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Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 4: CARDIOVASCULAR CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for cardiovascular conditions.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
3.1 Ischaemic heart disease and atherosclerosis, prevention	Oxygen	Directions for use amended
	HMGCoA reductase inhibitors (statins), oral	Treat to target approach not added; indications amended
	Simvastatin, oral	Dose amended and additional guidance provided (drug-drug interactions; side-effects)
	Atorvastatin, oral	Dose amended and additional guidance provided (drug-drug interactions; side-effects)
3.2.1 ST elevation myocardial infarction (STEMI)	Clopidogrel, oral	Not amended (loading dose not recommended & duration of therapy not amended)
	Aspirin, oral	Dose amended
	Thrombolytics, IV	Added as a therapeutic class, absolute contraindications amended
	Streptokinase, IV	Retained as an example of class; Thrombolytic time window retained as < 6 hours, with a caveat
	Alteplase, IV	Added as example of thrombolytic class; Thrombolytic time window retained as < 6 hours, with a caveat
	Tenectaplase, IV	Not added as example of thrombolytic class
- *Adjunctive therapy*	Low molecular weight heparin (LMWH)	Added as adjunct therapy with alteplase **but** not with streptokinase; not recommended as therapeutic class
	Enoxaparin, IV/SC	Added as adjunct therapy with alteplase; loading dose retained
- Ongoing chest pain/unresolved ischaemia	Nitrates, oral/IV	Placed first in treatment protocol
	Morphine, IV	Placed last in treatment protocol
- *Ongoing chest pain, to control hypertension or treat pulmonary oedema*	Glyceryl trinitrate, IV	Retained
	Isosorbide dinitrate, IV	Not considered as an alternative to glyceryl trinitrate, IV
- Clinically stable without signs of heart failure, hypotension, bradydysrhythmias or asthma	HMGCoA reductase inhibitors (statins), oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
- *LV dysfunction following myocardial infarction, heart failure or ejection fraction < 40%*	ACE-inhibitor	Indication not amended
3.2.2 Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)	Clopidogrel, oral	Loading dose retained; duration of therapy not amended
	Aspirin, oral	Dose amended
- *Anticoagulation*	Enoxaparin, SC	Retained – first line option
	Unfractionated heparin, IV	Retained – second line option
	Fondaparinux, SC	Not recommended as an alternative to LMWH/UFH
- persistent pain and if oral therapy is insufficient	Glyceryl trinitrate, IV	Retained
	Isosorbide dinitrate, IV	Not recommended as alternative to glyceryl trinitrate, IV
- severe pain unresponsive to nitrates	Morphine, IV	Directions for use amended
3.2.3 Chronic management of STEMI / NSTEMI / UA	Referral criteria	Amended
3.2.4 Angina pectoris, stable	Aspirin, oral	Dose amended
	Nitrates, short acting	Directions for use amended
	Isosorbide dinitrate, oral	Retained and dose amended
	Isosorbide mononitrate, oral	Added as an alternative therapeutic option
	Beta-blockers, oral	Added as a therapeutic class
	Atenolol, oral	Retained as an example of class (listed in STG)
	Propranolol, oral	Not added as an example of class
	Bisoprolol, oral	Added as an example of class (listed in therapeutic interchange database)

	Carvedilol, oral	Added as an example of class (listed in therapeutic interchange database)
	Metoprolol, oral	Added as an example of class (listed in therapeutic interchange database)
	Statins, oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
3.2.5 Atherosclerotic peripheral arterial disease	Statins, oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
3.3 Cardiac dysrhythmias	Resuscitation Council of South Africa algorithm	Not added
3.3.1.1 Atrial fibrillation	New oral anticoagulants (NOACs)	Not added
	Warfarin, oral	Retained
	Aspirin, oral	Deleted
	Amiodarone, IV	Indication not amended
3.3.2.1 Regular wide QRS tachycardias	DC cardioversion	Retained as first line therapy
	Amiodarone, oral	Dosing amended
3.3.2.2 Sustained (>30 seconds) irregular wide QRS tachycardias	DC cardioversion	Emphasised as the safest treatment option
3.3.2.3 Non-sustained (< 30 seconds) irregular wide QRS tachycardias	Amiodarone, parenteral	Retained as 1st line therapy
	Beta-blockers, oral	Not added as 1st line therapy
	Ca Na blockers (lidocaine, parenteral)	Retained as 1st line therapy in haemodynamically stable patients
3.3.3 Heart block (second or third degree)	Adrenaline (epinephrine), IV	Directions for use amended
3.4 Congestive cardiac failure (CCF)	Pneumococcal vaccine	Not added
	ACE-inhibitors, oral	Amended (note added)
	Eplerenone, oral	Not added
	Angiotensin II receptor blockers (ARBs)	Recommended only in ACE-I intolerance
	Enalapril, oral	Daily dose retained
	Angiotensin II receptor blockers (ARBs) + ACE-Inhibitor combination therapy	Not added
	Sacubitril valsartan hydrate, oral	Not added (referred for T&Q review)
	Digoxin, oral	High risk patient group - amendment
3.5 Endocarditis, infective **-** *Enterococcal infection*	Gentamicin, IV	Dosing amended from"12 hourly for 4-6 weeks" to "8 hourly for 2-6 weeks"
- Empiric therapy (native valve): If staphylococcal infection is suspected (acute onset)	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
- Directed therapy (native valve): Staphylococcal (cloxacillin/ methicillin sensitive)	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
- Directed therapy for prosthetic valve endocarditis	Guidance provided	Early referral for consideration of repeat cardiac surgery
3.6 Hypertension	BP target of <140/90 mmHg	Not amended to <130/80 mmHg
- Investigations	Automated office blood pressure monitors (AOBP)	Not added
	Waist circumference cut-off	Not amended to assess central obesity
- General	Antihypertensive management	Guidance added (i.e. bedtime dosing, fixed dose combination for chronic BP management)
	ACE-inhibitor, oral	Dosing amended (at night)
	Calcium channel blocker, oral	Dosing amended (at night)
	Beta-blockers, oral	Dosing amended (at night)
	Antihypertensive management	Guidance added (i.e. bedtime dosing, fixed dose combination for chronic BP management)
	ACE-inhibitor, oral	Dosing amended (at night)
- Medicine treatment choices without compelling indications	Algorithm for step-wise management of hypertension	Added
	Hydrochlorothiazide, oral	Retained as 1st line option
	Calcium channel blocker, oral (i.e. amlodipine)	Not added as 1st line option
	Enalapril, oral	Retained and daily dosing not amended
	Spironolactone, oral	Added
	Atenolol, oral	Retained
	Angiotensin II receptor blockers (ARBs)	Directions for use not amended

- *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
- *Management of hypertension*	Treatment algorithm	Stepped-care approach emphasised
	ACE-inhibitor, oral	Directions of use amended (bedtime dosing)
	Calcium channel blocker, oral	Directions of use amended (bedtime dosing)
	Beta-blockers, oral	Directions of use amended (bedtime dosing)
	Medicine formulations	Fixed dose combinations encouraged if available and affordable

3.1 ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS, PREVENTION

Oxygen: *directions for use amended*

Text of the STG was updated to align with the NEMLC approved PHC STGs and EML, 2018 for consistency; throughout the STGs and EML:

• Oxygen, ~~if hypoxaemic~~ if saturation < 94%.
NEMLC meeting of 5 July 2018:[1] ***NEMLC Recommendation:*** *Oxygen: Recent meta-analysis*[2] *shows that administering oxygen where saturation levels are greater than 94% increases the risk of death.*

HMGCoA reductase inhibitors (statins): *treat to target approach not added; indications amended*
Simvastatin, oral: *dose amended and additional guidance provided (drug-drug interactions; side-effects)*
Atorvastatin, oral: *dose amended and additional guidance provided (drug-drug interactions; side-effects)*

A number of comments were received to consider treating dyslipidaemia with statin therapy to target LDL level of 1.8 mmol/L. However, management of dyslipidaemia for primary and secondary prevention are aligned to NEMLC approved recommendations and guidance in the PHC STGs and EML, 2018. Refer to the PHC Cardiovascular NEMLC report (2016-2018), published on the NDoH website for detailed information (indications, dosing, drug-drug interactions, side-effects, members of therapeutic groups).
Available at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc

PHC_Cardiovascular _NEMLC report_2016

Myalgia

The Adult Hospital Level STGs and EML, 2019 recommends that if myalgia develops whilst on a statin, then to reduce the dose to simvastatin 10 mg or equivalent. The Adult Hospital Level Committee recommends that provision be made for 20 mg simvastatin or equivalent and that this be listed on the therapeutic interchange database.

