV, 15–20 mg/kg 12 hourly, is the antibiotic of choice. It is essential to monitor trough concentrations of vancomycin regularly and adjust doses accordingly, starting after the third dose. (See Appendix II for guidance on prescribing and therapeutic drug monitoring).

Level of Evidence: Guidelines

Empiric and directed therapy: Amended to align with the 2015 ESC Guidelines for the management of infective endocarditis,[66] that was appraised in duplicate using the AGREE2 tool to be of good quality (overall score of 83%).

Gentamicin, IV dosing: Observational data[67] suggests that daily dose IV gentamicin is less nephrotoxic, and is more cost-effective by reducing provides a cost-effective method for administration of aminoglycosides by reducing ancillary service time and serum aminoglycoside monitoring. Daily dosing of gentamicin, IV is recommended in major guidelines.
Level of Evidence: Low certainty evidence

Benzylpenicillin (penicillin G), IV: Concerns with the erratic supply of penicillin G, warrants the recommendation of ampicillin, IV as an alternative, where appropriate.

Cloxacillin, IV: Erratic supplies of cloxacillin warrants the inclusion of cefazolin as an alternative option (second line).

MIC values: Aligned to the 2015 ESC Guidelines.

Empiric therapy – native valve
Benzylpenicillin (penicillin G), IV: *deleted*
Ampicillin, IV: *added*
Cloxacillin, IV: *added as first-line option to cefazolin*
Cefazolin, IV: *retained as second-line option to cefazolin*

Empiric therapy – prosthetic valve
Vancomycin, IV: *retained*
Rifampicin, IV: *retained*
Most guidelines recommend the above regimen, but recent evidence[68] has emerged that shows that a systematic review of 4 RCTs does not suggest a benefit of either adjunctive gentamicin or rifampin in staphylococcal prosthetic valve endocarditis. Furthermore, safety concerns of nephrotoxicity, hepatotoxicity, and risk of drug-drug interactions warrants the removal of these agents from guidelines.
Recommendation: The emerging evidence be monitored, and once matured to be considered for review and translation into guidelines, possibly during the next review cycle.
Level of Evidence: Moderate certainty evidence

Directed therapy (native valve) – streptococcal: fully/moderately resistant
Ampicillin, IV: *added*
Benzylpenicillin (penicillin G), IV: *retained*

[65] SAMF, 2022
[66] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128.
[67] Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5.
[68] Ryder JH, Tong SYC, Gallagher JC, McDonald EG, Thevarajan I, Lee TC, Cortés-Penfield NW. Deconstructing the Dogma: Systematic Literature Review and Meta-analysis of Adjunctive Gentamicin and Rifampin in Staphylococcal Prosthetic Valve Endocarditis. Open Forum Infect Dis. 2022 Oct 31;9(11):ofac583. https://pubmed.ncbi.nlm.nih.gov/36408468/

Directed therapy (native valve) – enterococcal: susceptible to penicillin
Ampicillin, IV: *added*
Benzylpenicillin (penicillin G), IV: *retained*
Ceftriaxone, IV*: added*
Ceftriaxone plus ampicillin has been shown to be non-inferior in observational trials, much less nephrotoxic, and more convenient than ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis.[69] This protocol is also listed as an option in the 2015 ESC Guidelines.

Directed therapy (native valve) – staphylococcal
Cloxacillin, IV: *added as first-line option to cefazolin*
Cefazolin, IV: *retained as second-line option to cefazolin*
Gentamicin, IV: *deleted*
Benefit of gentamicin has not been established, and toxicity issues warrants deletion – aligned with major guidelines based on a prospective cohort study of safety data from a RCT of therapy for *S. aureus* bacteremia and native valve infective endocarditis (n=236 from 44 hospitals in 4 countries).[70] The study showed that initial low-dose gentamicin as is nephrotoxic and should not be used routinely, given the minimal existing data supporting its benefit.
Level of Evidence: Low certainty evidence

3.6 HYPERTENSION

Alcohol (lifestyle modifications): *guidance amended*
A standard drink is use as the measure for the reduction of alcohol intake, defined as follows and aligned with the National Institute of Alcohol Abuse and Alcoholism[71] – STG text amended accordingly:

(1 standard drink is = a can of beer = a glass of wine = a shot of spirits)

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. [72]

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.[73] 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) below. Also refer to the previous NEMLC recommendation regarding this matter:

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.

[69] Fernández-Hidalgo N, Almirante B, Gavaldà J, Gurgui M, Peña C, de Alarcón A,et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis. 2013 May;56(9):1261-8.
[70] Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, Rupp ME, Chambers HF, Karchmer AW, Boucher HW. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713–
[71] https://www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink
[72] Cardiovascular Journal of Africa: Vol 30 No 3 (May/June 2019) (cvja.co.za)
[73] 2020 International Society of Hypertension Global hypertension Practice guidelines. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026Hypertension. 2020;75:1334–1357

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[74 75 76 77 78 79], Expert Opinion

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[80] that informed the National Heart, Lung, and Blood Institute (NHLBI) guidelines[81].

Level of Evidence: Low certainty evidence

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[82]. A copy of the complete evidence review may be found at the end of this report, or alternatively on the NHI webpage.

[74] 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

[75] 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

[76] 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

[77] 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

[78] 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

[79] 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

[80] 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/

[81] 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/

[82] 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:[83] [84]

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*

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

[84] 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:[85]

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*[86] *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*[87] *and perhaps renal cell carcinoma*[88] *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.

[85] 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.

[86] 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.

[87] 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.

[88] 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[89] 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[90] 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[91] – 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 comment received that initial 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).

Enalapril, oral: *dosing not amended*

NEMLC had previously reviewed this matter, noting that most hypertensive RCTs likely administered enalapril daily to study participants.

NEMLC REPORT FOR THE ADULT HOSPITAL LEVEL STGS AND EML REVIEW (2017-2019):
Enalapril dosing: External commentator queried the evidence for daily dosing of enalapril as the authors concluded that, "Enalapril 20 mg should be prescribed as 10 mg twice daily and measures taken to improve patient compliance"; with greater blood pressure reduction on the twice daily regimen, though adherence was better on once daily.
Rationale: As per the PHC 2018 review, there is no RCT evidence that shows superiority of twice daily vs once daily dosing for

[89] 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
[90] 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
[91] 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

management of blood pressure. Small observational study (n=20) [92] showed adherence was better with once daily dosing, but twice daily dosing may improve sitting BP but not ambulatory BP. However, this study is probably hypothesis generating and more prospective studies are required to confirm the findings. Patient adherence is a major contributory factor to adequate BP control and the long half-life of enalapril[93] and cost are additional considerations.
Level of Evidence: III Observational studies (low quality)[95] [94], Expert opinion

Enalapril – once versus twice daily: *Retained*

In response to an external query on the recommendation for once versus twice daily administration of enelapril 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[95]

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[96] (*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[97, 98](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[99]). ***Level of evidence: III Observational studies (low quality), Expert opinion***

Angiotensin II receptor blocker: *directions for use amended*

Indication amended to include angioedema, besides an intractable cough associated with ACE-inhibitors and aligned with the SAMF.[100]

Level of Evidence: Guidelines

Amiloride, oral*: not added*

External comment 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).

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

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

[92] 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

[93] SAMF, 2016

[94] Davies RO, Gomez HJ, Irvin JD, Walker JF. An overview of the clinical pharmacology of enalapril. Br J Clin Pharmacol. 1984;18 Suppl 2:215S-229S. https://www.ncbi.nlm.nih.gov/pubmed/6099737

[95] 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.

[96] 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.

[97]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

[98] 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

[99] Contract circular HP09-2016SD, average weighted prices used.

[100] SAMF, 2022

External comment received that there is no current evidence to suggest that any of the beta-blockers hold a mortality benefit over one another, and that a good cardiac, specific beta-blocker (such as bisoprolol) should be available across the public sector in all provinces. One of the principles for the STGs and EML, though, is that the more affordable agent in the therapeutic class for the specific indication is listed in the STG, which is atenolol for hypertension. Bisoprolol is listed in the therapeutic interchange database.

Medicine treatment choices without compelling indications.

Stepped care approach to BP 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[101]

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 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.
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	

[101] 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.

				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[102]

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[103]

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) 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

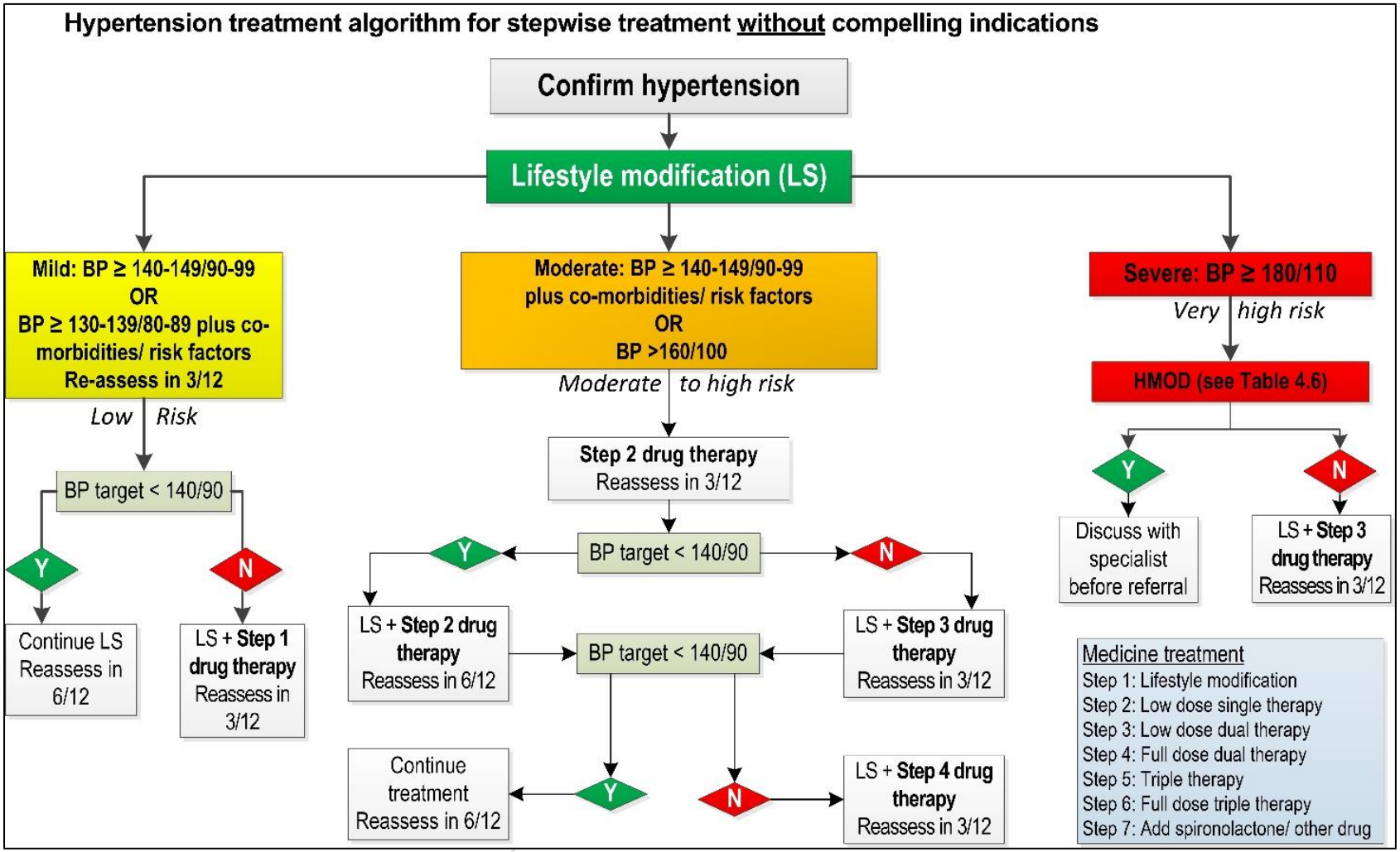
NEMLC recommends that the STGs on hypertension in the PHC and AH CV chapters be amended from night time dosing to once daily dosing. The timing of the dose should be guided by the time of day that is most convenient for patients and that would optimize adherence and minimize side effects for individual patients.

[102] 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.

[103] 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.

Hypertension algorithm: *amended*

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



3.6.1 HYPERTENSION, ASYMPTOMATIC SEVERE

Anxiolytic agent: *not added*

RCT data for an anxiolytic agent for acute care for severe asymptomatic hypertension could not be sourced. Therapy most applicable to peri-operative care.

3.6.2 HYPERTENSIVE URGENCY

Management: *amended (specialist consult)*

The following STG text was amended, noting the need for continuous monitoring:

> Ideally, all patients with hypertensive urgency should be treated in hospital.
> Commence treatment with two oral agents and aim to lower the DBP to 100 mmHg slowly over 48-72 hours. Specialist should be consulted.

3.6.3 HYPERTENSIVE CRISIS, HYPERTENSIVE EMERGENCY

Angiotensin II receptor blocker: *directions for use amended*

Indication amended to include angioedema, besides an intractable cough associated with ACE-inhibitors and aligned with the SAMF.[104]

Level of Evidence: Guidelines

APPENDIX II – PRESCRIBING INFORMATION FOR SPECIFIC MEDICINES

WARFARIN

Guidance on the prescribing and monitoring of warfarin as included in Appendix II of the AH EML has been updated may be accessed at the end of this report, or alternatively on the Knowledge Hub or NHI webpage.

APPENDIX VII – CARDIOVASCULAR RISK ASSESSMENT

Appendix VII – Cardiovascular risk assessment: *New chapter added to the AH standard treatment guidelines*

Appendix VII – 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.

[104] SAMF, 2022

NON-LABORATORY BASED RISK SCREENING

BMI-BASED RISK ASSESSMENT

» Measure body mass index (BMI): BMI=weight (kg)/[height (m) x height (m)]

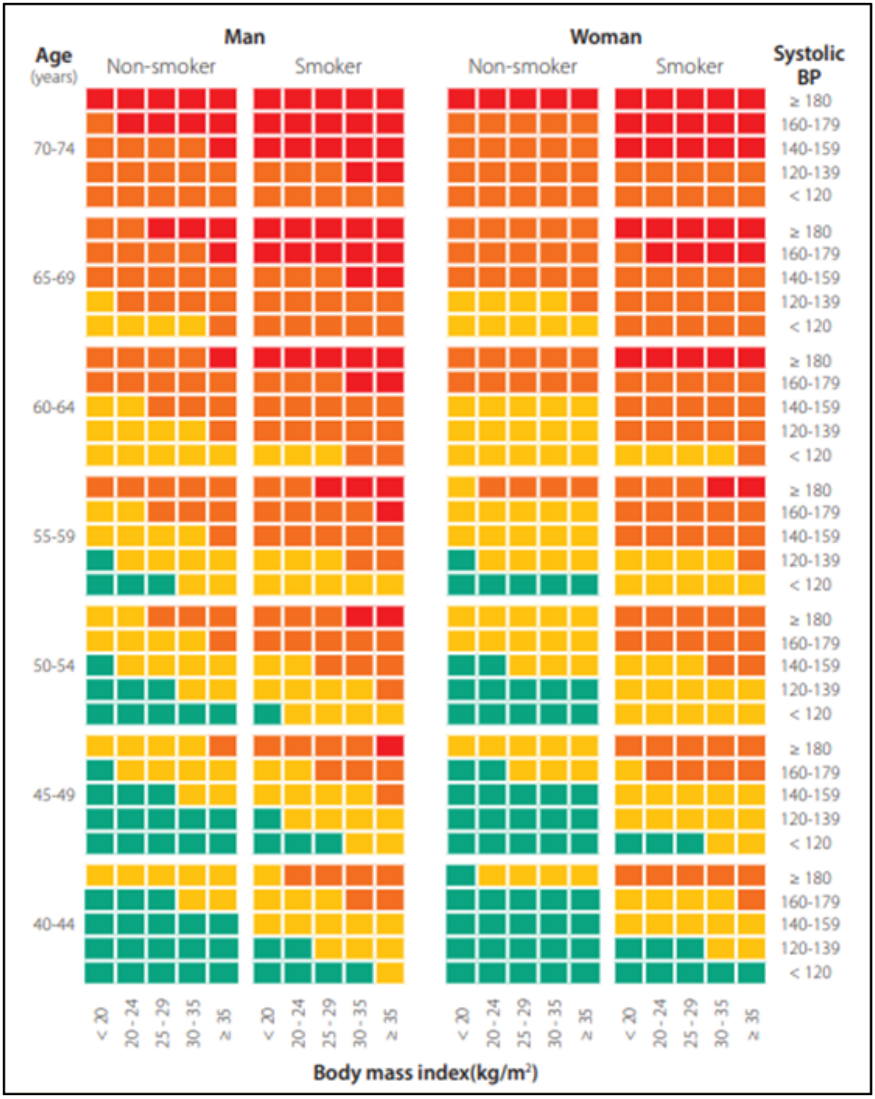
» Measure blood pressure. *LoE:IIIb*[1]

» 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:

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

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

  <u>A female patient > 70 yrs old with systolic BP > 160 mmHg on treatment would score</u>:
  - 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

[1] BMI-based CVD risk assessment: D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53. https://www.ncbi.nlm.nih.gov/pubmed/18212285

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.