Drug interaction of statins with amlodipine

Simvastatin, oral (or equivalent): *dose amended from "10 mg" to "10-20 mg"*

Background: An external comment was received about the use of a dose higher than simvastatin 10 mg with concomitant amlodipine.

Review: Simvastatin is metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) and is a substrate of CYP3A4. Amlodipine is a weak inhibitor of CYP3A4, with simvastatin being susceptible to the inhibitory effect of amlodipine.

[1] Minutes of the NEMLC meeting of 5 July 2018.
[2] Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018 Apr 28;391(10131):1693-1705. https://www.ncbi.nlm.nih.gov/pubmed/29726345

Amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin.[3] Concomitant administration of amlodipine with simvastatin could lead to a greater risk of adverse effects such as myopathy and rhabdomyolysis. A dose of maximum 20 mg simvastatin together with amlodipine 10 mg, has been found to be safe and effective.[4] A dose exceeding 20 mg simvastatin in combination with 10 mg amlodipine is not recommended.
Atorvastatin, a substrate of CYP3A4, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine. The dose of atorvastatin is not to exceed 80 mg with concomitant administration of amlodipine 10 mg.[5]

Recommendation: Reduced dose of simvastatin 10 to 20 mg be recommended for patients on concomitant amlodipine.
Rationale: Drug-drug interaction of simvastatin with amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin with possible subsequent myopathy and rhabdomyolysis. Pharmacokinetic studies suggests that maximum dose of simvastatin 20 mg is safe when used in combination with amlodipine 10 mg. Atorvastatin, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine and thus, atorvastatin 20 mg is recommended for use with concomitant amlodipine.
Level of Evidence: III Pharmacokinetic studies, Guidelines

3.2.1 ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

External comments were received pertaining to the criteria for diagnosing STEMI. Therefore the text of the STG was amended as follows, and the Adult Hospital Level Committee recommended that a hyperlink be included to an ECG application to assist clinicians:

Ischaemic chest pain that is prolonged, or associated with nausea, sweating and syncope ~~ongoing >30 minutes~~ or associated with persistent ST elevation or new or presumed new left bundle branch block (LBBB). Repeat ECG at 20-30 minute intervals ~~if regularly as~~if initial ECG not diagnostic. ~~clinically indicated.~~

- **CLOPIDOGREL**

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[6] 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[7], 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

Clopidogrel, oral: *duration of therapy not amended*

[3] Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7.
[4] Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8.
[5] SAMF, 2016/2020
[6] 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
[7] 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

The mean duration of therapy of clopidogrel in COMMIT[8] was 15 days and given the available calendar pack size of clopidogrel, it had been recommended in the previous Adult Hospital Level STGs and EML review cycle that clopidogrel 75 mg be recommended for a month for STEMI.
Level of Evidence: I RCT, Expert opinion

- **ASPIRIN**

Aspirin, oral: *dose amended*
South African Medical Association agreed with the dose amendment of aspirin *(from "150 mg" to "100 mg", daily),* and the evidence cited for CURRENT OASIS 7[9] but was unclear about the evidence (Berger et al[10]) basis for low dose aspirin, as the "low dose" in this trial was 162mg aspirin, and the analysis was a post-hoc analysis. Evidence was submitted for TRANSLATE-ACS[11], observational study in the United States that evaluated outcomes of study participants who underwent PCI and were discharged on either 325 or 81 mg of aspirin. The rate of major adverse cardiovascular events (death, MI, stroke, or unplanned revascularization) was similar between the two groups by six months (aHR 0.99; 95%CI 0.85 to 1.17) but the rate of bleeding, as defined by the Academic Research Consortium- was higher with high-dose aspirin (24.2 vs 19.5 percent; aHR 1.19; 95% CI 1.05-1.34) - mostly due to bleeding not requiring hospitalization. The Adult Hospital Level Committee acknowledges that TRANSLATE-ACS shows that lower dose aspirin is safer; however, is not generalisable to secondary level of care as PCIs not performed at this level in the public sector. Evidence base for the low-dose aspirin recommendation amended to CURRENT OASIS 7 RCT, only.
Level of Evidence: I RCT

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"[12].
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.

- **THROMBOLYTICS**

Thrombolytic therapy, IV: *added as a therapeutic class; absolute contraindications amended*
In the previous review cycle (2012-2015), thrombolytics had been accepted by the NEMLC as a therapeutic class for STEMI (Refer to the medicine review: Thrombolytics – medicine class for STEMI, 25 July 2015[13]).

Absolute contraindication, "*Symptoms or signs suggestive of an aortic dissection*", added to the text of the STG, aligned with package insert and SAMF, 2016 guidance; though a (relatively) rare condition.
Level of Evidence: III Guidelines[14]

Streptokinase, IV: *retained as an example of class (listed in the STG; thrombolytic time window retained as < 6 hours, with a caveat*
Alteplase, IV: *added as example of thrombolytic class (only if streptokinase is unavailable); thrombolytic time window retained as < 6 hours, with a caveat*
Tenectaplase, IV*: not added as example of thrombolytic class*

[8] 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
[9] Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363(10):930-42.
[10] Berger JS, Stebbins A, Granger CB, Ohman EM, Armstrong PW, Van de Werf F, White HD, Simes RJ, Harrington RA, Califf RM, Peterson ED. Initial aspirin dose and outcome among ST-elevation myocardial infarction patients treated with fibrinolytic therapy. Circulation. 2008 Jan 15;117(2):192-9. https://www.ncbi.nlm.nih.gov/pubmed/18086929
[11] Xian Y, Wang TY, McCoy LA, Effron MB, Henry TD, Bach RG, Zettler ME, Baker BA, Fonarow GC, Peterson ED. Association of Discharge Aspirin Dose With Outcomes After Acute Myocardial Infarction: Insights From the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) Study. Circulation. 2015 Jul 21;132(3):174-81. https://www.ncbi.nlm.nih.gov/pubmed/25995313
[12] 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]
[13] National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Thrombolytics, therapeutic class for STEMI, July 2015. http://www.health.gov.za/
[14] SAMF, 2016

Streptokinase, IV is easier to administer and less expensive than the alternatives (alteplase and tenectaplase) and was retained in the STG as the example of class. However, supply challenges warrant an alternative option and alteplase, IV recommended as it is cheaper than tenectaplase.
Cost minimisation (using direct medical costs only, modelled on a 70 kg adult using SEP prices/contract price):

Price	Price of comparative dose:
– Alteplase 50 mg = R 9141.25[15]	– Alteplase dose: 100 mg = R 18,282.50
– Tenectaplase 40mg = R 18,408.79[16]	– Tenectaplase dose: 40 mg = R18,408.79
– Streptokinase 1.5 MU = R 3680.00[17]	– Streptokinase dose: 1.5 MU = R 3680.00

Thrombolytic window: Comments to revise the thrombolytic time window to <12 hours were received, including a comment through the Western Cape (WC) Pharmaceutical and Therapeutics Committee (PTC).
Risk vs benefit and cost-benefit: In the previous review cycle (2012-2015), STEMI was recommended to be treated with lytic agents for up to 6 hours. There is available evidence for efficacy beyond 6 hours; however, the cost-benefit becomes rapidly unfavourable because of the small effect size. NEMLC had requested further information (in particular how cost-effectiveness and affordability were considered) from the WC PTC in order to determine if the STGs and EML needs amending to ensure consistent and equitable access to healthcare across Provinces. However, no further information was forthcoming.
Pragmatic implications: NEMLC was of the opinion that cases that present beyond 6 hours of the onset of STEMI requires specialist consultation for further guidance.
Rationale: Available evidence shows that the greatest benefit occurs in the first 1-2 hours, and the NNT starts to plateau before 6 hours (i.e. fibrinolytics are less effective when administered later). Despite there being evidence for efficacy beyond 6 hours, the cost-benefit becomes rapidly unfavourable because of the small effect size (with risk of haemorrhage consistent from 1 to 12 hours)[18]. 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[19], Expert opinion

Alteplase, IV: Comment received to extend thrombolytic time window to <12 hours. The rationale for treating within 6 hours applies to all fibrinolytics (after 6 hours benefit declines rapidly and harms remain the same) and moreso with alteplase which is more costly than streptokinase. However, management was aligned with streptokinase, IV; where STEMI cases present beyond 6 hours of the onset of STEMI, specialist should be consulted for further management.

- **ADJUNCTIVE THERAPY**

Low molecular weight heparin (LMWH), IV/SC: *added as adjunct therapy with alteplase **but** not with streptokinase*; not recommended as a therapeutic class

The PHC Committee reported (PHC NEMLC report, 2 March 2017 - see below)[20] that there is uncertainty about the role of intravenous unfractionated heparin (UFH) and LMWH in patients with ST-elevation myocardial infarction (STEMI) treated with aspirin and thrombolysis[21].

PHC NEMLC report, 2 March 2017:
LMWH: Streptokinase co-administered with LMWH (compared with streptokinase plus placebo) reduced the risk of re- infarction (OR=0.72; 0.58 to 0.9; NNT 167); but showed a modest reduction in death (OR=0.9; 0.8 to 0.99); with an increased risk of major bleeding[22].

[15] SEP Price, accessed 12 November 2019. https://mpr.code4sa.org/#search:alteplase (price not changed on 12 February 2020)
[16] SEP Price, accessed 12 April 2019. https://mpr.code4sa.org/#search:tenect (price not changed on 12 February 2020)
[17] Contract circular RT297-2019
[18] 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
[19] 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
[20] NEMLC report for PHC Chapter 4: Cardiovascular conditions, 2 March 2017. http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc
[21] Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67.
[22] Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67.

UFH: During hospitalization UFH did not reduce reinfarction (OR 1.08; 0.58 to 1.99) or death (4.8% versus 4.6%; OR, 1.04; 95% CI, 0.62 to 1.78) and did not increase major bleeding (OR, 1.21; 0.67 to 2.18) but increased minor bleeding (OR, 1.72; 1.22 to 2.43), compared to placebo.[23]

Alteplase+UFH:The only available study that could be sourced that compared heparin vs placebo in patients who were thrombolysed with alteplase reported no statistically significant difference between UFH vs placebo for reducing reinfarction during hospitalisation (OR 0.99; 0.40 to 2.40) or death during hospitalisation (OR 0.80; 0.58 to 1.96).[24]

***PHC Committee Recommendation:** Adjunctive heparin could be considered at hospital level (all STEMI patients are referred urgently from primary level of care), due to cost implications if LMWH is added to the PHC EML.*

Jinatongthai et al, 2017: Meta-analysis showed an overall moderate benefit of fibrinolytics in STEMI, but reinforces the recommendation of the cheapest option to be administered within 6 hours of the onset of symptoms. A greater risk for major bleeding was associated with streptokinase+parenteral anticoagulants (PAC) compared to streptokinase or alteplase+parenteral anticoagulants (see Figures 2 and 4, below).

Recommendation: LMWH be co-administered with alteplase, **but not with streptokinase**, for acute STEMI. However, heparin not to be added as adjunct therapy with streptokinase for acute STEMI.

Rationale: There is no clear evidence of any advantage of using UFH with alteplase (or any other thrombolytics), and disadvantages include increased risk of bleeding and need for frequent aPTT monitoring. The accelerated regimen is as used in the Gusto trial[25], with the addition of fibrinolytic treatment as an alternative to percutaneous coronary interventions/reperfusion. Also, Jinatongthai et al's meta-analysis[26] showed that streptokinase on its own held less risk of bleeding (RR 0.51, 95% CI 0.31 to 0.83 vs 0.63, 95% CI 0.44 to 0.92) but more risk of all-cause mortality (RR 1.30, 95% CI 1.12 to 1.50 vs 1.49, 95% CI 1.24 to 1.79) than the alteplase/parenteral anticoagulant regimen. In clinical trials alteplase was generally given with standard of care, which included some form of heparin. Treatment regimen aligned with standard of care.

Level of Evidence: I Meta-analyses[27, 28], 29

[23]Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67.

[24] de Bono DP, Simoons ML, Tijssen J, Arnold AE, Betriu A, Burgersdijk C, Lopez Bescos L, Mueller E, Pfisterer M, Van de Werf F, Zijlstra F, Verstraete M. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. Br Heart J. 1992;67:122–128.

[25] GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993 Sep 2;329(10):673-82. https://www.ncbi.nlm.nih.gov/pubmed/8204123

[26] Jinatongthai P, Kongwatcharapong J, Foo CY, Phrommintikul A, Nathisuwan S, Thakkinstian A, Reid CM, Chaiyakunapruk N. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. Lancet. 2017 Aug 19;390(10096):747-759. https://www.ncbi.nlm.nih.gov/pubmed/28831992

[27] Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67.

[28] De Luca G, Marino P. Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. Am Heart J. 2007 Dec;154(6):1085.e1-6. https://www.ncbi.nlm.nih.gov/pubmed/18035079

[29] Jinatongthai P, Kongwatcharapong J, Foo CY, Phrommintikul A, Nathisuwan S, Thakkinstian A, Reid CM, Chaiyakunapruk N. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. Lancet. 2017 Aug 19;390(10096):747-759https://www.ncbi.nlm.nih.gov/pubmed/28831992