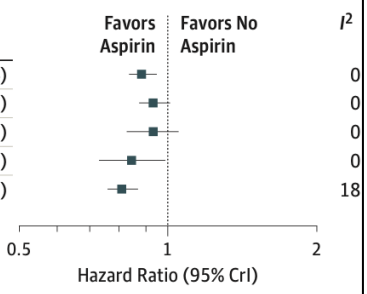
Safety

- 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.

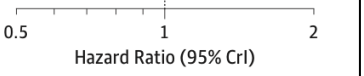
Therefore, the use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding.

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

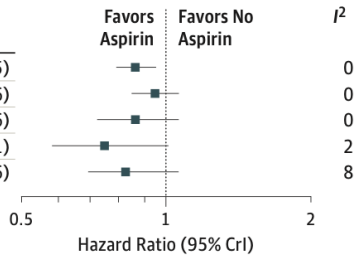
In studies where the primary 10-year risk for a cardiovascular outcome was low, heterogeneity was low for all outcomes in patients (I^2 range, 0%-11%).

- *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.

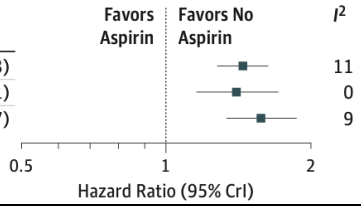
Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Patients at High and Low Risk for the Primary CV Outcome and With Diabetes

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



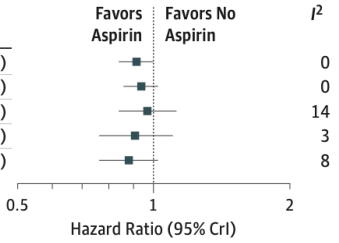
High CV risk subgroup

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%).

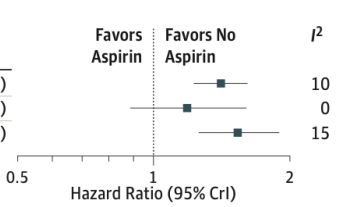
- *Efficacy:* Aspirin use was associated with reductions in the primary composite cardiovascular outcome compared with no aspirin - HR 0.91 (95% CI 0.84 to 0.98); ARR 0.63% (95% CI 0.18 to 1.03%); NNT 160 (95% CI 96 to 555).
- *Safety:* Aspirin use was associated with an increase in major bleeding compared 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



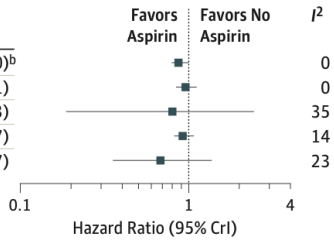
Diabetes subgroup

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%).

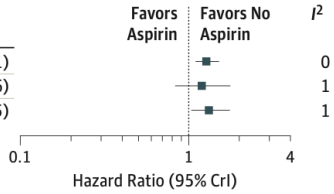
- Efficacy: Aspirin use was associated with reductions in the primary composite cardiovascular outcome – HR. 0.90 (95% CI 0.82 to 1.00); ARR 0.65% (95% CI 0.09 to 1.17); no difference shown.
- *Safety:* Aspirin use was associated with an increase in major bleeding compared to no bleeding - HR 1.29 (95% 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.

RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [x] Uncertain [ ]	**Price of medicines/ month (28 days)** – *Aspirin up to 150mg/daily* **Medicine** / **Price (ZAR)*** Aspirin 300mg tablet (14)* – 4.37 Aspirin 80-81 mg tablet ** – 25.20 Aspirin 100mg tablet*** – 27.52 * 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
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 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.
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	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.

References

1. Fanaroff AC, Hasselblad V, Roe MT, et al. Antithrombotic agents for secondary prevention after acute coronary syndromes: A systematic review and network meta-analysis. *Int J Cardiol* 2017; **241**: 87-96.
2. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet (London, England)* 1988; **2**(8607): 349-60.
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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.
7. de Gaetano G, Collaborative Group of the Primary Prevention P. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet (London, England)* 2001; **357**(9250): 89-95.
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9. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002; **106**(3): 388-91.
10. British Cardiac S, British Hypertension S, Diabetes UK, Heart UK, Primary Care Cardiovascular S, Stroke A. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91 Suppl 5**: v1-52.
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:

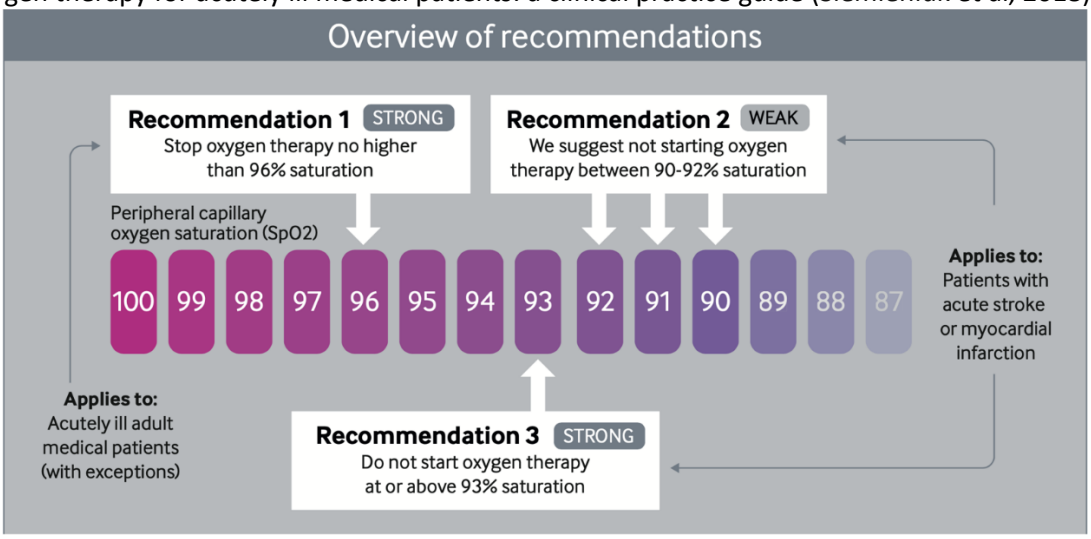
Guidelines:
A 2018 clinical guideline provided guidance based on the 2018 meta-analysis by Chu et al.

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]

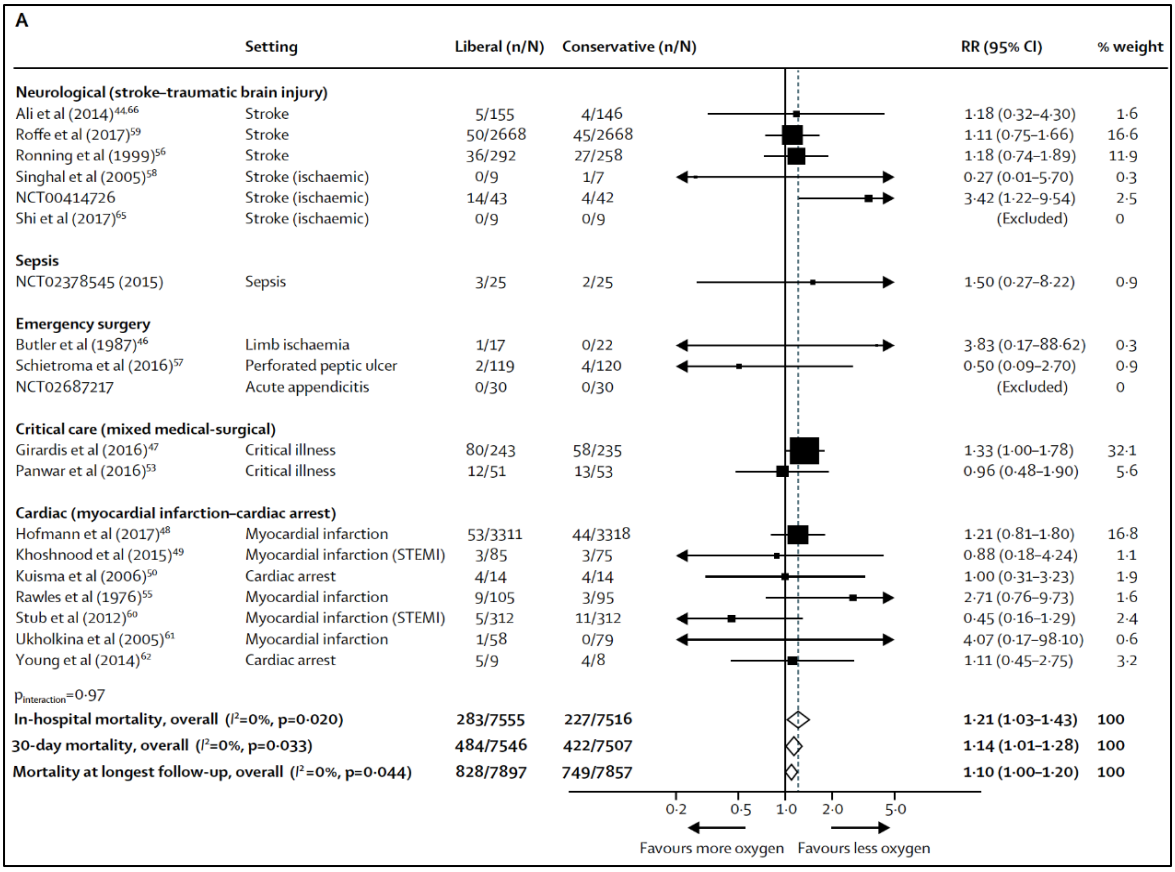


Systematic reviews and meta-analyses:

- *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)

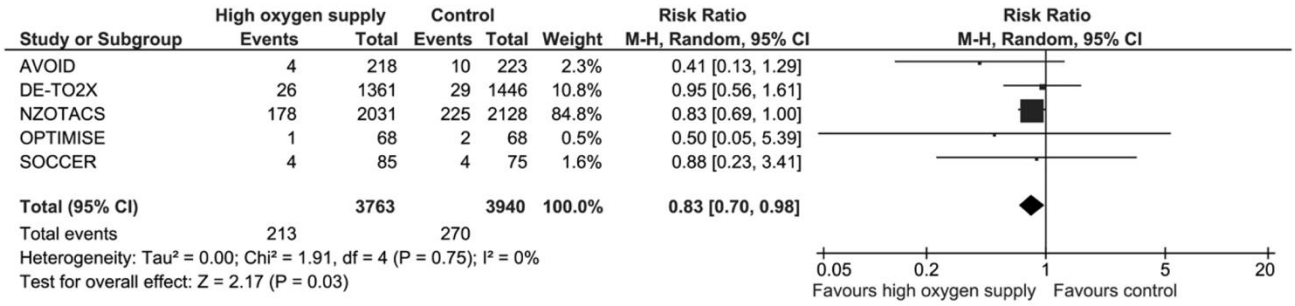


Furthermore, a search was conducted on PUBMED (search strategy – appendix 2), restricting to SRs of RCTs for oxygenation strategies in acute cardiovascular conditions to search for additional literature after 2018. Two SRs were retrieved, and a review of the most recently published SR (2021) follows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

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

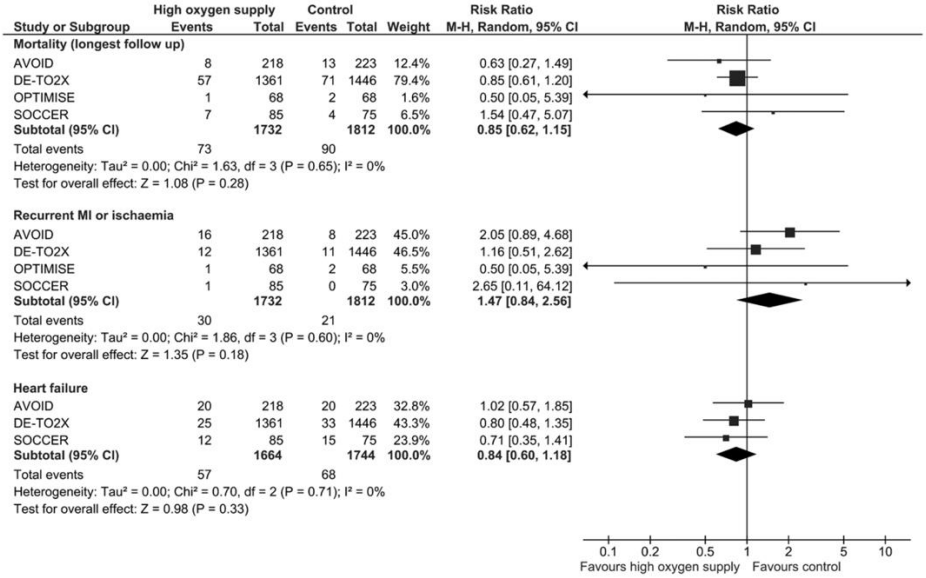
Alves *et al.* assessed the clinical effect of high oxygen supply in patients with STEMI using a systematic review of the available literature. All randomized controlled trials (RCTs) evaluating the systematic use of high oxygen (6 L/min or higher) versus room air or lower oxygen supply in STEMI patients 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)

Outcome no. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (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 $SPO_2 \geq 93\%$ (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.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South African National Essential Medicine List
Primary Healthcare & Adult Hospital Level of Care Medication Review Process
Component: Cardiovascular conditions

MEDICINE REVIEW

Title: Evidence review of the clinical benefits and harms of Direct Oral Anticoagulants (DOACs) compared to warfarin for adult patients with chronic non-valvular atrial fibrillation (AF).

Date: 26 March 2022

Key findings

- We conducted a rapid review of evidence regarding the use of DOACs versus warfarin for adult patients with chronic non-valvular atrial fibrillation.
- We found one systematic review with meta-analysis (Jia[12] et al. which was deemed to be of critically low quality on the AMSTAR-2 rating see Figure 10 below), which included five randomized controlled trials (RCTs) that were mostly of good quality.
- Compared to warfarin, "higher dose" DOACs resulted in a reduced risk of stroke and systemic embolism (relative risk [RR] = 0.80; 95% CI, 0.71-0.91; Number needed to treat to benefit [NNT] =149 [95% CI: 103 to 331]). Low-dose DOACs had similar efficacy in reducing the risk of stroke and systemic embolism compared to warfarin (RR = 1.03; 95% CI, 0.84-1.27). Certainty of evidence: High
- DOACs reduced the risk of all-cause mortality, with a similar reduction noted whether a high dose (RR = 0.90; 95% CI, 0.85-0.95; NNT 177 [118 to 354]) or low dose DOAC regimen (RR = 0.89; 95% CI, 0.83-0.96; NNT 161 [95% CI: 104-442]) was used. Certainty of evidence: High
- Compared to warfarin, DOACs reduce the risk for major bleeding (RR = 0.86; 95% CI: 0.74-0.99; NNT 119 [95% CI: 64-1660]). Lower dose DOAC regimens probably also result in a reduced risk for major bleeding (RR = 0.63, 95% CI: 0.38-1.04). Certainty of evidence: High.
- The use of DOACs result in a lower risk of intracranial bleeding compared with warfarin use (RR = 0.48, [95% CI: 0.41-0.56]; NNT = 136 [95% CI: 120 to 161]). This reduction is more pronounced when a low dose regimen is used (RR = 0.31, [95% CI: 0.24-0.41]; NNT = 103 [95% CI: 93 to 120]). Certainty of evidence: High.
- The risk of gastrointestinal bleeding was significantly increased with the use of DOACs compared with warfarin (RR = 1.24 [95% CI: 1.10-1.39]; Number needed to harm = 224 [95% CI: 138 to 538]). This risk may be reduced with the use of low-dose DOAC regimens (RR = 0.85, [95% CI: 0.72-1.00]). Certainty of evidence: High.
- Overall, the combined results of efficacy and safety support use of the DOACs as an alternative to warfarin for the long-term prevention of stroke in patients with chronic atrial fibrillation.

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 DOACs not be used for anticoagulation in atrial fibrillation.

Rationale: Direct oral anticoagulants (DOACs) have similar efficacy to warfarin in preventing ischaemic stroke and systemic embolism. They are associated with reduced mortality and lower rates of intracranial haemorrhage and major bleeding events. Despite these benefits, DOACs are not currently affordable. A rivaroxaban price reduction of at least 35% would be required for rivaroxaban to be considered as cost-effective using an ICER threshold of R100,000/QALY, while a price reduction of 75% would be required for cost-neutrality (Approximately R153.00 per patient per month).

Level of Evidence: High certainty evidence

Review indicator: Price reduction

NEMLC RECOMMENDATION (MEETING OF 31 MARCH 2022):

The medicine review and supporting economic analysis was done with consideration of the generic formulations of rivaroxaban. As the patent of the originator rivaroxaban formulation is currently still valid, the evidence review and

economic analysis needs to be updated and re-tabled at the next NEMLC meeting. • *Medicine review – key findings:* It was recommended that the AMSTAR assessment of the critically low evidence to be added to the key findings. **NEMLC RECOMMENDATION (MEETING OF 8 DECEMBER 2022):** The Committee ratified the review and related costing analyses for DOACS for the management of AF for publication, pending editorial amendments to the costing analysis.
Monitoring and evaluation considerations
Research priorities

(Refer to the Evidence to decision framework – Appendix A)

1. Executive Summary

Date: 30 November 2021
Medicine (INN): Rivaroxaban, dabigatran, apixaban
Medicine (ATC): Antithrombotic agents B01A (B01AF01, B01AE07, B01AF02)
Indication (ICD10 code): Atrial fibrillation (I48.2)
Patient population: Adults with chronic non-valvular atrial fibrillation
Prevalence of condition: 0.5 – 3.0% in LMIC[1]
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse, Medical Doctor, Specialist
Current standard of Care: Warfarin
Efficacy and safety estimates:

Ischaemic stroke/Systemic embolism:

- **High dose regimen:** RR = 0.80 (95% CI 0.71-0.91); Absolute risk reduction (ARR): -0.67% (95% CI: -0.97% to -0.3%); NNT =149 (95% CI 103 to 331)
- **Low dose regimen:** RR = 1.03 (95% CI 0.84-1.27); ARR: 0.1% (95% CI -0.54% to 0.91%)

All-cause mortality:

- **High dose regimen:** RR = 0.90 (95% CI 0.85-0.95); ARR: -0.57% (95% CI -0.85% to -0.28%); NNT 177 (95%CI 118-354)
- **Low dose regimen:** RR = 0.89 (95% CI 0.83-0.96); ARR: -0.62% (95% CI -0.96% to -0.23%); NNT 161 (95% CI 104-442)

Major bleeding:

- **High dose regimen:** RR = 0.86 (95% CI 0.74-0.99); ARR: -0.84% (95% CI -1.57% to -0.06%); NNT 119 (95% CI 64 to 1660)
- **Low dose regimen:** RR = 0.63 (95% C, 0.38-1.04)

Intracranial bleeding:

- **High dose regimen:** RR = 0.48 (95% CI: 0.41-0.56); ARR: -0.74% (95% CI: -0.84% to -0.62%); NNT 136 (95% CI 120-161)
- **Low dose regimen:** RR = 0.31 (95% CI: 0.24-0.41); ARR: -0.98% (95% CI: -1.08% to -0.84%); NNT 103 (95% CI93-120)

Gastrointestinal bleeding:

- **High dose:** RR = 1.24 (95% CI: 1.10-1.39); ARR: 0.45% (95% CI: 0.19% to 0.73%); NNH 224 (9% CI 138-538)
- **Low dose:** RR = 0.85 (95% CI: 0.72-1.00); ARR: -0.28% (95% CI: -0.52% to 0%)

Motivator/reviewer name(s): Hannah May Gunter, Rephaim Mpofu, and Enkosi Mondleki
PTC affiliation: Enkosi Mondleki (Groote Schuur Hospital), Rephaim Mpofu (Red Cross War Memorial Children's Hospital)

2. Name of author(s)/motivator(s)

Hannah May Gunter, Rephaim Mpofu, Enkosi Mondleki, Tamara Kredo, Marc Blockman, Jacqui Miot, Trudy Leong

3. Author affiliation and conflict of interest details

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- Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University
- Marc Blockman: University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa
- Jacqui Miot: Health Economics and Epidemiology Research Office (HE²RO), University of the Witwatersrand
- Trudy Leong: Essential Drugs Programme, Affordable Medicines Directorate, National Department of Health.

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4. BACKGROUND

Atrial fibrillation (AF) is the most common clinically significant arrhythmia, and is characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[1, 2] There is a wide variation in reported

prevalence of AF in low- and middle-income countries (LMIC), and it is uncertain whether this is due to poor surveillance, under-reporting, or a possible genetic predisposition.[3]

Patients with chronic atrial fibrillation are at risk of systemic emboli, ischaemic stroke and medication-related complications such as major bleeds, which affects morbidity and mortality. The main aims of management for patients with atrial fibrillation are that of reduction of stroke and systemic embolic risk, rate control, and the relief of symptoms attributed to atrial fibrillation.

The CHA_2DS_2-VASc score is used to stratify risk of stroke associated with non-valvular atrial fibrillation and may not be applicable to patients with atrial fibrillation and rheumatic mitral valve disease. A score of 2 or more is generally considered to be a risk of thromboembolism, and warfarin therapy is indicated. Anticoagulation can be considered for patients with a score of 1. The higher the score, the greater the risk of stroke and therefore the more compelling the use of effective anticoagulation.[4]

Warfarin, a vitamin K antagonist, is the anticoagulant recommended in the Adult Hospital level Standard Treatment Guideline and Essential Medicines List, 2019.[5] Anticoagulation is aimed at preventing thrombo-embolic events. Warfarin is usually prescribed at a starting oral dose of 5 mg, and the dose is adjusted according to the international normalised ratio (INR). Known difficulties with warfarin are that it has a narrow therapeutic index that requires frequent INR monitoring with dose adjustments, and is associated with many drug-drug and drug-food interactions.[6]

A motivation was received for the inclusion of the direct acting oral anticoagulants (DOACs) on the National Essential Medicines List for chronic non-valvular atrial fibrillation at secondary level of care. DOACs have been registered by the Medicines Control Council (now South African Health Products Regulatory Authority) and are available on the South African market. DOACs directly inhibit coagulation factors, with dabigatran inhibiting thrombin, and rivaroxaban and apixaban inhibiting factor Xa. As therapeutic alternatives to warfarin, DOACs have a more predictable pharmacokinetic profile, do not require frequent monitoring, have less reported drug-drug or drug-food interactions, and are easier to administer compared to warfarin.[7] They are also thought to result in less major bleeding overall, particularly intracranial bleeding. On the other hand, an increase in gastrointestinal (GI) bleeding has been reported with the use of DOACs compared to warfarin.[6] Additionally, unlike for warfarin, accessibility to reversal agents for DOACs that may be required in the event of over-anticoagulation or toxicity is limited.[8] These relative benefits and harms of DOACs will be important in the assessment of their overall efficacy and safety.

A review of the available evidence follows to compare the efficacy of warfarin to the direct acting oral anticoagulants (also known as new/novel oral anticoagulants) to prevent thromboembolic events in patients with non-valvular atrial fibrillation.

5. OBJECTIVE AND RESEARCH QUESTION:

Amongst adult patients with chronic non-valvular atrial fibrillation, are the direct acting oral anticoagulants (DOACs) more efficacious than warfarin in preventing ischaemic stroke, systemic embolism and mortality, and safer than warfarin with regards to major bleeds?

PICO framework of the technical review

- **Population:** Adults with non-valvular atrial fibrillation, otherwise unspecified
- **Intervention:** DOACs (rivaroxaban, apixaban, dabigatran) (therapeutic review). Where applicable, data were analysed by subgroup according to whether a high-, or low-dose regimen was used. High dose regimens included all data where the highest dose was used in the study, even if the study only had one intervention dose arm. The low dose subgroup was limited to studies that had intervention arms with multiple dosage regimens.
- **Comparison:** Warfarin

Outcome: Mortality, ischaemic stroke, systemic embolism, major bleeds. We also assessed intracranial and gastrointestinal bleeding separately due to their clinical importance as subgroups of major bleeding.

6. METHODS

PubMed, the Cochrane Database of Systematic Reviews, Epistemonikos databases were searched up to 12 October 2021, and references of systematic reviews were scanned. There was no restriction on date, language, or publication status. We also looked at the clinical guidelines such as National Institute for Health and Care Excellence, American College of Cardiology, Canadian Agency for Drugs and Technologies in Health, American Society of Hematology, and European Society of Cardiology. The search strategy was adapted for each database used (Appendix A). Included were systematic reviews of randomized controlled trials. We only included studies that had a direct comparison between DOACs (including edoxaban, not SAHPRA-registered) and warfarin.

The most up to date systematic review with the highest quality was then selected for further reporting. We cross checked that all trials reported in other reviews were also reported in the up to date, high quality review.

a. Excluded studies:

Most studies initially screened were excluded as they did not match the pre-specified PICO framework for the review. We also excluded trials, case reports, case series, and narrative reviews.

b. Data extraction

Three reviewers independently assessed the screened systematic reviews for eligibility. We determined the list of eligible systematic reviews based on their relevance by discussion and assessed their quality. Reviewers independently assessed the quality of the selected systematic review, and consensus was reached by discussion. The most appropriate systematic review was selected based its recency and quality.

Eligible trials information and outcome data were extracted from the eligible systematic review by a single reviewer and verified by the other 2 reviewers and were reported in Table 1. We extracted point estimates of effects and their respective 95% confidence interval bounds. Due to the presence of double counting in the reviewed meta-analysis, we reported point estimates and confidence intervals from subgroup analyses where applicable rather than the overall pooled estimates and corresponding confidence intervals. Numbers needed to treat to benefit (NNTB) or harm (NNTH) were obtained by using baseline risks of outcomes that were calculated from the extracted data with inverse variance weighting (Appendix Table 1).

We assessed the study quality of the potentially eligible systematic reviews using AMSTAR-2, a critical appraisal tool for systematic reviews that include randomised and non-randomised studies.[9] Risk of bias from individual studies was assessed using the modified Cochrane Collaboration risk of bias tool.[10] Certainty of evidence was assessed using the GRADE framework, and the summary of findings table was created in GRADEPro.[11]

Sensitivity analysis

Our literature search identified the meta-analysis by Jia[12] et al. as the most appropriate report for this review, however, it was still deemed to be of critically low quality on the AMSTAR-2 rating. Major concerns included the presence of double-counting of control groups in estimate pooling, the lack of *a priori* protocol formulation or reporting indicating a pre-specified analysis plan, and significant heterogeneity in the majority of pooled analyses without any reported attempt to investigate for potential causes. In addition, the meta-analysis included trials that assessed edoxaban, which was not part of the original PICO definition, and we wanted to assess whether the inclusion of these data would significantly affect the magnitude and/or direction of results. We therefore conducted a separate meta-analysis by extracting the data from the studies that were included in our primary review, namely RE-LY[13], ROCKET-AF[14], J-ROCKET-AF[15], ARISTOTLE[16], and ENGAGE-AF-TIMI 48[17]. The outcomes used were in accordance with the pre-specified PICO definition. In addition, we also analysed intracranial bleeding and major

gastrointestinal bleeding separately. Risk ratios were calculated to assess the measure of effect, as well as 95% confidence intervals for each of the pooled estimates. The inverse variance and random effects methods were used for this sensitivity analysis. Heterogeneity was assessed using the I^2 statistic. In order to prevent double counting of participants from control treatment arms and to assess potential differences in efficacy and safety between dosage regimens, 3 separate analyses were conducted to assess the outcomes, stratified by treatment regimen: 1) all dosage regimens, which included all studies and participants regardless of dosage administered, 2) low dosage regimens, which was limited to participants in studies that received a low dosage regimen in a multi-dose treatment trial, i.e. RE-LY[13] and ENGAGE-AF-TIMI 48[17], and 3) high dosage regimens, which only included participants in studies that received a high dosage regimen in a multi-dose treatment trial (RE-LY[13] and ENGAGE-AF-TIMI 48[17]). Finally, we assessed whether the inclusion of studies assessing edoxaban would significantly alter the magnitude and/or direction of effect by comparing the forest plots with, and without, these data.

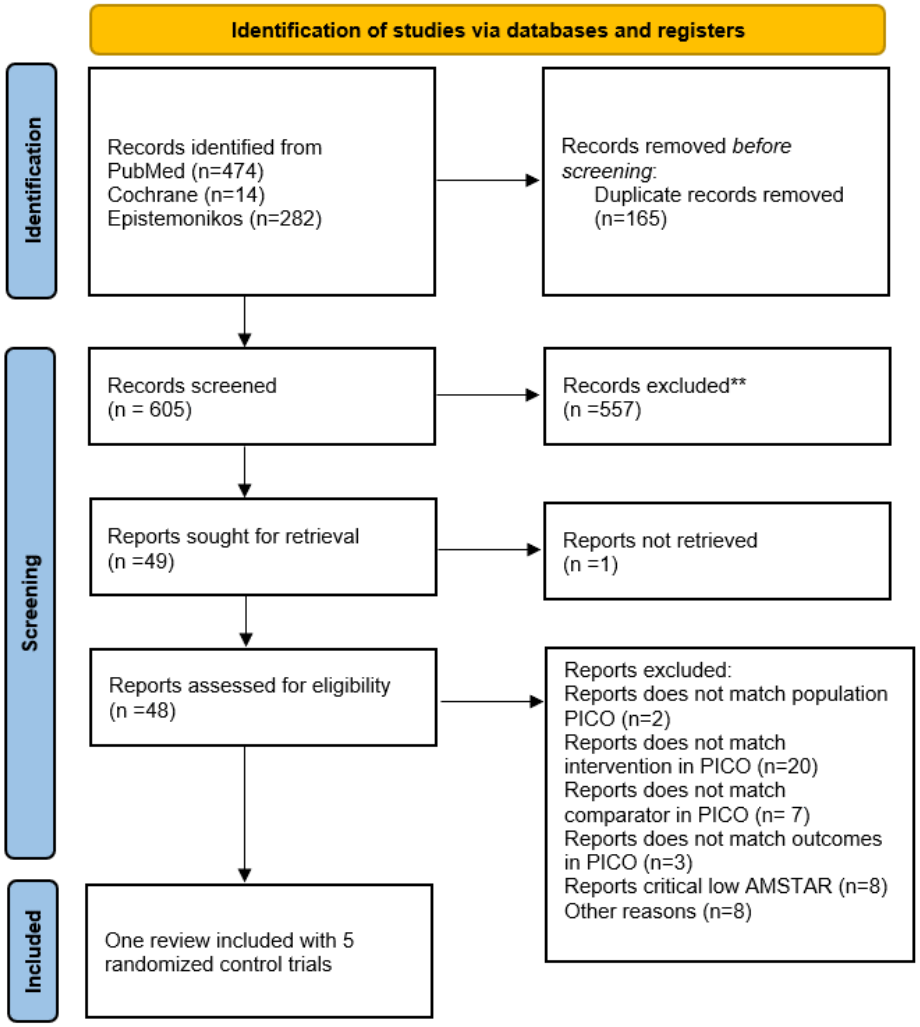

Figure 1. PRISMA flow-chart detailing study identification, selection, and exclusion

7. RESULTS

Table 1. Characteristics of the studies and treatments included in the systematic review by Jia et al (2014)