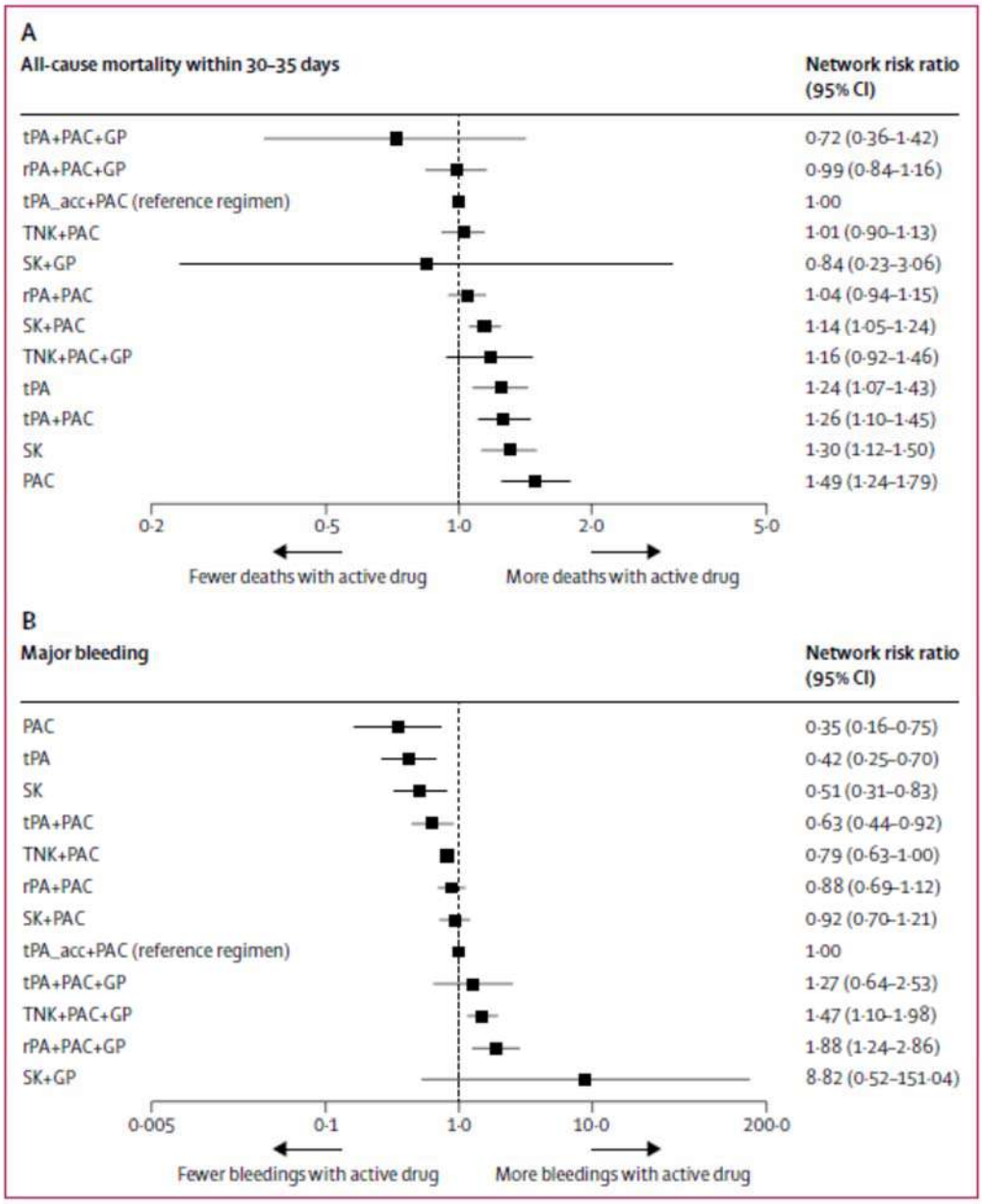

***Figure 2*: Network meta-analysis of reperfusion therapy with fibrinolytic drugs compared with accelerated infusion alteplase plus parenteral anticoagulants for primary efficacy and safety outcomes**

(A) All-cause mortality within 30–35 days. (B) Major bleeding. Summary estimates represent risk ratio (95% CI) of all-cause mortality within 30–35 days and major bleeding. Interventions are ranked by Surface Under the Cumulative RAnking curve values. tPA=alteplase (non-accelerated infusion). PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. tPA_acc=alteplase (accelerated infusion). rPA=reteplase. TNK=tenecteplase. SK=streptokinase.

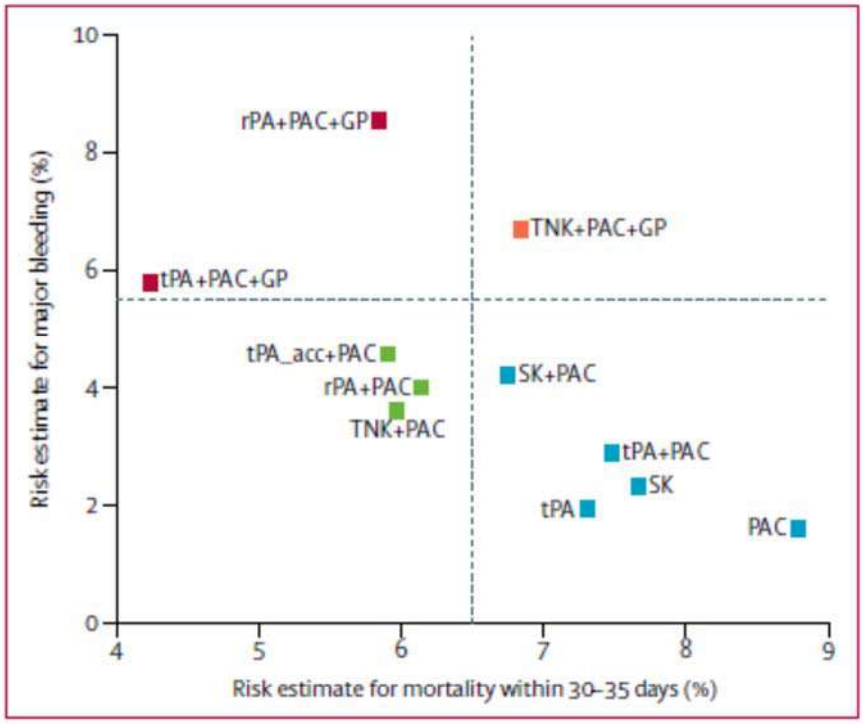

***Figure 4*: Cluster rank plot of risk estimates for mortality within 30–35 days and major bleeding**

The risk estimate plot of treatment with streptokinase plus glycoprotein IIb/IIIa inhibitors is omitted because it is out of the range of the plot. The dashed lines represent the different quadrants of the risk estimates. rPA=reteplase. PAC=parenteral anticoagulants. GP=glycoprotein IIb or IIIa inhibitors. TNK=tenecteplase. tPA=alteplase (non-accelerated infusion). tPA_acc=alteplase (accelerated infusion). SK=streptokinase.

Enoxaparin, IV/SC: *added as adjunct therapy with alteplase*; *loading dose retained*

The treatment of Acute Coronary Syndrome has been restricted to enoxaparin, aligned with European ACS Guidelines[30] as enoxaparin is the most studied LMWH and for which there is the most clinical experience.

External comment to remove the IV loading dose and dose as 0.75 mg/kg SC every 12 hours was not accepted, as the recommended dosing regimen as indicated below is as recommended in RCTs[31] and as guided by the Adult Hospital Level evidence review: LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A and B, April 2018.

Recommended dosing in the STG:

Adjunctive treatment

- Enoxaparin (after alteplase, do not use heparins after streptokinase).
  - *Loading dose:* IV, 30 mg as a bolus, followed by SC, 1 mg/kg as a single dose (total cumulative dose not to exceed 100mg).
  - *Maintenance dose*: SC, 1.5 mg/kg daily **or** 1 mg/kg 12 hourly.

In the elderly (> 75 years of age):

- *Loading dose*: SC, 0.75 mg/kg as a single dose.
- *Maintenance dose*: SC, 1.5 mg/kg daily **or** 1 mg/kg 12 hourly.

[30] 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.

[31] Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation. 2005 Dec 20;112(25):3855-67. https://www.ncbi.nlm.nih.gov/pubmed/16344381

LMWH (adjunctive to alteplase): De Luca G, Marino P. Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. Am Heart J. 2007 Dec;154(6):1085.e1-6. https://www.ncbi.nlm.nih.gov/pubmed/18035079

- **ONGOING CHEST PAIN/UNRESOLVED ISCHAEMIA**

Nitrates, oral/IV: *placed first in treatment protocol*
Morphine, IV: *placed last in treatment protocol*

The CRUSADE registry[32] suggested harm associated with morphine, and there is emerging evidence that morphine appears to interact with antiplatelet agents.

CRUSADE Quality Improvement Initiative (retrospective observational registry, n=17003):
Results:
- (29.8%) received morphine within 24 hours of presentation.
- Patients with non-ST-segment elevation acute coronary syndromes treated with morphine vs no morphine had a higher adjusted risk of death: OR 1.48, 95% CI 1.33 to 1.64.
- Patients administered morphine vs nitroglycerin had a higher adjusted likelihood of death: OR 1.50, 95% CI 1.26 to 1.78.
- Morphine was associated with increased in hospital mortality: OR 1.41, 95% CI 1.26 to 1.57, using propensity score matching method.
- Increased risk of death in patients receiving morphine persisted across subgroups.