Characteristics	Dabigatran RE-LY[13]	Rivaroxaban ROCKET-AF[14]	Apixaban ARISTOTLE[16]	J–ROCKET-AF[15]	ENGAGE, AF-TIMI 48[17]
Number of participants (n)	18 113	14 264	18 201	1 278	21 105
Experimental Drug	Dabigatran 150 mg or 110 mg, twice daily	Rivaroxaban 20 mg or 15 mg (RDA), once daily	Apixaban 5 mg or 2,5 mg (RDA), twice daily	Rivaroxaban 15mg or 10mg (RDA), once daily	Edoxaban 60mg or 30mg, once daily
Experimental (n)	12 091	7 131	9 120	639	14 036
High dose	6 076	5 624	8 702	498	7 035
Low dose	6 015	1 597	428	141	7 034
Control drug	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 2-3, once daily	Warfarin dose-adjusted to INR 1.6-2.6 ≥ 70yrs; INR 2-3 <70yrs, once daily	Warfarin dose-adjusted to INR 2-3, once daily
Control (n)	6 022	7 133	9 081	639	7 036
Mean TTR (%)	64.4	55.2	62.2	44	64.9
Median TTR (%)	67	58	66	-	68.4
Trial Phase	III	III	III	III	III
Design of randomised control trial	Multicentre, PROBE†	Multicentre double-blind	Multicentre double-blind	Multicentre double- blind, double-dummy	Multicentre double-blind, double- dummy
Adjudicating committee & blinded adjudication of outcomes	Yes	Yes	Yes	Yes	Yes
Interim analysis (n)	2	1	1	1	1
Analysis type	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority
Non-inferiority margin	Relative risk < 1.46	Relative risk < 1.46	Relative risk < 1.38	Relative risk < 2	Relative risk<1.38
Main efficacy outcome	Stroke and SEE	Stroke and SEE	Stroke and SEE	Stroke and SEE	Stroke and SEE
Main efficacy population	Intention-to-treat	Per protocol	Intention-to-treat	Intention-to-treat and Per protocol	Intention-to-treat
Main safety outcome	Major bleeding	Clinically relevant bleeding	Major bleeding	Major & non-major bleeding	Major bleeding
Main safety population	Safety population	Safety population	Safety population	Safety population	Safety population
Secondary efficacy outcomes	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding	IS, HS, all-cause mortality, and MI Safety – ICB and GIT bleeding
Quality of evidence§	Poor	Good	Good	Good	Good
Median length follow-up (days)	730	707	657	584	907

*After treatment discontinuation

GIT: gastrointestinal; HS: haemorrhagic stroke; ICB: intracranial bleeding; INR: International normalized ratio; IS: ischaemic stroke;

†PROBE: prospective, open-label, blinded endpoint; RDA: renal dose adjusted, SEE: systemic embolic events; TTR: time in therapeutic range

§See Figure 11 for risk of bias summary

8. Evidence synthesis

a. Ischaemic stroke and systemic emboli

The pooled risk of stroke and systemic embolism in patients randomised to DOACs was 20% lower (RR = 0.80 95% CI, 0.71-0.91, Figure 2) than those randomised to warfarin (high certainty evidence). This benefit was mostly driven by the large reduction of haemorrhagic stroke (RR = 0.50; 95% CI, 0.41-0.62, Figure 3).

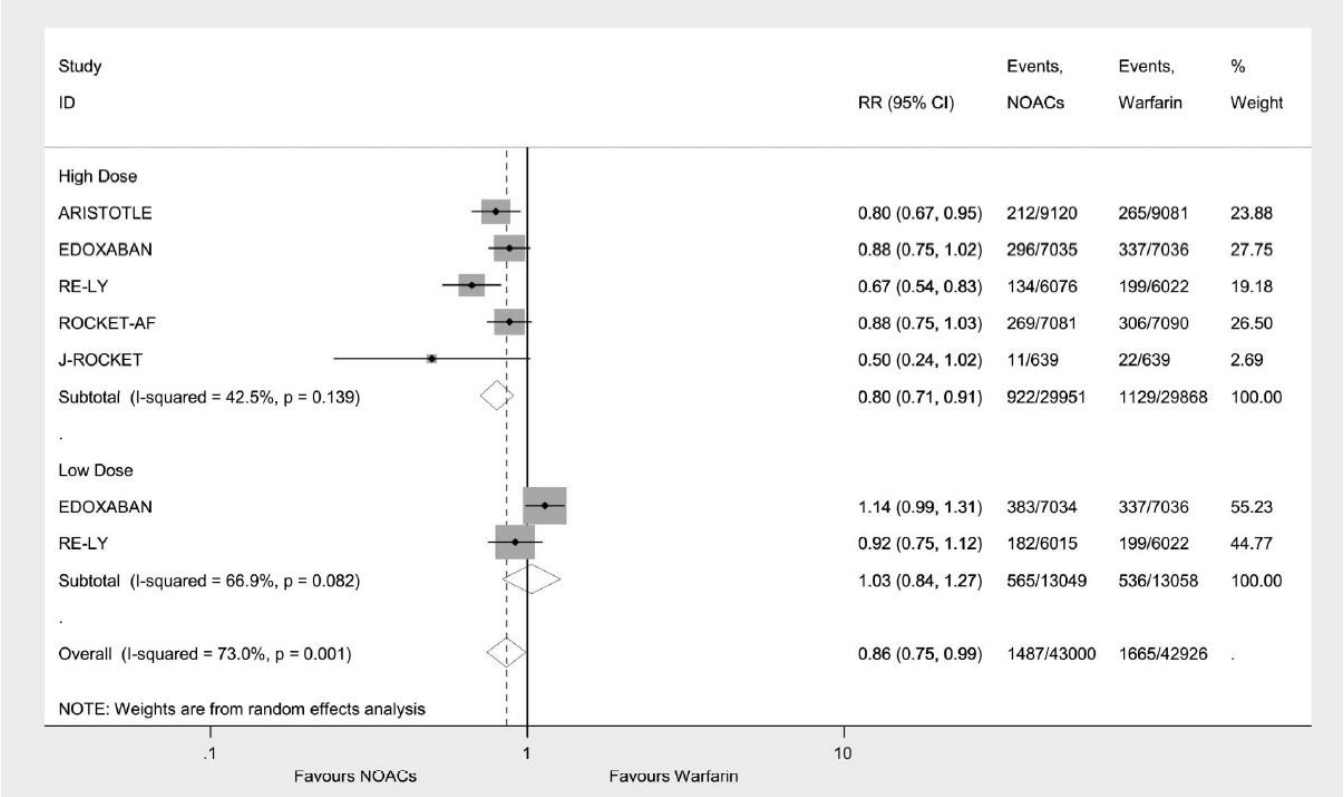

Figure 2. Meta-analysis of stroke and systemic embolism for high dose and low dose regimens, by Jia et al (2014).[12]

For low-dose regimens, DOACs demonstrated similar efficacy to warfarin for prevention of stroke and systemic emboli in each study (RR = 1.03; 95% CI, 0.84-1.27). If differentiated by stroke types, the large reduction in the risk of haemorrhagic stroke (RR = 0.33; CI, 0.23-0.46) was offset by the increase in ischaemic stroke (RR = 1.31; 95% CI, 1.14-1.49). The number needed to treat to prevent one additional ischaemic stroke or systemic embolism (NNTB) was 149 (95% CI: 103-331) for high dose regimens.

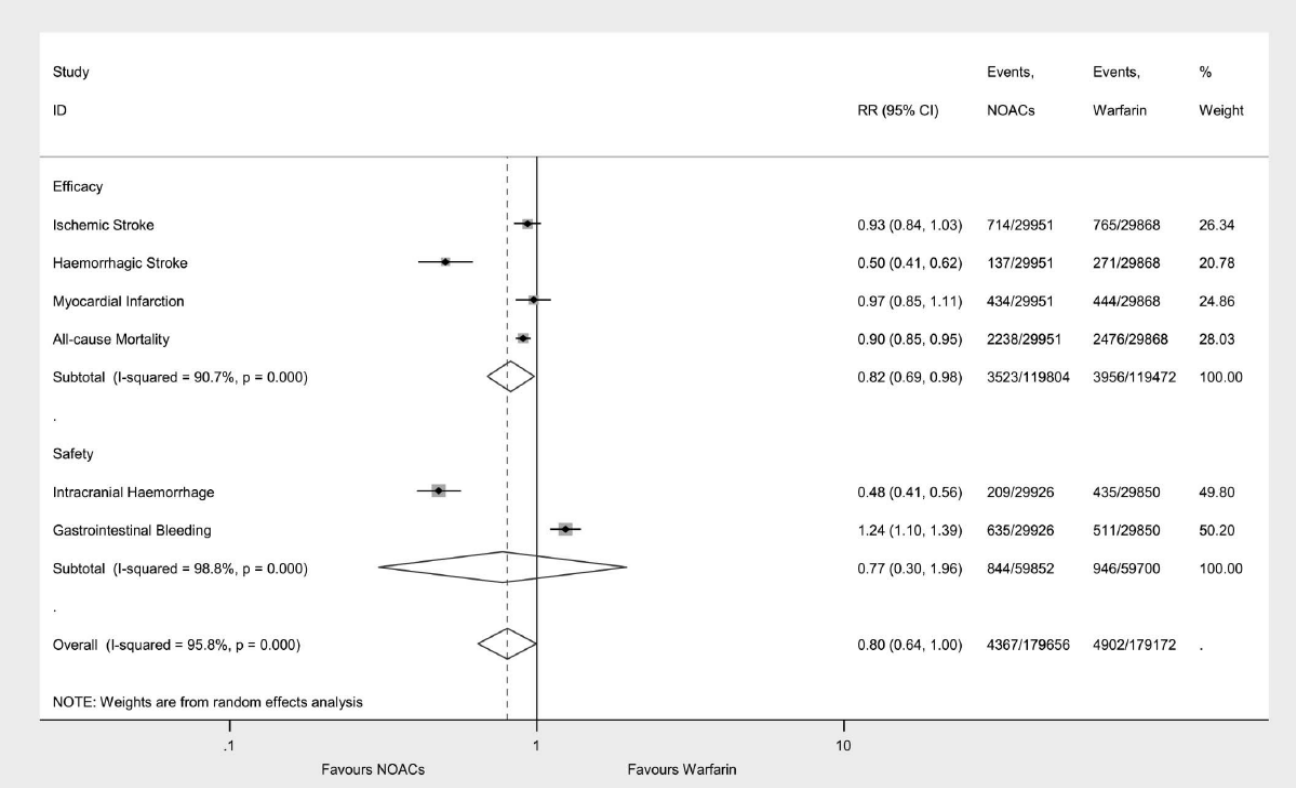

Figure 3. Forest plot of efficacy and safety for high-dose regimen, by Jia et al (2014).[12]

b. <u>All-cause mortality</u>

Compared with warfarin, DOACs were associated with a reduced risk for mortality The high dosage regimen was associated with a relative risk reduction of 10% (RR = 0.90 [95% CI: 0.85-0.95]), and the low dosage regimen was associated with a relative risk reduction of 11% (RR = 0.89 [95% CI: 0.83-0.96], Figure 4; Certainty of evidence: High). The numbers needed to treat to prevent one additional death (NNTB) were 177 (95% CI: 118-354) for the high dose regimen, and 161 (95% CI: 104-442) for the low dose regimen.

c. <u>Major bleeding</u>

Overall, the risks for major bleeding associated with the use of a high dose regimen of DOACs were lower compared with warfarin use (RR = 0.86 [95% CI: 0.74-0.99], Figure 5*;* Certainty of evidence: High). Lower dose DOAC regimens probably reduce major bleeding (RR = 0.63, 95% CI: 0.38-1.04). The number needed to treat with a high dose DOAC to prevent one major bleed is 119 (95% CI: 64-1660).

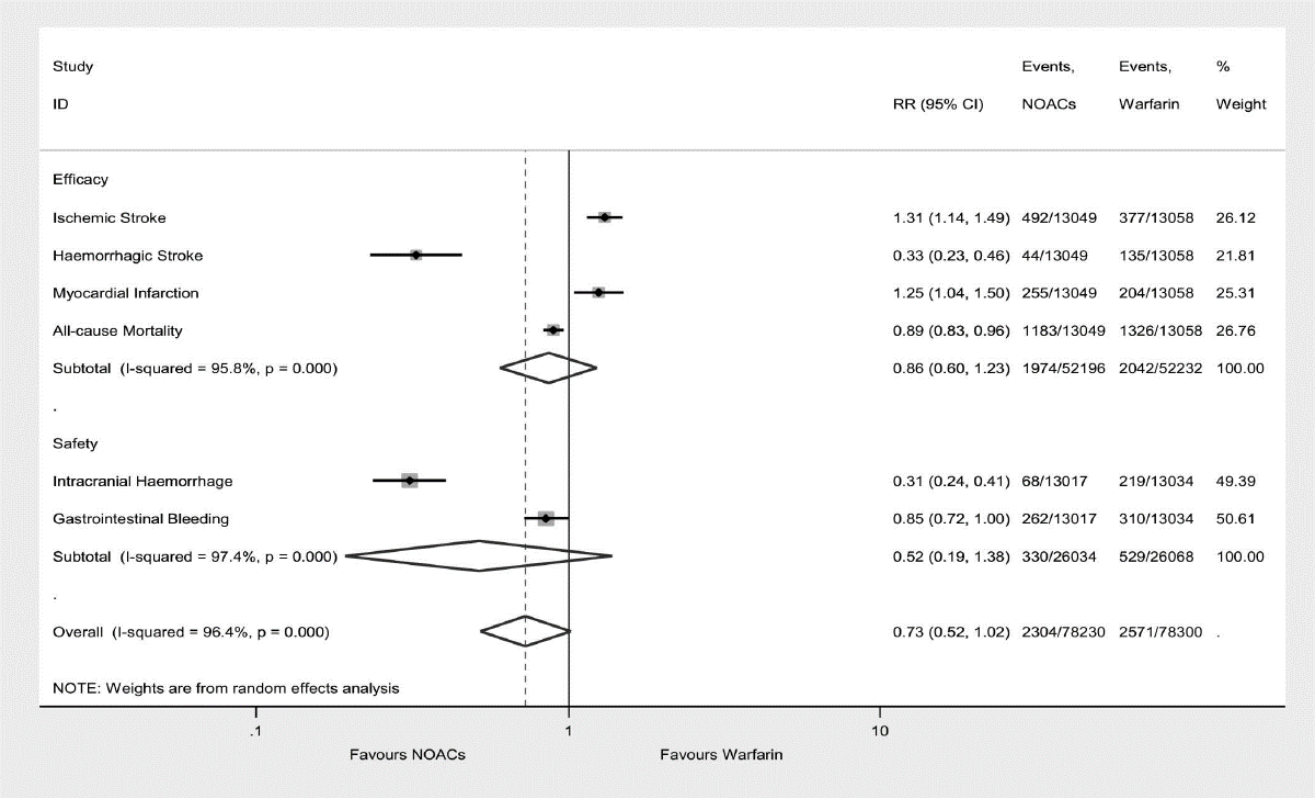

Figure 4. Forest plot of efficacy and safety for low-dose regimen by Jia et al (2014).[12]

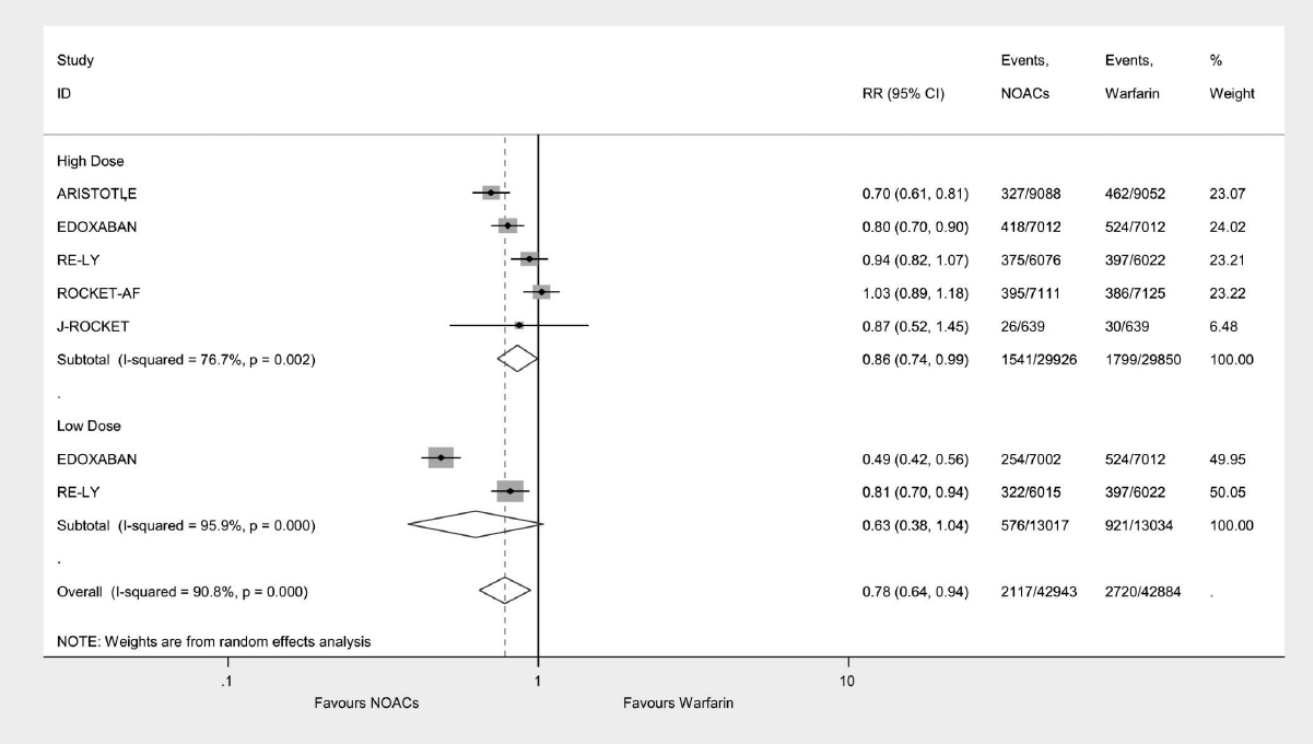

Figure 5. Forest plot of major bleeding for high-dose and low-dose regimen, Jia et al (2014).[12]

Intracranial bleeding

The use of DOACs resulted in a large reduction in intracranial bleeding risk, with a 69% relative decrease observed when a low dose regimen was compared with warfarin therapy (RR = 0.31, [95% CI: 0.24-0.41]; Figure 3), and a relative risk reduction of 52% when high dose DOAC regimens were compared with warfarin (RR = 0.48, [95% CI: 0.41-0.56]; Figure 4; Certainty of evidence: High). The numbers needed to treat to prevent one additional episode of intracranial haemorrhage (NNTB) were 136 (95% CI: 120-161) and 103 (95% CI: 93-120) using high-, and low-dose regimens respectively.

Gastrointestinal bleeding

There was an increased risk of gastrointestinal bleeding with high-dose DOAC regimens compared with warfarin (RR = 1.24 [95% CI: 1.10-1.39]; Certainty of evidence: High). However, this risk was reduced when low-dose DOAC regimens were used (RR = 0.85, [95% CI: 0.72-1.00]). The number needed to treat to cause (NNTH) one additional episode of GI bleeding with the high dose regimen was 224 (95% CI: 138-538).

9. Sensitivity analysis

Sensitivity analyses assessing outcomes that considered all dosage regimens with the exclusion of edoxaban-related trials (i.e. ENGAGE-AF-TIMI 48[17]) were similar in direction and magnitude (Figure 6) when compared with the data from the reviewed meta-analysis. When edoxaban data were excluded for the outcome of mortality, a minor change in risk ratio was noted from 0.90 (95% CI: 0.85-0.94) when edoxaban studies included, to 0.89 (95% CI: 0.83-0.96) without edoxaban studies. For the composite outcome of ischaemic stroke and systemic embolism, the risk ratio changed from 0.82 (95% CI: 0.74-0.90) to 0.85 (95% CI: 0.77-0.93). For the outcome of major bleeding, the risk ratio changed from 0.85 (95% CI: 0.69-1.03) to 0.91 (95% CI: 0.75-1.09). Similarly, the outcomes of intracranial bleeding and gastrointestinal bleeding also showed non-significant changes from 0.47 (95% CI: 0.34-0.63) to 0.44 (95% CI: 0.35-0.55) with, and without, edoxaban-related studies, and from 1.10 (95% CI: 0.81-1.50) to 1.07 (95% CI: 0.84-1.37) with, and without, edoxaban-related studies respectively. Therefore, the inclusion of edoxaban-related studies in the main evidence synthesis does not change the interpretation or outcomes of this therapeutic review. Other sensitivity analyses to assess the potential influence of double-counting noted in the main therapeutic review also showed a similar direction of effect, though the point estimates differed slightly. (Figure 7-9).

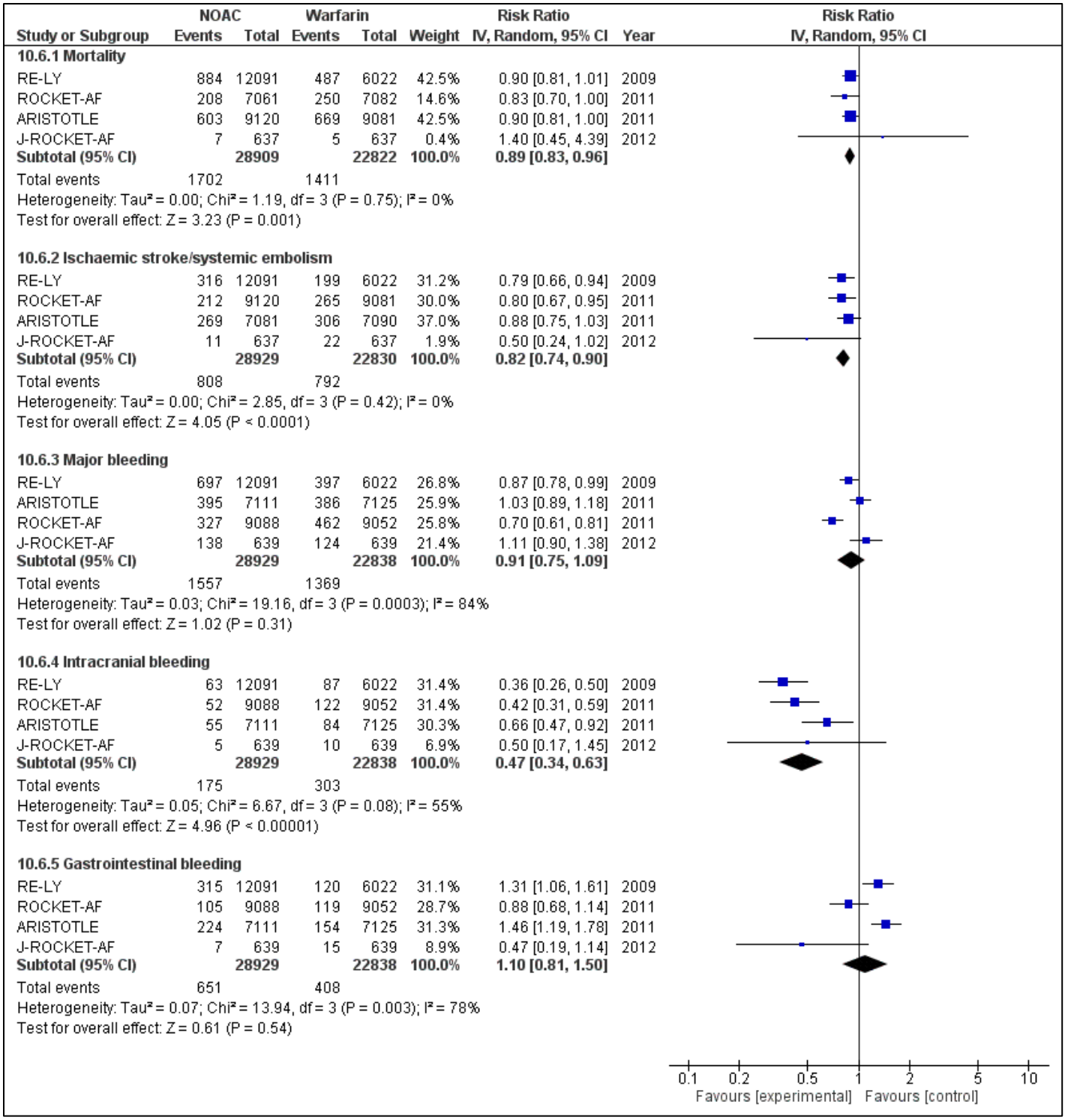

Figure 6. Sensitivity analysis forest plot assessing outcomes using all dosage regimens excluding edoxaban studies

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Random, 95% CI	Year
7.6.1 Mortality							
RE-LY	884	12091	487	6022	24.1%	0.90 [0.81, 1.01]	2009
ROCKET-AF	208	7061	250	7082	8.3%	0.83 [0.70, 1.00]	2011
ARISTOTLE	603	9120	669	9081	24.2%	0.90 [0.81, 1.00]	2011
J-ROCKET-AF	7	637	5	637	0.2%	1.40 [0.45, 4.39]	2012
ENGAGE AF-TIMI 48	1510	14069	839	7036	43.2%	0.90 [0.83, 0.97]	2013
Subtotal (95% CI)		**42978**		**29858**	**100.0%**	**0.90 [0.85, 0.94]**	
Total events	3212		2250				
Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 4 (P = 0.87); I² = 0%							
Test for overall effect: Z = 4.14 (P < 0.0001)							
7.6.2 Ischaemic stroke/systemic embolism							
RE-LY	316	12091	199	6022	22.9%	0.79 [0.66, 0.94]	2009
ROCKET-AF	212	9120	265	9081	22.2%	0.80 [0.67, 0.95]	2011
ARISTOTLE	269	7081	306	7090	26.1%	0.88 [0.75, 1.03]	2011
J-ROCKET-AF	11	637	22	637	1.7%	0.50 [0.24, 1.02]	2012
ENGAGE AF-TIMI 48	435	14069	232	7036	27.0%	0.94 [0.80, 1.10]	2013
Subtotal (95% CI)		**42998**		**29866**	**100.0%**	**0.85 [0.77, 0.93]**	
Total events	1243		1024				
Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 4 (P = 0.29); I² = 19%							
Test for overall effect: Z = 3.45 (P = 0.0006)							
7.6.3 Major bleeding							
RE-LY	697	12091	397	6022	20.8%	0.87 [0.78, 0.99]	2009
ARISTOTLE	395	7111	386	7125	20.3%	1.03 [0.89, 1.18]	2011
ROCKET-AF	327	9088	462	9052	20.2%	0.70 [0.61, 0.81]	2011
J-ROCKET-AF	138	639	124	639	17.7%	1.11 [0.90, 1.38]	2012
ENGAGE AF-TIMI 48	672	14014	524	7012	21.0%	0.64 [0.57, 0.72]	2013
Subtotal (95% CI)		**42943**		**29850**	**100.0%**	**0.85 [0.69, 1.03]**	
Total events	2229		1893				
Heterogeneity: Tau² = 0.05; Chi² = 42.22, df = 4 (P < 0.00001); I² = 91%							
Test for overall effect: Z = 1.65 (P = 0.10)							
7.6.4 Intracranial bleeding							
RE-LY	63	12091	87	6022	23.0%	0.36 [0.26, 0.50]	2009
ROCKET-AF	52	9088	122	9052	23.0%	0.42 [0.31, 0.59]	2011
ARISTOTLE	55	7111	84	7125	22.0%	0.66 [0.47, 0.92]	2011
J-ROCKET-AF	5	639	10	639	4.1%	0.50 [0.17, 1.45]	2012
ENGAGE AF-TIMI 48	102	14014	132	7012	27.8%	0.39 [0.30, 0.50]	2013
Subtotal (95% CI)		**42943**		**29850**	**100.0%**	**0.44 [0.35, 0.55]**	
Total events	277		435				
Heterogeneity: Tau² = 0.03; Chi² = 7.85, df = 4 (P = 0.10); I² = 49%							
Test for overall effect: Z = 7.09 (P < 0.00001)							
7.6.5 Gastrointestinal bleeding							
RE-LY	315	12091	120	6022	23.6%	1.31 [1.06, 1.61]	2009
ROCKET-AF	105	9088	119	9052	21.6%	0.88 [0.68, 1.14]	2011
ARISTOTLE	224	7111	154	7125	23.9%	1.46 [1.19, 1.78]	2011
J-ROCKET-AF	7	639	15	639	6.0%	0.47 [0.19, 1.14]	2012
ENGAGE AF-TIMI 48	361	14014	190	7012	24.9%	0.95 [0.80, 1.13]	2013
Subtotal (95% CI)		**42943**		**29850**	**100.0%**	**1.07 [0.84, 1.37]**	
Total events	1012		598				
Heterogeneity: Tau² = 0.06; Chi² = 19.09, df = 4 (P = 0.0008); I² = 79%							
Test for overall effect: Z = 0.54 (P = 0.59)							

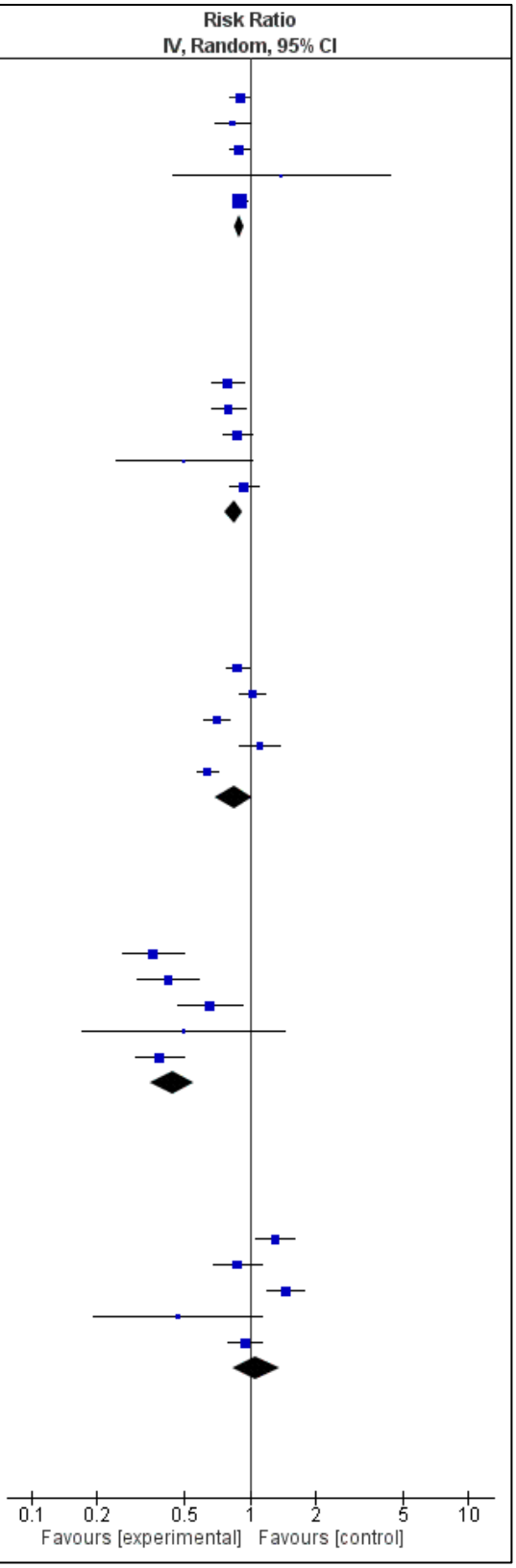

Figure 7. Sensitivity analysis forest plot assessing outcomes using all dosage regimens including edoxaban studies