Level of Evidence: III Registry data

- **ONGOING CHEST PAIN, TO CONTROL HYPERTENSION OR TREAT PULMONARY OEDEMA**

Glyceryl trinitrate, IV: *retained*
Isosorbide dinitrate, IV: *not considered as an alternative to glyceryl trinitrate, IV*
In the event that there are supply challenges of glyceryl trinitrate, IV and sublingual isosorbide dintrate has been ineffective, patient to be referred for further management[33].
Despite the similar pharmacological action of isosorbide dintrate and glyceryl trinitrate, Isosorbide dinitrate has a longer half-life (1 to 4 hours) compared to glyceryl trinitrate (1 to 4 minutes) with sustained action due to active metabolites. Thus, there is a greater risk of hypotension and shock to isosorbide dinitrate, IV[34].
Level of Evidence: III Guidelines, Expert opinion

- **CLINICALLY STABLE WITHOUT SIGNS OF HEART FAILURE, HYPOTENSION BRADYDYSRHYTHMIAS OR ASTHMA**

HMGCoA reductase inhibitors (statins), oral: *amended*
Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention

- **LV DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION, HEART FAILURE OR EJECTION FRACTION < 40%**

ACE-inhibitors, oral: *indication not amended*
Despite most international guidelines pragmatic approach of recommending ACE-inhibitors post MI to all patients, RCT evidence recommends ACE-inhibitors only for patients with LV dysfunction following MI, heart failure or ejection fraction of less than 40%.
Level of Evidence: I RCTs[35]

[32] Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV Jr, Gibler WB, Peterson ED; CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005 Jun;149(6):1043-9. https://www.ncbi.nlm.nih.gov/pubmed/15976786
[33] NDoH. Safety notice: Management of conditions requiring glyceryl trinitrate, IV, if unavailable, October 2019 (Ref: 2019/10/23/AMD/EDP/01). www.health.gov.za
[34] SAMF, 2016
[35] Rutherford JD, Pfeffer MA, Moyé LA, Davis BR, Flaker GC, Kowey PR, Lamas GA, Miller HS, Packer M, Rouleau JL, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. Circulation. 1994 Oct;90(4):1731-8. https://www.ncbi.nlm.nih.gov/pubmed/7923656
-Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993 Oct 2;342(8875):821-8. https://www.ncbi.nlm.nih.gov/pubmed/8104270
-SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 Aug 1;325(5):293-302. https://www.ncbi.nlm.nih.gov/pubmed/2057034
-CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987 Jun 4;316(23):1429-35. https://www.ncbi.nlm.nih.gov/pubmed/2883575
-ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995 Mar 18;345(8951):669-85. https://www.ncbi.nlm.nih.gov/pubmed/7661937

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).

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

Clopidogrel, oral: *loading dose retained; duration of therapy not amended*

Loading dose: Loading dose (300 mg) recommended for NSTEMI, based on RCT data - CURE RCT[36]; whilst STEMI RCT[37] used clopidogrel 75 mg with urokinase.

Recommendation: The clopidogrel dose for STEMI to be retained as 75 mg daily for one month, and for NSTEMI as 300 mg loading dose, followed by 75 mg daily for three months.

Rationale: RCT evidence supports the dosing regimens for clopidogrel for STEMI and NSTEMI.

Level of Evidence: I RCTs

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[38] 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

Aspirin, oral: *dose amended*

Aligned with aspirin dose for treatment of acute STEMI for consistency and evidence from CURE RCT that suggested that dose-dependent increase in bleeding in patients receiving aspirin plus placebo[39]. (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[40] 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"[41].

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.

[36] 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. http://www.ncbi.nlm.nih.gov/pubmed/14504182

[37] 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

[38] 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

[39] 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

[40] 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

[41] 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]

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[42] as enoxaparin is the most studied LMWH and for which there is the most clinical experience (Refer to the LMWH medicine review, Appendix B).

LMWH for VTE and ACS - Adult review_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

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[43]).

For persistent pain and if oral therapy is insufficient
Glyceryl trinitrate, IV: *retained*
Isosorbide dinitrate, IV: *not considered as an alternative to glyceryl trinitrate, IV*
Aligned with section 3.2.1 ST elevation myocardial infarction (STEMI), see rationale, above.

Severe pain unresponsive to nitrates
Morphine, IV: *directions for use amended*
Management was aligned to section 3.2.1 ST elevation myocardial infarction (STEMI) - see above.

3.2.3 CHRONIC MANAGEMENT OF STEMI / NSTEMI / UA

Referral criteria: *amended*
Narrative of the STG was amended for clarity purposes and to encourage patient-centric care:

The patient's co-morbidities and willingness to undergo revascularisation, which may involve coronary surgery, should be taken into account when advising such referral.

Level of Evidence: III Expert opinion

3.2.4 ANGINA PECTORIS, STABLE

Aspirin, oral: *dose amended*
Aligned with recommendations for management of STEMI, NSTEMI, UA and a meta-analysis[44] 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, 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"[45]. **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.

[42] 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.
[43] 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
[44] 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
[45] 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]

Nitrates

Nitrates, short acting: *directions for use amended*
Isosorbide dinitrate, oral: *retained and dose amended*
Isosorbide mononitrate, oral: *added*

These agents only offer symptomatic relief and long-term use is commonly associated with adverse drug reactions (e.g. headaches, etc). Isosorbide mononitrate was re-added to the STG and EML to assist healthcare workers if supply challenges occur of either agent. The dose of isosorbide dinitrate was amended to formulations that are currently available on the South African market[46].

Level of Evidence: III Guidelines, Expert opinion[47, 48]

Text was editorially amended for clarity and correctness as follows, aligned with SAMF 2016:

Relief of angina:

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

Level of Evidence: III Guidelines

Beta-blockers, oral: *added as a therapeutic class*
Atenolol, oral: *retained as an example of class (listed in STG)*
Propranolol, oral: *not added as an example of class (listed in STG)*
Bisoprolol, oral: *added as an example of class (listed in therapeutic interchange database)*
Carvedilol, oral: *added as an example of class (listed in therapeutic interchange database)*
Metoprolol, oral: *added as an example of class (listed in therapeutic interchange database)*
Acebutolol, oral: *added as an example of class (listed in therapeutic interchange database)*

INDICATION: **Relief of angina**		
Medicine	**Comparative maintenance dose**	**Price (ZAR)**
Atenolol	50-100mg	4.15 – 4.18*
Bisoprolol	10-20 mg	96.08 – 192.16**
Carvedilol	12.5-50 mg (given in 12 hrly divided doses)	103.04 – 160.14**
Metoprolol	100-400 mg	509.43 – 2037.72**
Acebutolol	400-900 mg	387.66 – 1603.17**

* Average weighted price from contract circular RT289-2019
** Cheapest generic price on SEP database, accessed 26 June 2019

Aligned with SAMF, 2016.

Level of Evidence: III Guidelines[49]

Propranolol (non-selective beta-blocker, which are not preferred[50]), oral not added to beta-blocker therapeutic group for relief of angina. Similar to propranolol, carvedilol is a non-selective beta-blocker agent, with additional vasodilator alpha-adrenergic properties. Carvedilol is preferred in patients because occasionally patients have both heart failure or evidence of left ventricular dysfunction and then carvedilol would be the agent of choice. Evidence suggests that carvedilol is comparable to atenolol in terms of anti-angina effect.

[46] SAMF, 2016
[47] Thadani U, Lipicky RJ. Short and long-acting oral nitrates for stable angina pectoris. Cardiovasc Drugs Ther. 1994 Aug;8(4):611-23. https://www.ncbi.nlm.nih.gov/pubmed/7848896
[48] Parker JO. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. Am J Cardiol. 1993 Oct 15;72(12):871-6. https://www.ncbi.nlm.nih.gov/pubmed/8213541
[49] SAMF, 2016
[50] Huang HL, Fox KA. The impact of beta-blockers on mortality in stable angina: a meta-analysis. Scott Med J. 2012 May;57(2):69-75. https://www.ncbi.nlm.nih.gov/pubmed/22555225 (*"Meta-analysis of relevant β-blocker trials in patients with stable angina did not find a significant impact of β-blockers on mortality in general but suggested a trend for cardioselective β-blockers to improve survival rates")*

Level of Evidence: III Disease oriented RCT[51], Guidelines [52]

Statins, oral: *dosing and directions for use amended*
Aligned with section: 3.1 Ischaemic heart disease and atherosclerosis, prevention.

3.2.5 ATHEROSCLEROTIC PERIPHERAL ARTERIAL DISEASE

Statins, oral: *dosing and directions for use amended*
Aligned with section: 3.1 Ischaemic heart disease and atherosclerosis, prevention.

3.3 CARDIAC DYSRHYTHMIAS

Resuscitation Council of South Africa algorithms: *not added*
Resuscitation Council of South Africa (RCSA) algorithms for bradycardia and tachydysrhythmias are not aligned with the text of the STGs. For bradycardia, the STG emphasises the use of external (transcutaneous) pacemaker which should be available in secondary level hospitals; whilst the tachydysrhythmias RCSA algorithm describes both adult and paediatric management, recommending first line pharmacological management with amiodarone for wide complex tachydysrhythmias, whilst the STG recommends initial non-pharmacological DC conversion.

3.3.1.1 ATRIAL FIBRILLATION

New oral anticoagulants (NOACs), oral: *not added*
NOAC medicine review and cost analysis was done for atrial fibrillation in the previous review cycle. Although effective, the agent was not affordable in this clinical setting when compared to standard of care (Refer to medicine review: NOACS, to reduce the risk of ischaemic stroke in patients with atrial fibrillation, 18 January 2016; Pharmacoeconomics and budget impact analysis report: Rivaroxaban for stroke prevention in atrial fibrillation, 11 December 2015 http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults).

Note: NOAC medicine review and cost analysis was likewise done for treatment of venous thromboembolism (VTE) and prevention of recurrence, 11 December 2015 and 19 January 2016 respectively. http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

The pharmacoeconomics model and budget impact analysis for NOACs for VTE treatment and prevention was updated, and rivaroxaban was still considered to be unaffordable.

Similar to the 2015 report, the model suggests that if the price of rivaroxaban was reduced by 80%, treatment of recurrent deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thrombolic events (VTE) with rivaroxaban for 3 to 6 months would become cost-saving. (Refer to the Pharmacoeconomics and budget impact analysis update: Rivaroxaban for stroke prevention in atrial fibrillation, 10 September 2017).

Rivaroxaban for VTE in Adults_Updat

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[51] Oh PC, Kang WC, Moon J, Park YM, Kim S, Kim MG, Lee K, Ahn T, Shin EK. Anti-Anginal and Metabolic Effects of Carvedilol and Atenolol in Patients with Stable Angina Pectoris: A Prospective, Randomized, Parallel, Open-Label Study. Am J Cardiovasc Drugs. 2016 Jun;16(3):221-8. https://www.ncbi.nlm.nih.gov/pubmed/27021556

[52] Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL; Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG). Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006 Jun;27(11):1341-81. https://www.ncbi.nlm.nih.gov/pubmed/16735367

Warfarin, oral: *retained*
Aspirin, oral: *deleted*
For patients with a CHA2DS2-VASc score of 1 there are different approaches, with some recommending no antithrombotic therapy, some recommending oral anticoagulant therapy, and some recommending antiplatelet therapy for selected patients. The particular risk factor present may influence decision making. In particular, older age is the most significant risk factor in these considerations. Clinical judgment will play an important role. Few such patients have been enrolled in clinical trials, and the risk of embolisation attributable to the individual risk factors is not the same.

Text of the STG was amended as follows:

~~If patient has a score of one, use either aspirin or warfarin.~~ When the score is ≥ 2, use warfarin or equivalent. The higher the score the greater the risk of stroke and therefore the more compelling the use of effective anticoagulation.

Level of Evidence: III Standard of care

Amiodarone,IV: *indication not amended*
External comment suggesting pre-treatment with amiodarone, prior to DC synchronised cardioversion. Pre-treatment with antiarrhythmics has historically shown to be harmful, and no evidence was provided for this recommendation. Evidence is mostly for antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.[53]
Level of Evidence: I Systematic review

3.3.2.1 REGULAR WIDE QRS TACHYCARDIAS

DC cardioversion: *retained as first line therapy*
External comment received querying DC cardioversion as 1st line treatment, but cardioversion considered the easiest and safest route of management for the "inexperienced". Furthermore, distinguishing between stable and unstable wide complex tachycardia is dependent on a doctor's skill and may even be missed by the very experienced.

Text of the STG was updated as follows:

DC cardioversion **is preferred and safest first line therapy** for regular wide QRS tachycardias. Medicines are needed if ventricular tachycardia (VT) recurs after cardioversion, or spontaneous termination.

Amiodarone, oral: *dosing amended*
Dosing of oral amiodarone was historically mostly based on expert opinion. Thus, dosing was thus amended to align with the British National Formulary, *"200 mg 8 hourly for 1 week reduced to 200 mg 12 hourly for a further week; maintenance, usually 200 mg daily for the minimum time required to control the arrhythmia".*
STG text was amended accordingly, with guidance for specialist consultation, before instituting long term (>than 1week) therapy.
Rationale: Aligned with guidelines, noting that when initiating oral therapy following IV dosing, both the total IV dose and the duration of IV treatment has to be considered as pharmacokinetics of amiodarone is altered when switching to chronic oral therapy[54].
Level of Evidence: III Guidelines[55]

3.3.2.2 SUSTAINED (>30 SECONDS) IRREGULAR WIDE QRS TACHYCARDIAS

DC cardioversion: *emphasised as the safest treatment option*
Recommending DC cardioversion as first line management in the treatment protocol may interfere with vagal manoeuvres. Following text was placed in a box for emphasis, applicable to both regular and irregular wide-complex tachycardia:

[53] Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2015 Mar 28;(3):CD005049. https://www.ncbi.nlm.nih.gov/pubmed/25820938
[54] NHS, Mid Essex Hospital Services. Clinical Guideline for the administration of IV amiodarone, 28 October 2012. https://www.meht.nhs.uk/search/?q=amiodarone
[55] British National Formulary, 78th edition (September 2019-March 2020).

If in doubt as to the nature of a tachycardia, and in all patients with haemodynamic compromise, DC cardioversion under IV sedation is the safest option.
DC cardioversion, 200 J, after sedation with:

- Midazolam IV, 1–2.5 mg, administered over 2-3 minutes.
  - Monitor and repeat dose after 2-3 minutes, as necessary.
  - If 200 J fails, use 360 J.

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

Amiodarone, parenteral: *retained as 1st line therapy*
Beta-blockers, oral: *not added as 1st line therapy*
Ca Na blockers (lidocaine, parenteral): *retained as 1st line therapy in haemodynamically stable patients*

The usual cause is acute myocardial infarction and most should be on beta-blocker as per sections 3.2.1: ST elevation myocardial infarction (STEMI) and 3.2.2: Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). Ca Na blockers (lidocaine) is recommended in the STG for haemodynamically stable patients.

3.3.3 HEART BLOCK (SECOND OR THIRD DEGREE)

For resuscitation of asystole in combination with CPR:
Adrenaline (epinephrine), parenteral: *directions for use amended*
Text was amended as follows for correctness:

- Adrenaline (epinephrine) 1:10 000, ~~slow~~ IV, 5 mL (0.5 mg).