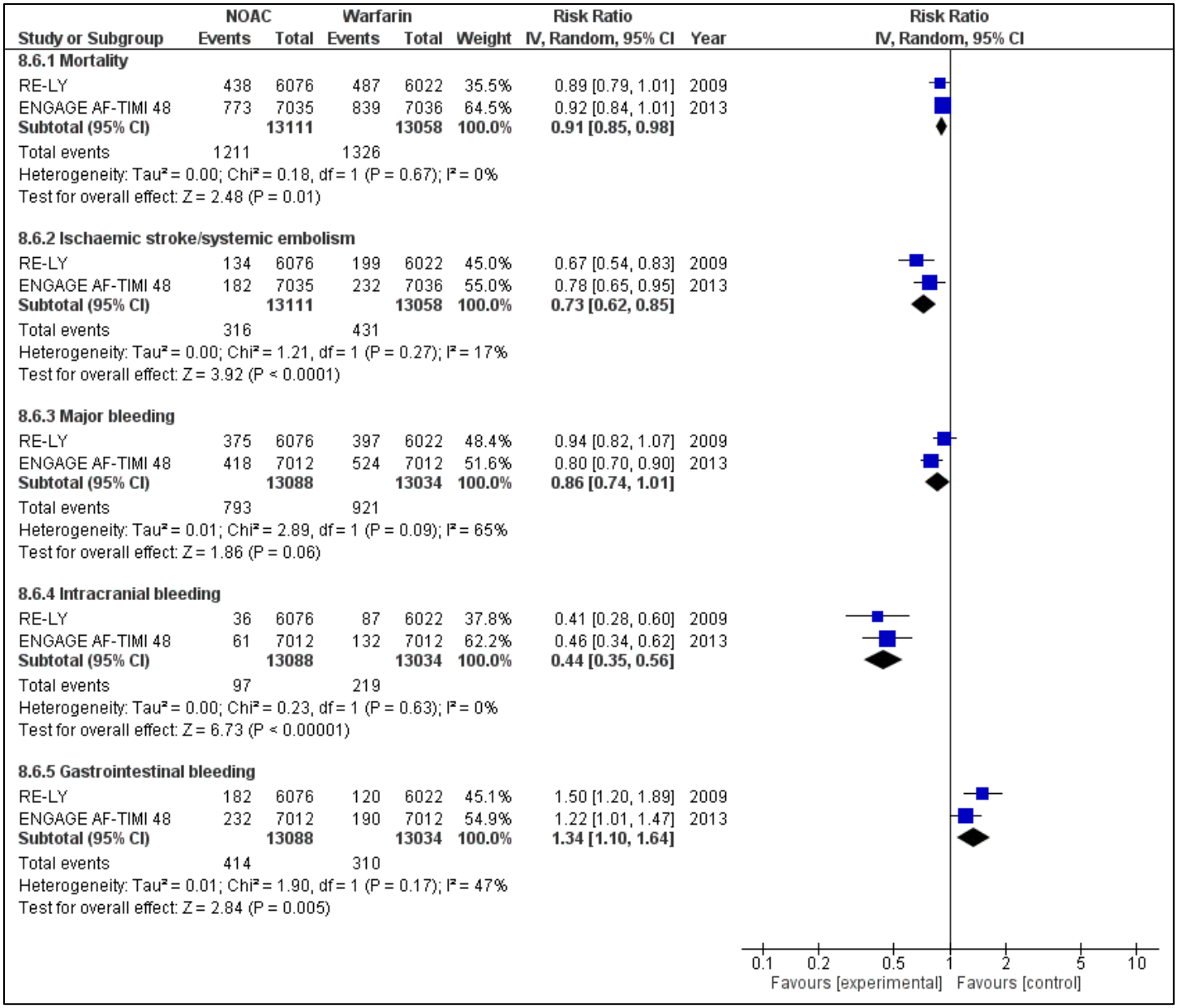

Figure 8. Sensitivity analysis forest plot assessing outcomes using high dosage regimens

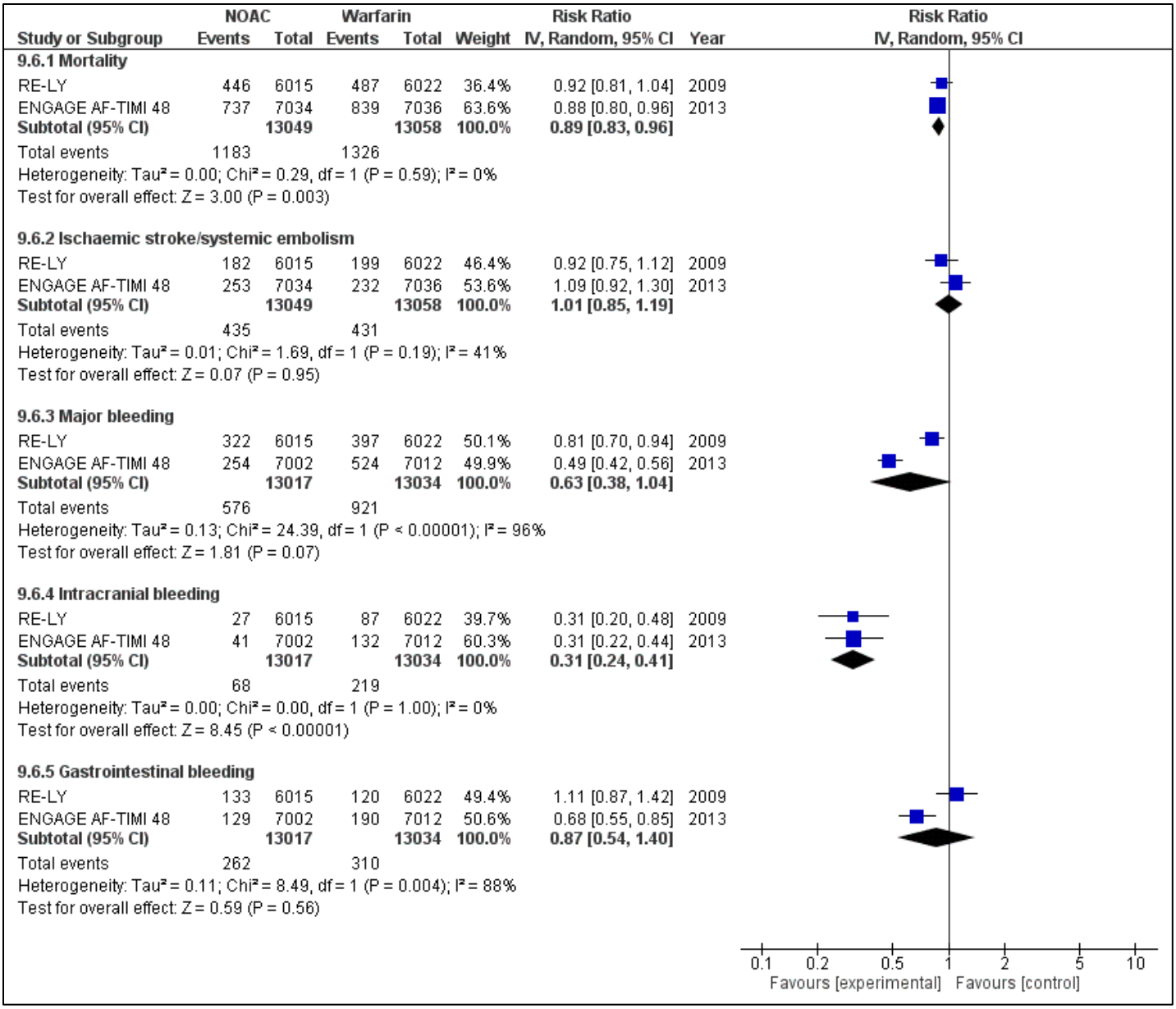

Figure 9. Sensitivity analysis forest plot forest plot assessing outcomes using low dosage regimens

Table 2. Excluded studies

Citation	Reference	Reason for exclusion
[18]	Adam, 2012	Critical low score on AMSTAR tool.
[19]	Almutairi, 2017	Population included those with DVT, not in keeping with PICO
[20]	Antza, 2019	Network meta-analysis with head-to-head comparisons
[21]	Bates, 2017	Outcomes and interventions not in keeping with PICO
[22]	Biondi-Zoccai, 2013	Network meta-analysis with head-to-head comparisons
[23]	Briere, 2019	No meta-analysis conducted
[24]	Caldeira, 2015	Edoxaban included in meta-analyses, not in keeping with PICO for this review
[25]	Canadian Agency for Drugs and Technologies in Health, 2012	Health technology appraisal summary, no new data synthesis included
[26]	Chai-Adisaksopha, 2014	Outcomes not in keeping with PICO
[27]	Chai-Adisaksopha, 2015	Population not in keeping with PICO
[7]	Capodanno, 2013	Critical low score on AMSTAR tool.

[28]	Coleman, 2019	Critical low score on AMSTAR tool.
[29]	Cope, 2015	Intervention not in keeping with PICO
[30]	Deitelzweig, 2017	No meta-analysis conducted
[31]	Deitelzweig, 2018	Network meta-analysis with head-to-head comparisons
[32]	Dogliotti, 2013	Interventions such as ximelagatran were included in the PICO definition
[33]	Dogliotti, 2014	Interventions such as aspirin and clopidogrel were included in the PICO definition
[34]	Escobar, 2018	Critical low score on AMSTAR tool, included Observational controlled studies
[35]	Fernandes, 2015	Unable to source full text
[36]	Gomez-Outes, 2013	Critical low score on AMSTAR tool.
[37]	Guo, 2017	Not in keeping with PICO for this review
[38]	Harenberg, 2012	Head-to-head comparisons conducted, not in keeping with PICO
[39]	Hicks, 2016	Phase 2 clinical trial data; edoxaban was included in the analysis
[40]	Hirschl, 2019	Vitamin K antagonists other than warfarin included in study
[41]	Kwong, 2014	Analysis included comparators other than warfarin
[42]	López-López, 2017	Intervention not in keeping with PICO
[43]	Lowernstern, 2018	Edoxaban included in meta-analyses, not in keeping with PICO for this review
[44]	Madzak, 2015	Customised composite endpoints used for their analysis, not in keeping with PICO for this review
[45]	Mendoza, 2017	Non-English manuscript, unable to obtain translated manuscript
[46]	Miller, 2012	Critical low score on AMSTAR tool.
[47]	Mitchell, 2013	Head-to-head comparisons conducted, not in keeping with PICO
[48]	Morimoto, 2015	Intervention not in keeping with PICO; study design
[49]	Ntaios, 2017	Vitamin K antagonists other than warfarin included in study
[50]	O'Dell, 2012	No meta-analysis conducted
[51]	Pirlog, 2019	Outcomes were not in keeping with PICO
[52]	Providência, 2014	Intervention not in keeping with PICO; study design
[53]	Rong, 2015	Methodological not in keeping with PICO for this review
[6]	Ruff, 2014	J-ROCKET not included in systematic review, , whilst was included in Jia et al (2014)
[54]	Siddiqui, 2019	Intervention not in keeping with PICO
[55]	Sun, 2019	Comparator not in keeping with PICO
[56]	Tahir, 2013	No meta-analysis conducted
[57]	Tereshchenko, 2016	Edoxaban and left atrial appendage occlusion interventions included in analysis
[58]	Testa, 2012	Critical low score on AMSTAR tool.
[59]	Verdecchia, 2015	Intervention only included apixaban
[60]	Wang, 2020	Edoxaban included in meta-analyses, methodology not in keeping with PICO for this review
[61]	Waranugraha, 2021	Edoxaban included in meta-analyses, methodology not in keeping with PICO for this review
[62]	Xu, 2021	Head-to-head comparisons; Comparator not in keeping with PICO

10. Evidence quality:

While the included meta-analysis was able to provide data to address the question, the overall confidence in data quality was assessed as critically low due to the presence of one or more critical errors and/or omissions according to the AMSTAR-2 critical appraisal tool (Figure 10). Study quality of the included RCTs were mostly of good quality (Figure 11-12).

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall confidence
Jia (2014)																	Critically low

Legend of answers to appraisal questions: Red = No, Orange = Partial yes, Green = Yes.
Greyed domain questions are deemed critical

Figure 10. Overall confidence in study quality assessment with AMSTAR-2 appraisal tool

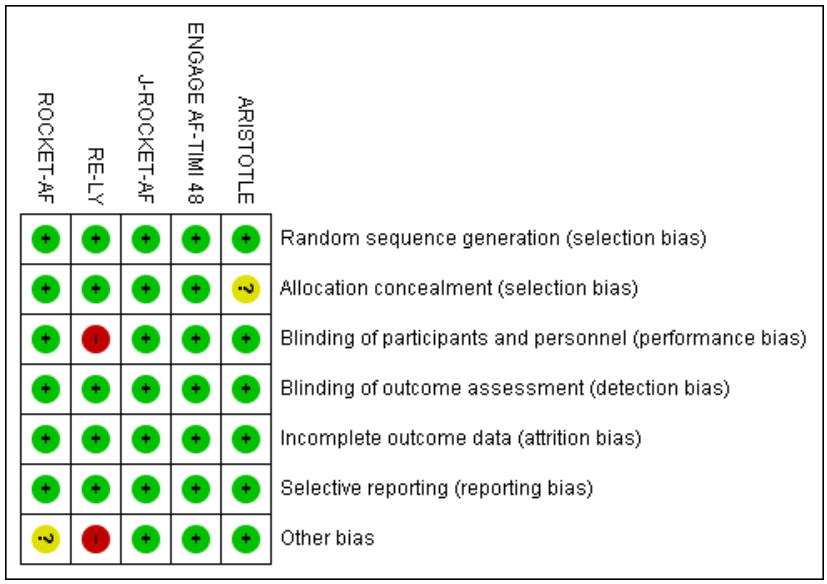

Figure 11. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

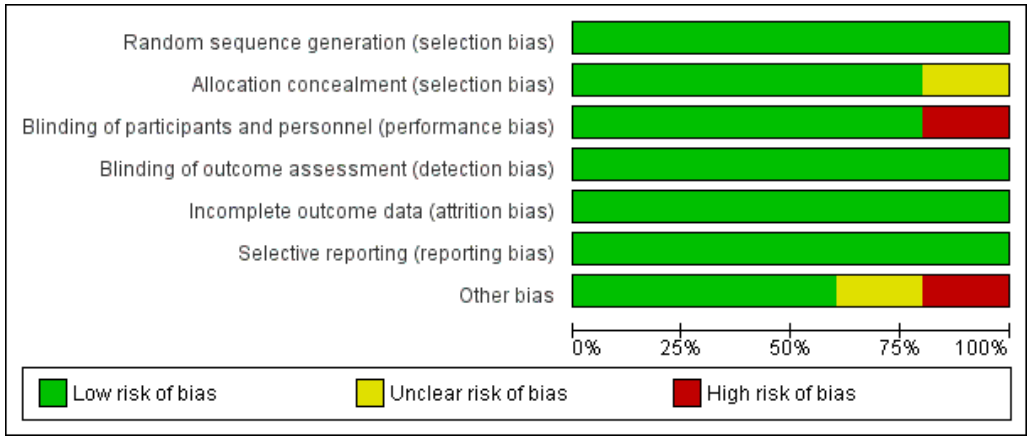

Figure 12. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 2: Summary of findings: DOACs compared to warfarin for anticoagulation in chronic non-valvular atrial fibrillation

DOACS compared to Warfarin for Chronic non-valvular atrial fibrillation

Patient or population: Chronic non-valvular atrial fibrillation
Intervention: DOACS
Comparison: Warfarin

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Warfarin	Risk difference with DOACS
Mortality	72836 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.90** (0.85 to 0.94)	75 per 1,000	**8 fewer per 1,000** (11 fewer to 5 fewer)
Ischaemic stroke/Systemic embolism	72864 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.85** (0.77 to 0.93)	34 per 1,000	**5 fewer per 1,000** (8 fewer to 2 fewer)
Major bleeding - All major bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.85** (0.69 to 1.03)	63 per 1,000	**10 fewer per 1,000** (20 fewer to 2 more)
Major bleeding - Intracranial bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 0.44** (0.35 to 0.55)	15 per 1,000	**8 fewer per 1,000** (9 fewer to 7 fewer)
Major bleeding - Gastrointestinal bleeding	72793 (5 RCTs)	⊕⊕⊕⊕ High	**RR 1.07** (0.84 to 1.37)	20 per 1,000	**1 more per 1,000** (3 fewer to 7 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CONCLUSION

Five phase III randomised controlled trials, namely ARISTOTLE[16], ENGAGE AF-TIMI 48[17], RE-LY[13], ROCKET-AF[14], and J-ROCKET-AF[15] were included in the meta-analysis that we selected for reporting in this therapeutic review. DOACs reduced the risk of stroke and systemic embolism compared with warfarin. The benefit was mainly driven by a substantial reduction in haemorrhagic stroke. Additionally, DOACs were associated with lower all-cause mortality compared to warfarin. For DOACs that assessed multiple dosage regimens, the lower dose appeared to reduce the risk of adverse bleeding, however, this was also associated with a reduction in the prevention of thromboembolic strokes and systemic emboli. Overall, when considering the balance of efficacy and safety DOACs are a viable alternative to warfarin for the long-term prevention of stroke in patients with chronic non valvular AF.

Besides potential therapeutic benefits, providing access to DOACs would eliminate the substantial burden to the health services of INR monitoring which is required with warfarin therapy which may be associated with healthcare access inequality.[18] The cost of DOACS needs to be considered as that be a potential barrier to adequate drug access: DOACs may be 4-8 fold more expensive when compared with warfarin, even when other associated treatment costs, e.g. monthly INR monitoring, are taken into account. It is possible that the additional benefits provided by DOACs may outweigh the incremental costs that would be incurred. To maximize feasibility, DOACs may potentially be considered for patients who have failed initial anticoagulation with warfarin (i.e. labile INRs, poor access to healthcare facilities, and adverse effects such as intracranial haemorrhage). Formal pharmacoeconomic assessments are needed.