Used as temporary treatment of complete heart block when other medicines are not effective.

3.4 CONGESTIVE CARDIAC FAILURE (CCF)

Pneumococcal vaccine: *not added*
WHO recommends that in countries that do not routinely administer PPV23 to high-risk populations, data are insufficient to recommend introducing this vaccine to reduce the morbidity and mortality associated with pneumonia. Possible herd immunity achieved by 2017 due to childhood vaccination with PCV (as part of the EPI schedule) may preclude patients from being vaccinated with PCV.

ACE-inhibitors, oral: *amended (note added)*
The following note was added to the text of the STG for rational use of ACE-inhibitors.

Note: All the guideline evidence presented here relates to treatment of patients in whom the heart failure syndrome is due to left ventricular systolic dysfunction and cannot necessarily be extrapolated to patients in whom heart failure is due to other causes of the syndrome.

Eplerenone, oral: *not added*
Refer to the medicine review, eplerenone for cardiac failure (July 2017) for detailed information:

Eplerenone_Cardiac Failure_AdultsReview

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

No direct comparative RCT evidence in terms of efficacy and safety of eplerenone vs. spironolactone could be sourced and eplerenone is currently more expensive than current standard of care, spironolactone.
Level of Evidence: I placebo controlled RCT[56], Expert opinion

56 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348(14):1309-1321. https://www.ncbi.nlm.nih.gov/pubmed/12668699

Angiotensin II receptor blockers (ARBs): *recommended only in ACE-I intolerance*
Evidence for mortality reduction is all in favour of ACEIs[57], and not ARBs. Only when first-line option ACEIs cannot be tolerated (e.g. intractable cough) should ARB be considered.
Level of Evidence: I Systematic review

Enalapril, oral: *daily dose retained*
It is acknowledged that Guidelines[58] recommends the option of 12 hourly dosing, but the trials that used high dose enalapril did not have spironolactone as co-therapy and the mean daily dose in CONSENSUS[59] was 16.6 mg – there is a risk of hyperkalaemia.
Level of Evidence: I RCT

Angiotensin II receptor blockers (ARBs) + ACE-Inhibitor combination therapy: *not added*
Evidence is of low quality and combination ACEI/ARB therapy associated with increased renal dysfunction.
Level of Evidence: III Guidelines[60]

Sacubitril valsartan hydrate, oral: *not added*
Indicated for refractory cases, but is expensive (50mg, 28: R958.10 and 100mg, 28: R958.10[61]), and reported that not used routinely in private sector.
Recommendation: Adult Hospital Level Committee requests the Tertiary & Quaternary Committee to review Sacubitril valsartan sodium hydrate for systolic dysfunction, noting that cost-benefit analysis is required and that the recent information about valsartan withdrawal needs to be considered.

Digoxin, oral: *high risk patient group amendment*
Females and acute coronary ischaemia were removed from the list of patients at high risk of digoxin toxicity.
Level of Evidence: III Guidelines, Expert opinion[62]

3.5 ENDOCARDITIS, INFECTIVE

Enterococcal infection
Gentamicin, IV: *dosing amended from"12 hourly for 4-6 weeks" to "8 hourly for 2-6 weeks"*
Guidelines[63] [64] [65] recommend multiple daily doses of gentamicin and anecdotal studies suggest that shorter duration of gentamicin therapy could minimize adverse effects without impacting the overall cure rate[66].
Recommendation: Gentamicin 8 hourly dosing be recommended for enterococcal infection in infective endocarditis.
Rationale: Aligned with international guidelines.
Level of Evidence: III Guidelines

[57] Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W, Li J, Zhang J, Xu Y, Lu H, Xu D. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2017 Oct 5;17(1):257. https://www.ncbi.nlm.nih.gov/pubmed/28982370
[58] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group . 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104. https://www.ncbi.nlm.nih.gov/pubmed/30165516
[59] CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987 Jun 4;316(23):1429-35. https://www.ncbi.nlm.nih.gov/pubmed/2883575
[60] SAMF, 2016
[61] SEP Database, 12 December 2018
[62] Drugs for the heart; Opie LH, Gersh B 8th Edition 2009 P 204, Table 6-7
[63] Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. Eur Heart J 2004; 25:267–76. https://www.ncbi.nlm.nih.gov/pubmed/14972429
[64] Elliott TS, Foweraker J, Gould FK, Perry JD, Sandoe JA. Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2004; 54:971–81. https://www.ncbi.nlm.nih.gov/pubmed/15546974
[65] Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86. https://www.ncbi.nlm.nih.gov/pubmed/26373316
[66] Olaison L, Schadewitz K, for the Swedish society of infectious diseases quality assurance study group for endocarditis. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycoside be used? Clin Infect Dis 2002; 34:159–66. https://www.ncbi.nlm.nih.gov/pubmed/11740702

An external comment was received recommending that gentamicin dosing be recommended from 4 to 6 weeks as per international guidelines [67] [68] [69], as opposed to the above-mentioned recommendation of "2 to 6 weeks"[70].
However, the duration of therapy of gentamicin therapy in combination with benzyl penicillin for moderately resistant enterococcal strains is aligned with the European Society of Cardiology Guidelines provides guidance for the management of infective endocarditis as follows:

- Benzylpenicillin (penicillin G), IV, 5 million units 6 hourly for 4 weeks.

AND

- Gentamicin, IV, 1mg/kg 8 hourly for 2 weeks.
  Six weeks of therapy may be required in cases with a history of > 3 months, or mitral or prosthetic valve involvement. (See Appendix II, for individual dosing and monitoring for response and toxicity)

Empiric therapy (native valve): If staphylococcal infection is suspected (acute onset)
Cloxacillin, IV: *deleted*
Cefazolin, IV: *added*
Staph aureus resistance to oxacillin has recently been reported in two Provinces, with 9% MRSA detected in community acquired pneumonia.[71]
NEMLC approved circular: Due to continuous supply challenges with Cloxacillin, IV, NEMLC[72] had approved a circular recommending cefazolin, IV in place of cloxacillin, IV for a number of indications based on the systematic review of cohort studies by Loubet et al[73].
Recommendation: Cloxacillin, IV be replaced with cefazolin, IV (that has cover against MSSA and streptococci).
Rationale: Aligned with Guidelines[74] and retrospective cohort study showed that cloxacillin comparable to cefazolin with regards to mortality at 90 days in ICU (HR 0.58; 95% CI 0.31 to 1.08)[75].
Level of Evidence: II Retrospective cohort study, Susceptibility study, Guidelines

Directed therapy (native valve): Staphylococcal (cloxacillin/ methicillin sensitive)
Cloxacillin, IV: *deleted*
Cefazolin, IV: *added*
As above.

Directed therapy for prosthetic valve endocarditis
The following editorial amendment was accepted:

Duration of therapy is usually a minimum of at least 6 weeks.
Seek expert opinion on antibiotic choice and the need for referral for repeat cardiac surgery early in the course of treatment.

[67] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; 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. https://www.ncbi.nlm.nih.gov/pubmed/26320109
[68] Elliott TS, Foweraker J, Gould FK, Perry JD, Sandoe JA. Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2004; 54:971–81. https://www.ncbi.nlm.nih.gov/pubmed/15546974
[69] Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86. https://www.ncbi.nlm.nih.gov/pubmed/26373316
[70] Minutes of the NEMLC meeting of 2 November 2017
[71] Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285
[72] Minutes of the NEMLC meeting of 2 November 2017.
[73] Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037
[74] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422
[75] Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

3.6 HYPERTENSION

BP target of <140/90 mm Hg: *not amended to <130/80 mmHg*

Please see below, summary document for blood pressure targets in adults (July 2018):

Blood Pressure Targets in Adults_Ev

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Adoption of the new BP target of < 130/80 mmHg, as recommended by the ACC/AHA Guidelines (2017) is not recommended.