Appendix A: 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	Randomised controlled trials Large sample size Despite the critically low assessment of the systematic review by Jia et al (2019), the GRADE assessments per outcome were generally graded as high certainty evidence (see below and the summary of findings table 2, above).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	• Stroke/systemic embolism: RR 0.86 (95% CI: 0.75-0.99), *high certainty evidence* • Ischaemic stroke: RR 0.93 (95% CI: 0.84-1.03) • Haemorrhagic stroke: RR 0.50 (95% CI: 0.41-0.62), *high certainty evidence* • Mortality: - High dose regimen: RR 0.90 (95% CI: 0.85-0.95), *high certainty evidence* - Low dose regimen: RR 0.89 (95% CI: 0.83-0.96), *high certainty evidence*
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	Randomised controlled trials Large sample size Despite the critically low assessment of the systematic review by Jia et al (2019), the GRADE assessments per outcome were generally graded as high certainty evidence (see below and the summary of findings table 2, above).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	Overall, DOACs are safer and result in lower rates of major bleeding and intracranial haemorrhage compared to warfarin; however, the risk of gastrointestinal bleeding is increased, particularly when higher doses are used. **Major bleeding:** - High dose regimen: 0.86 (95% CI: 0.74-0.99), *high certainty* - Low dose regimen: 0.63 (95% CI: 0.38-1.04), *high certainty*

		Intracranial bleeding: - High dose regimen: 0.48 (95% CI: 0.41-0.56), *high certainty* - Low dose regimen: 0.31 (95% CI: 0.24-0.41), *high certainty* **Gastrointestinal bleeding:** - High dose regimen: 1.24 (95% CI: 1.10-1.39), *high certainty* - Low dose regimen: 0.85 (95% CI: 0.72-1.00), *high certainty*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available?**	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	DOACs may potentially be considered, noting that management with warfarin is more complex requiring INR-monitoring with respective dose adjustments.
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	**Price of medicines – 30 days** **Medicine (30 days) / SEP (ZAR) / 60% of SEP** Dabigatran, 150 mg 12 hourly / 1133.06 / 679.84 Dabigatran, 110 mg 12 hourly / 1133.06 / 679.84 Rivaroxaban, 20 mg daily / 637.50** / 382.50 Apixaban, 5 mg 12 hourly / 983.40 / 590.04 Warfarin, 5 mg daily / 52.09 / 31.32 ** generic price on SEP database *References:* SEP database, 24 December 2021 NHLS price list for public sector, 2021 **Other resources:** *SEP of warfarin only; additional cost of R51.62 per INR test Frequency of INR testing: every 2-3 days upon initiation for the first 2 weeks or until stability of INR, then weekly/as clinically indicated **Pharmacoeconomic and budget impact analysis** *(refer to the detailed report update by J Miot and TD Leong, 26 March 2022):* This economic analysis was conducted from the payer's perspective (i.e. Department of Health), using a discount rate of 5% for both cost and clinical inputs. ***Incremental cost-effectiveness ratio:*** Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, the model assimilated on local costs (including generic rivaroxaban pricing) and population information produced an incremental cost-effectiveness ratio (ICER) of R188 000/QALY. ***Sensitivity analysis:*** In the current model, the cost of rivaroxaban, followed by stroke event rates with rivaroxaban and warfarin use had the largest impacts on cost effectiveness. Reducing the price of rivaroxaban by 35% produced an ICER of R100 000/QALY, and a reduction of 74.5% resulted in cost neutrality (compared to warfarin).

		Reducing the stroke event rate by ≤ 20% on rivaroxaban decreased the ICER to R128 809/QALY, while increasing the stroke event rate by ≥20% while on warfarin decreased the ICER to R 124 512/QALY. ***Estimated budget impact:*** The incremental budget impact analysis for 2021 was estimated as R231 million (for generic rivaroxaban-use compared to warfarin-use), over a five-year period. Note that the prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be – very dependent on uptake and utilization.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Committee expert opinion, as no local survey data is available.
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	Access to DOACs would reduce monitoring requirements of warfarin therapy, which are currently associated with healthcare access inequality.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	26 March 2022	HMG, RM, EM, TK, MB, JM, TL	DOACs not be used for anticoagulation in atrial fibrillation. DOACs have similar efficacy to warfarin in preventing ischaemic stroke and systemic embolism and are associated with reduced mortality and lower rates of intracranial haemorrhage and major bleeding events. However, DOACs are not currently affordable.

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Appendix B: Search strategy

Database: PubMed
Date: 12 October 2021

Search	Query	Results
#1	(((Non-valvular atrial fibrillation) OR (atrial fibrillation) OR (NVAF) OR (Nonvalvular atrial))) AND ((warfarin) OR (vitamin K antagonist)) AND ((direct oral anticoagulant) OR (novel oral anticoagulant) OR (DOAC) OR (NOAC) OR (non-vitamin k oral anticoagulant*) OR (oral anticoagulant) OR (rivaroxaban) OR (dabigatran) OR (apixaban) OR (factor Xa inhibitor) OR (thrombin inhibitor))	N = 474

Database: Epistemonikos
Date: 12 October 2021

Search	Query	Results
#1	((title:(non-valvular atrial fibrillation) OR abstract:(non-valvular atrial fibrillation)) OR (title:(atrial fibrillation) OR abstract:(atrial fibrillation))) AND ((title:(warfarin) OR abstract:(warfarin)) OR (title:(vitamin k antagonist) OR abstract:(vitamin k antagonist))) AND ((title:(direct oral anticoagulant) OR abstract:(direct oral anticoagulant)) OR (title:(novel oral anticoagulant) OR abstract:(novel oral anticoagulant)) OR (title:(oral anticoagulant) OR abstract:(oral anticoagulant))	N = 282

Database: Cochrane Library
Date: 12 October 2021

Search	Query	Results
#1	((Non-valvular atrial fibrillation) OR (atrial fibrillation) OR (NVAF) OR (Nonvalvular atrial)) AND ((warfarin) OR (vitamin K antagonist)) AND ((direct oral anticoagulant) OR (novel oral anticoagulant) OR (DOAC) OR (NOAC) OR (non-vitamin k oral anticoagulant*) OR (oral anticoagulant) OR (rivaroxaban) OR (dabigatran) OR (apixaban) OR (factor Xa inhibitor) OR (thrombin inhibitor))	N = 14

Appendix C: Table with calculated numbers needed to treat to benefit/harm

Number needed to treat to benefit/harm (95% CI)					
		High dose regimen		Low dose regimen	
Outcome	**Control event incidence**	**Absolute risk reduction**	**NNTB/H**	**Absolute risk reduction**	**NNTB/H**
Mortality	*5.66% (95% CI: 5.05%-6.27%)*	-0.57% (95% CI: -0.85% to -0.28%)	NNTB 177 (118-354)	-0.62% (95% CI: -0.96% to -0.23%)	NNTB 161 (104-442)
Ischaemic stroke/systemic embolism	*3.36% (95% CI: 2.9%-3.82%)*	-0.67% (95% CI: -0.97% to -0.3%)	NNTB 149 (103-331)	0.1% (95% CI: -0.54% to 0.91%)	NNTH 993 (NNTB 187 to ∞ to NNTH 111)
Ischamic stroke	*2.35% (95% CI: 1.95%-2.75%)*	-1.17% (95% CI: -1.39% to -0.89%)	NNTB 609 (NNTB 267 to ∞ to NNTH 1420)	0.73% (95% CI: 0.33% to 1.15%)	NNTH 138 (87-305)
Systemic embolism	*0.25% (95% CI: 0.12%-0.37%)*	Not available	Not available	Not available	Not available
Major bleeding	*6.03% (95% CI: 5.32%-6.73%)*	-0.84% (95% CI: -1.57% to -0.06%)	NNTB 119 (NNTB 64-1660)	-2.23% (95% CI: -3.74% to 0.24%)	NNTB 45 (NNTB 27 to ∞ to NNTH 415)
Intracranial bleeding	*1.42% (95% CI: 1.11%-1.72%)*	-0.74% (95% CI: -0.84% to -0.62%)	NNTB 136 (120-161)	-0.98% (95% CI: -1.08% to -0.84%)	NNTB 103 (93-120)
Gastrointestinal bleeding	*1.86% (95% CI: 0.15%-2.22%)*	0.45% (95% CI: 0.19% to 0.73%)	NNTH 224 (138-538)	-0.28% (95% CI: -0.52% to 0%)	NNTB 359 (NNTB 192 to ∞ to NNTH ∞)

Notes: NNTB = Number needed to treat to benefit; NNTH = Number needed to harm.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

National Essential Medicines List
Pharmacoeconomics and Budget impact analysis
Adult Hospital Level
Component: Cardiovascular conditions

Initial report: December 2015
Report update: 8 December 2022 (third update)
Medication: Rivaroxaban
Indication: Stroke prevention in atrial fibrillation

1 INTRODUCTION

A motivation was received for rivaroxaban to be added to the EML for the following conditions;

- Post hip and knee surgery prophylaxis
- Treatment of DVT and pulmonary embolism
- Stroke prevention in treatment of non-valvular atrial fibrillation

A pharmacoeconomics simulation was developed in December 2015 to determine the incremental cost effectiveness ratio (ICER) and budget impact analysis (BIA) for the use of rivaroxaban compared to warfarin in the prevention of stroke in patients with non-valvular atrial fibrillation (AF)

The report was updated 25th March 2022 to reflect the updated ICER and BIA based on updated costs (including generic rivaroxaban prices) and population statistics for 2021. At the time there were two generic rivaroxaban formulations available and the cheapest Rivaxored® was selected, however due to the subsequent court action by Bayer, there is now only one generic available, Ixarola® which is the clone of the originator brand Xarelto®.

The model has been revised based on the current Single Exit price of Ixarola®. Other agents currently available on the South African market, include dabigatran and apixaban, which also have clinical evidence for use in AF and other conditions. Rivaroxaban 20mg is a once daily dosing and does not require differential dosing dependent on age. Dabigatran is a twice daily dose and recommends 150mg in patients under 80 years of age, with a 110mg dose of patients over 80 years; and apixaban is dosed 5mg twice a day with dose adjustment to a 2.5mg dose in patients over 80 years, weight under 60 kg and a decreased serum creatinine above 1.5 mg/dL. These formulations are more expensive than the rivaroxaban clone.

2 PHARMACOECONOMICS MODEL - METHODS

A simple markov model was developed. The health states selected for the model were; well (i.e. well with atrial fibrillation), stroke, intracranial haemorrhage, gastrointestinal bleed (major bleed), death. The base case of the model ran for a 10 year time horizon. The age of patients entering the model was 75 years – this was based on the age of entry for the ROCKET trial.

A discount rate of 5% was selected for both cost and clinical inputs.

The only incremental medicine cost was that of the rivaroxaban vs warfarin+INR – i.e. all treatments for atrial fibrillation remained the same.

Only one event could happen to a patient in the duration of the model – for example if they had a stroke in year 2, the model did not allow for a GI bleed in year 3.

A more sophisticated model is probably required to better analyse the concurrent nature of long term consequences, however, it is unclear whether this would materially impact the outcome.

3 CLINICAL INPUTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources. The main effect size variables were taken from the ROCKET-AF trial (Patel MR 2011). These inputs were also used in the published health economic studies and included in the systematic review used in the NEMLC Medicine Review of 26 March 2022.

In order to determine a transition probability (assuming a 1-year cycle period) for the health economics model, an annual event rate is required rather than a total event rate over the duration of the trial. Therefore the event rate per year as reported in the ROCKET trial was used (see table below).

Baseline Event Risk and Relative Treatment Efficacy

All patients were as per the demographics of the ROCKET trial i.e. 75 years or older

Outcome	**Base-case (% per year)**	**Range (CI of HR)**	**P value**
Stroke or Systemic Embolism (ITT)			
Warfarin	2.40%		Combined CHADS2 Scores
Rivaroxaban	2.10%	0.75-1.03	
ROCKET showed p<0.001 for non-inferiority and p=0.12 for superiority			
Using Safety, as-treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.65-0.95	p<0.001 non-inferiority, p=0.02 superiority
Using Per Protocol, as treated population			
Warfarin	2.20%		
Rivaroxaban	1.70%	0.66-0.96	p<0.001 non-inferiority
Intracranial Haemorrhage			
Warfarin	0.70%		
Rivaroxaban	0.50%	0.47-0.93	p=0.02
Major GI Haemorrhage			
Warfarin	2.20%		
Rivaroxaban	3.20%	1.04-1.41	p<0.001
Mortality			
Warfarin	2.20%		
Rivaroxaban	1.90%	0.7-1.02	p=0.07

Table 1. Effect size used in model based on ROCKET trial data

The utilities used to calculate the QALYs were obtained from 2 cost-effectiveness analyses. It was assumed that the utility value applied to the cycle (i.e. 1 year) in which the event occurred. Thereafter the utility returned to that of the Well state (i.e. well with AF).

Health State	***Utilities***
Well with AF	0.98
Ischaemic stroke	0.39
Ischaemic stroke disability	0.75
Post ischaemic stroke no disability	0.95
Haemorrhagic stroke	0.39
Haemorrhagic stroke disability	0.75
Post haemorrhagic stroke no disability	0.95
Major bleed	0.96

Death	0.00

Table 2. Utility values for events and health states

4 COST INPUTS

The medicine costs were based on 2021 data, and the price of warfarin and generic rivaroxaban was obtained from the Single Exit Price database (i.e. a private sector price). The impact of varying the price of rivaroxaban was analysed in the sensitivity analysis.

The total annual medicine cost of treating a patient is shown below;

	per month	**per annum**
Rivaroxaban 20mg	R856.92	R10,283.04
Warfarin	R18.29	R219.42
Warfarin+INR	R74.11	R889.37

Table 3. Annual medicine cost of treating for prevention of stroke

It was assumed that, on average, patients had 12 INRs per annum at a cost of R55.83 per test. In the event of lack of warfarin control, it is likely that patients would have more than 12 INRs in the year and therefore a sensitivity analysis was carried out to assess the impact of up to 36 INRs per annum.

The event costs were adapted from private sector data. These costs need further confirmation as they are currently estimates. Variance in the costs of each event was analyzed in the sensitivity analysis

Event Costs pa	***Rands***
Mortality Cost	1000
Ischaemic Stroke event cost	55000
Post-Ischaemic stroke disability costs	17000
Intracranial Haemorrhagic stroke event cost	55000
Post-Haemorrhagic stroke disability costs	17000
Major bleed disability costs	17000
Major bleed cost	25000
No major bleed cost	360
No disability costs	360

Table 4. Estimated costs per event per annum

5 MODEL RESULTS

The base case incremental cost-effectiveness ratio for the model was **R462 544/QALY.**

		Costs	**Inc Costs**	**QALYs**	**Inc QALYs**	**ICER**
10 yrs	Rivaroxaban	152 281	81 388	6.62	0.18	462 544
	Warfarin	70 893		6.44		
5 yrs	Rivaroxaban	72 060	40 853	3.99	0.06	649 413
	Warfarin	31 206		3.93		
1 yr	Rivaroxaban	12 646	9 256	0.94	0.01	1 756 296
	Warfarin	3 390		0.94		

Table 5. 1-5 year ICERS for Rivaroxaban compared to Warfarin

A sensitivity analysis was carried out to determine which parameters had the most impact on the ICER result. The sensitivity analysis included varying costs, clinical event rates as well as discount rate or time horizon. The Tornado diagram below indicates that the model was most sensitive to a variation in time horizon from 1 to 10 years and stroke event rates. When the benefit of rivaroxaban was increased (i.e. reduced stroke rate), the ICER decreased to R325 935/QALY, when the benefit of warfarin was decreased (increased stroke rate) the ICER also reduced to a similar ICER at R306 385/QALY. When the stroke event rates for warfarin and rivaroxaban were equivalent (i.e. assuming non-inferiority), the ICER increased to above R932 836/QALY. Although the number of INRs did shift the ICER, even at 36 INRs per year, this only dropped the ICER to just above R400 000/QALY. Gastrointestinal bleeds (major) also showed some sensitivity both in utility variation as well as to changes in the event rate of GI bleeds for warfarin.

The model was insensitive to changes in costs or utilities of strokes. Changes in ICH costs and utility also did not have much impact on the sensitivity of the model.

The only parameter which shifted the ICER range in any way below an ICER of R250 000/QALY was the cost of rivaroxaban at a 50% discount.

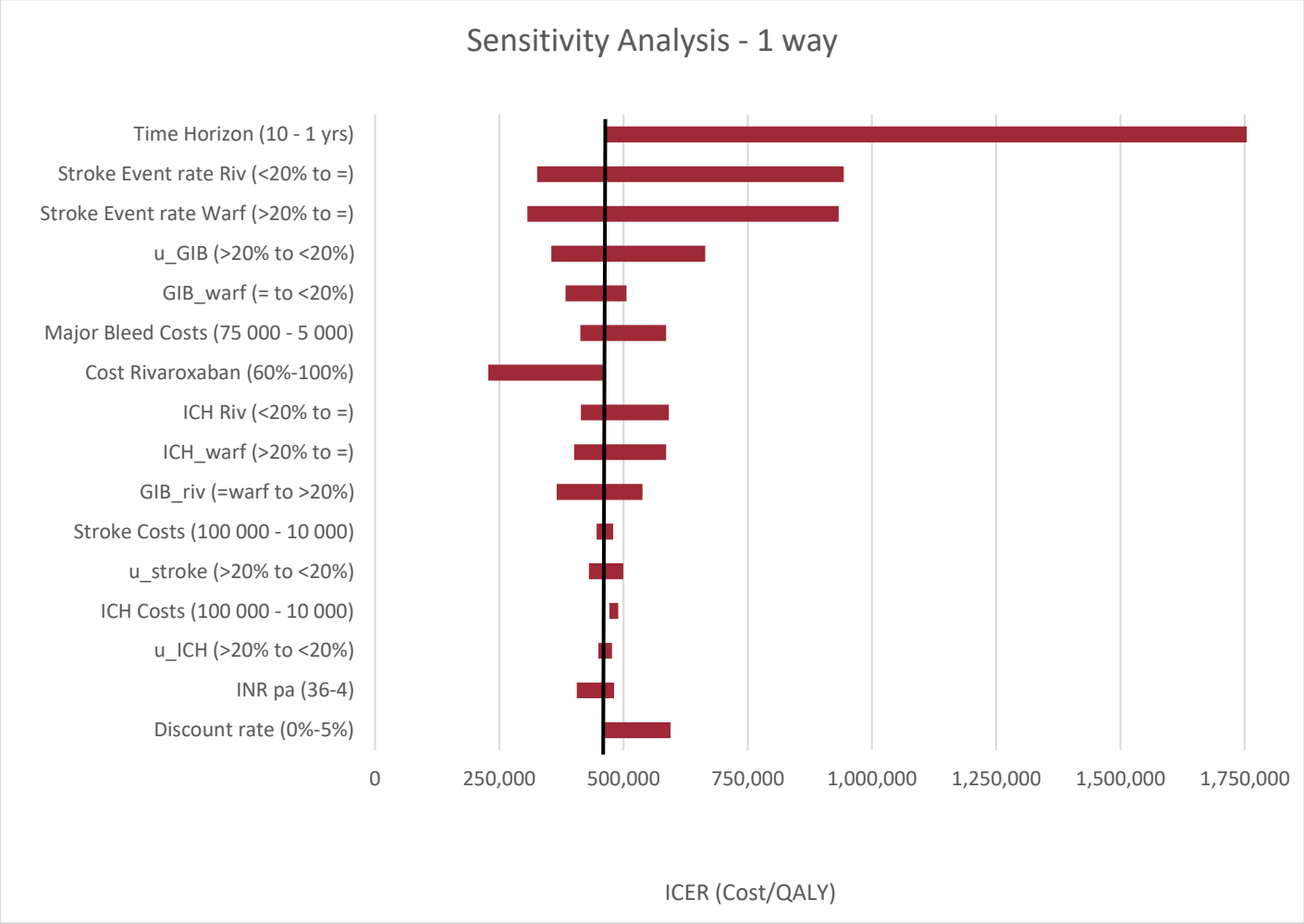

Figure 1. Tornado diagram of one-way Sensitivity Analysis

This model does not take into account multiple simultaneous variations in parameters (i.e. probabilistic sensitivity analysis).

5.1 PUBLISHED COST-EFFECTIVENESS STUDIES

The cost-effectiveness of the DOACs has been carried out in a number of settings and countries. 2 systematic reviews of cost-effectiveness analyses of the DOACs have been published recently (Zheng Y 2014, Ferreira J 2015) as well as a review of the methodologies and results of the DOAC cost-effectiveness studies (Singh SM 2015).

The table below shows the different rivaroxaban studies and the cost-effectiveness model outcomes from these studies

Study	ICER	Setting	Comment
Harrington, 2013	USD 11 150/QALY	USA	Cost effective in 14.9% of simulations
Lee, 2012	USD27 498/QALY	USA	Price of rivaroxaban USD6.8
Kleintjens, 2013	EUR 8 809/QALY	Belgium	Threshold EUR 35 000/QALY
Coyle, 2013	CAD 55 757/QALY	Canada	Cost-effective in 2.1% of simulations
Kansal, 2012	CAD 22 475/QALY	Canada	Threshold CAD 30 000/QALY
Bowrin, 2020	EUR 6 006/QALY	France	Based on real world data for outcomes
Wei, 2021	USD 5 548/QALY	China	Threshold USD 28 443/QALY

Table 6. Summary of published cost-effectiveness outcomes

A meta-analysis of the data up to 2013 by Ferreira et al showed that the mean ICER for rivaroxaban was EUR 17 960±12 005/QALYs which was deemed to be cost effective at a willingness to pay (WTP) threshold of EUR 30 000/QALY.

In the Zheng et al study, a meta-analysis of the data was used to create a new model which showed an ICER of £7203/QALY. At a cost-effectiveness threshold of £20 000/QALY this was considered to be cost-effective. However, this model also showed that dabigatran was more cost-effective than either rivaroxaban or apixaban compared to warfarin and, in fact, was shown to be dominant (i.e. costs less and has better clinical outcomes)

There are a number of uncertainties in the published cost-effectiveness studies and in the analysis carried out here.

The uncertainties related to the clinical trial data include the following;

- Duration of treatment and follow-up; the average duration of follow-up in the trials is around 2 years and therefore the trial-based clinical data is obtained from this information. However, AF is a lifelong condition and therefore treatment is likely to continue on a long-term basis. The clinical outcomes beyond 2 years are uncertain and based on assumption and extrapolations
- Wafarin control (TTR) – generally poorer warfarin control in the public sector in SA than in the trials
- Baseline stroke or haemorrhage risk in SA population
- Age of patients – average age in the trials is around 71-73 years. In SA, the average age of AF patients is similar in the private sector but unclear in the public sector.
- Management of bleeding – treatment patterns and cost

6 THRESHOLD PRICE ANALYSIS

A price threshold analysis was conducted to determine the impact of different prices of rivaroxaban on the ICER. The price of rivaroxaban needed to be discounted by 77.5% to reach an ICER threshold of R100 000/QALY at 10 years and a discount of 90% to reach cost-neutrality.

Price analysis	ICER (R/QALY)
Rivaroxaban 100%	462 544
Rivaroxaban 80%	368 744
Rivaroxaban 70%	321 844
Rivaroxaban 50%	228 044

Table 7. Price impact and threshold analysis of rivaroxaban

7 BUDGET IMPACT ANALYSIS

For the budget impact analysis (BIA), an excel spreadsheet model was developed to take into consideration the following factors; total AF population, patients on warfarin, uptake of rivaroxaban, cost of INR tests, change in effect size of intracranial haemorrhage and major bleeds. The BIA was based on a total population of 50 219 387 million people (Day C 2014). This excluded the approximately 8 million people covered under medical insurance in the private healthcare sector.

The prevalence of AF in males (565/100 000) and females (366/100 000) was derived from the Global AF Study (Chugh et al, 2014). The proportion of patients with non-valvular AF was determined from two studies to give a lower limit of 56% (Stewart et al, 2008 Soweto Heart study) and upper limit of 73% (Jardine et al, 2014). In the Jardine et al AF Survey in South Africa, the proportion of patients on warfarin was around 75%.

	No of Patients
Total AF patients	467 954
AF Males	284 091
AF Females	183 853
Pts with non-valvular AF	262 049
Growth rate in patients with AF	2%
Uptake of rivaroxaban	20% plus 10% pa

Table 8. Estimated prevalence data for non-valvular AF

The costs of treating AF with either warfarin+INR vs rivaroxaban were not inflation adjusted per annum (assuming prices remained static), however a 2% growth rate in the number of AF patients was included. An uptake of 20% in utilization of patients taking rivaroxaban was used for Year 1 in the model and increased by 10% each thereafter. This may vary considerably and it is likely this is an over-estimate in the first year, however may be surpassed in subsequent years once rivaroxaban utilization is established. It is expected that use of rivaroxaban, as with warfarin, is ongoing chronic lifelong treatment. Based on these figures, the incremental budget impact analysis for 2022 (over 5 years) would be approximately R365 million.

Population:	**2022**	**2023**	**2024**	**2025**	**2026**
Pts on Warfarin - total	197 061	201 002	205 022	209 122	213 305
Pts on Warfarin new	157 649	140 701	123 013	104 561	85 322
Pts on Rivaroxaban	39 412	60 301	82 009	104 561	127 983
Costs:					
Cost wafarin+INR - total	668 051 865	681 412 902	695 041 161	708 941 984	723 120 823
Cost wafarin+INR - new	534 441 492	545 130 322	556 032 928	567 153 587	578 496 659
Cost rivaroxaban	498 396 414	508 364 342	518 531 629	528 902 261	539 480 307
Total Cost new	1 032 837 906	1 053 494 664	1 074 564 557	1 096 055 848	1 117 976 965
Incremental cost	**364 786 041**	**372 081 761**	**379 523 397**	**387 113 865**	**394 856 142**

Table 9. Incremental cost-impact analysis of rivaroxaban vs warfarin+INR

8 CONCLUSION

Although numerous published cost-effectiveness analyses suggest that rivaroxaban is cost-effective in a long-term setting, there is still considerable uncertainty around the long-term outcomes and clinical benefits in a mixed population, real-world setting.

In this model, the only variable that could be changed sufficiently to reduce the incremental cost-effectiveness ratio (ICER) to below R250 000/QALY was to reduce the price of the currently available rivaroxaban produce (Ixarola®) by 50% and this is unlikely to be considered cost-effective. A more sophisticated model (with probabilistic sensitivity analysis and more health

states) may have the outcome of further reducing the ICER but at the current model outcome of R462 544/QALY it is unlikely to reduce the ICER to a point which could be considered cost-effective in the public health setting.

Furthermore, the budget impact needs to be considered. The prevalence figures for non-valvular AF in the public sector are simply estimates and it is challenging to predict what the actual budget impact is likely to be. This will be very dependent on uptake and utilization.

Other factors need to be considered;

- How to define warfarin failure or true warfarin intolerance in order to be eligible for DOACs
- The baseline risk of patients in the current healthcare setting compared to the clinical trial setting
- How to improve warfarin control and monitoring (TTR) as an alternative strategy

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Model (2015) developed by: Dr J Miot
Affiliation: Health Economics and Epidemiology Research Office (HE²RO)

Report and model updated (2022) by:
Dr J Miot (Health Economics and Epidemiology Research Office (HE²RO, University of Witwatersrand))
TD Leong (Secretariat to the NEMLC, Essential Drugs Programme, National Department of Health);

Conflicts of interest: JM and TDL have no conflicts of interests related to rivaroxaban.

Version	Date	Reviewer(s)	Conclusion
First	11 December 2015	J Miot	There is an incremental cost per patient for use of rivaroxaban compared to warfarin for the management of atrial fibrillation of R600 000/QALY. Despite a price reduction of rivaroxaban by 80%, the ICER of R600 000/QALY is not cost-effective. Other factors such as affordability, defining warfarin failure/ true warfarin intolerance, baseline risk of patients in clinical setting and how to improve warfarin control and monitoring as an alternative strategy, needs to be considered.
Second	25 January 2022	J Miot, TD Leong	Generic rivaroxaban available at a reduced price was shown not to be cost-effective with a simulated ICER of R188 000/QALY. A reduction in price by 35% (R388/month) reduces the ICER to R100 000/QALY; and a further reduction by 74.5% of the price of generic rivaroxaban (R153/month) results in cost-neutrality with warfarin management. Other factors as described above also needs consideration.
Third	17 November 2022	J Miot	Currently the only generic rivaroxaban that is available (Ixarola®) is the clone at 85% of the SEP of the originator brand. This increases the ICER to R462 544/QALY which is not considered to be cost-effective. Rivaroxaban is currently the cheapest DOAC available on the market.

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).

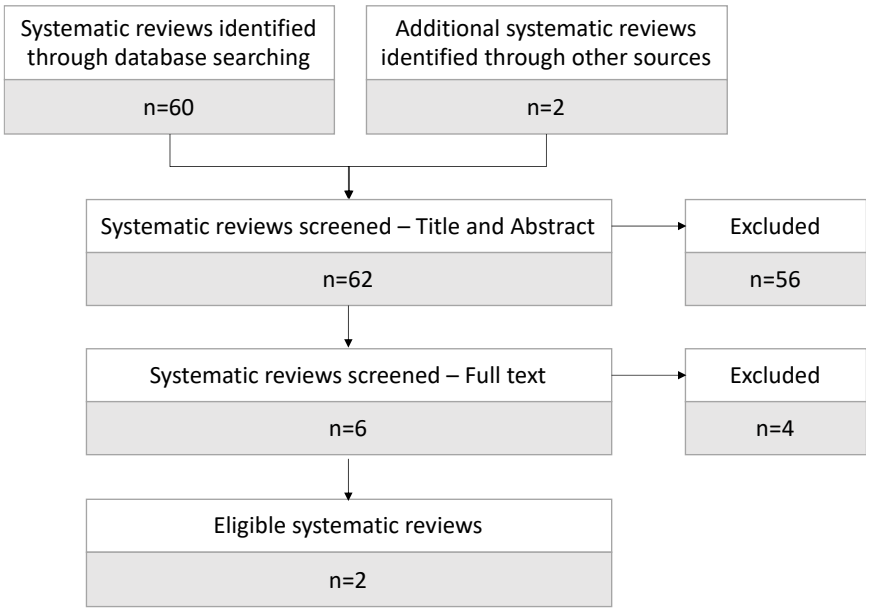


Figure 1. Prisma flow diagram of search results: systemic reviews

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											

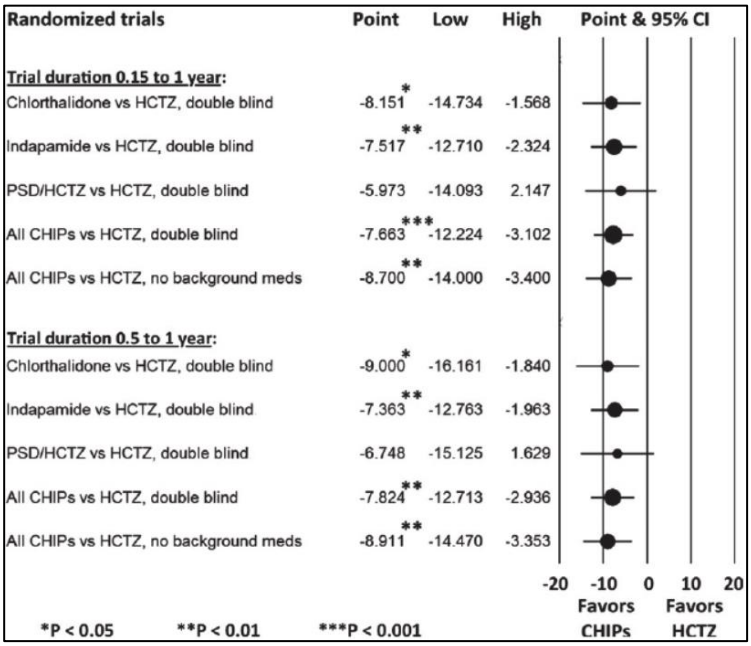
ABPM – Ambulatory Blood Pressure Monitoring, BDZ – bendroflumethiazide, CTD – chlorthalidone, DBP – diastolic blood pressure, HCTZ- hydrochlorothiazide, IND – indapamide, NS – not significant, SS – statistically significant, SBP – systolic blood pressure

*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?** Large [ ] 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:

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

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.