Rationale: There is conflicting evidence in the literature with regards the benefit of BP control below the current standard. There is also uncertainty as to which group of people benefit with lower blood pressures and evidence of possible harm. The patient cohorts in the RCTs may not be generalisable to the South African population, and the sub group analysis of SPRINT showed hetrogeneity in outcomes between groups.

The SPRINT trial protocol for measuring BP tried to reduce all external causes of a falsely elevated BP, unless BP is measured this way people with reactive elevated BP's would be inappropriately treated.

An additional factor that was considered was the affordability of intensive antihypertensive treatment, both to the health system and patients.

Level of Evidemnce: I Systematic reviews, RCT[76] [77] [78] [79] [80] [81], Expert Opinion

Investigations

Automated office blood pressure monitors (AOBP): *not added*

An external comment to recommend AOBPs was noted, but falls outside NEMLCs mandate. A Health Technology Assessment would be required to determine the relevant AOBPs for the public healthcare sector.

Waist circumference cut-off: *not amended to assess central obesity*

External comment was received to change the waist circumference cut-off to 81 cm for both men and women to assess obesity. Cross-sectional study was submitted and reviewed by the Adult Hospital Level Committee.

Evidence review: The data from the cross-sectional study done in Sub-Saharan Africa, suggesting that the optimal weight circumference for identifying increased cardiometabolic risk amongst men may be higher than guideline recommendations, was acknowledged. However, the authors of the study conclude that prospective studies are required to confirm this hypothesis.

Recommendation: Optimal weight circumference for men and women not be amended.

Rationale: More data is required to confirm the lower optimal weight circumference for men in Sub Saharan Africa, to predict cardiometabolic risk.

Level of Evidence: III Cross-sectional study[82]

[76] 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

[77] 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

[78] 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

[79] 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

[80] 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

[81] 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

[82] Ekoru K, Murphy GAV, Young EH, Delisle H, Jerome CS, Assah F, et al. Deriving an optimal threshold of waist circumference for detecting cardiometabolic risk in sub-Saharan Africa. Int J Obes (Lond). 2017 Oct 3. doi: 10.1038/ijo.2017.240. https://www.ncbi.nlm.nih.gov/pubmed/29087388

MEDICINE TREATMENT CHOICES WITHOUT COMPELLING INDICATIONS

Algorithm for the management of hypertension was included in the STG (refer to the chapter)

Hydrochlorothiazide, oral: *retained as 1st line option*

Calcium channel blocker, oral (i.e. amlodipine): *not added as 1st line option*

An external comment was received that hydrochlorothiazide as first line option for management of hypertension was not evidence based. NEMLC noted that a motivation, to replace first line therapy, hydrochlorothiazide with amlodipine to treat hypertension without compelling indications, had previously been submitted to the PHC Committee for review. The outcomes of the PHC review follows below (i.e. hydrochlorothiazide, oral was retained as first line therapy). The recommendation below was accepted by the NEMLC, and the Adult STG was aligned to the PHC STG, accordingly.

PHC CVS NEMLC report of 2 November 2017[83]:
Stepwise treatment of hypertension without compelling indications
Hydrochlorothiazide, oral: retained as 1st line option
Calcium channel blocker, oral: not amended to 1st line option

Background:
The current PHC STG recommends that patients with mild hypertension be started on hydrochlorothiazide (HCTZ), unless there is a compelling indication to initiate therapy with a different agent (see chapter for details). No comments were received when the chapter was initially circulated. However during the second round of external review the following comment was received "Strongly suggest that amlodipine is drug of first choice, safest, effective and minimal monitoring."
Evidence review:
NICE Guidelines[84] recommends that people aged over 55 years and black people of African or Caribbean family origin of any age with mild hypertension be started on a calcium-channel blocker (CCB), whilst those younger than 55 years should be started on angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB).
The recommendation not to use a diuretic as a first-line agent is based on the findings of the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial[85] which showed that the combination of HCTZ with an ACE inhibitor was less effective in reducing cardiovascular events than the same ACE inhibitor with a CCB.
However, this findings of the ACCOMPLISH trail has not been replicated in other trials, and a number of other trials have not demonstrated superiority of ACE inhibitors or CCBs over HCTZ when used as monotherapy (ALLHAT[86], INSIGHT[87], STOP-HT2[88], CONVINCE[89]).
Furthermore the European (2013)[90] and the American (2014)[91] Hypertension Guidelines retain HCTZ as a first choice option in the treatment of mild hypertension. The PHC Committee therefore recommends that the guideline is not changed.
Recommendation: *HCTZ be retained as first line therapy for management of hypertension in adults.*
Rationale: *Current evidence regarding the superiority of CCBs over HCTZ as monotherapy in those without a compelling indication is inconclusive.*
Level of Evidence: I RCTs, Guidelines

In addition, refer to the discussion on the Ettehad et al meta-analysis, below, that showed differences among various drug classes in reducing the risk of specific clinical outcomes.

[83] NEMLC report (2016-2018 review) for the PHC STGs and EML, 2018 edition: Cardiovascular conditions. http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc

[84] National Institute for Health and Clinical Excellence (NICE).Hypertension.The clinical management of primary hypertension in adults.Clinical Guideline 127. 2011. www.nice.org.uk/guidance/CG127

[85] Bakris GL, Serafidis PA, Weir MR, Dalhof B, Pitt B, Jamerson K, et al., ACCOMPLISH Trial Investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of randomised controlled trial. Lancet 2010; 375:1173–1181. https://www.ncbi.nlm.nih.gov/pubmed/20170948

[86] ALLHAT officers and co-ordinators for the ALLHAT collaborative research group. The antihypertensive and lipid lowering treatment to prevent heart attack trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288:2998–3007. https://www.ncbi.nlm.nih.gov/pubmed/12479764

[87] de Leeuw PW, Ruilope LM, Palmer CR, Brown MJ, Castaigne A, Mancia G, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial. Arch Intern Med 2004; 164:2459–2464. https://www.ncbi.nlm.nih.gov/pubmed/15596636

[88] Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension).Lancet 1991; 338:1281–1285. https://www.ncbi.nlm.nih.gov/pubmed/1682683

[89] Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, et al., CONVINCE Trial group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003; 289:2073–2082. https://www.ncbi.nlm.nih.gov/pubmed/12709465

[90] Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC Guidelines for the management of arterial hypertension Journal of Hypertension. 2013, 31:1281–1357. https://www.ncbi.nlm.nih.gov/pubmed/23817082

[91] Eighth Joint National Committee (JNC 8) 2014 Evidence-Based Guidelines for the Management of High Blood Pressure in Adults, 2014. http://www.aafp.org/patient-care/clinical-recommendations/all/highbloodpressure.html

Hydrochlorothiazide caution: Previously the NEMLC[92] reviewed the skin cancer risk of hydrochlorothiazide[93] [94] and a circular was disseminated advising that hydrochlorothiazide would be retained in the National Essential medicines List for the management of congestive cardiac failure, hypertension, myocarditis, stroke and neurological disorders, with a caution to risk-assess patients with a history or family history of skin cancer and to counsel all exposed to HCTZ on sun avoidance and sun protection[95]. Caution was added to the STGs accordingly.

Enalapril, oral: *retained and daily dosing not amended*

Safety of enalapril: The Pharmacovigilance Committee of MCC/SAHPRA forwarded a report to the Affordable Medicines Directorate with a request to comment on the safety of essential medicine, enalapril. For the period January to December 2017, ADRs associated with enalapril reported to SAHPRA included:

- 211 ADRs of cough
- 125 ADRs of angioedema
- 79 ADRs of lip swelling

WHO Uppsala Vigibase[96]: 3736 cases of angioedema reported to Uppsala up to and including 1 November 2018.

RSAPharmadatabase: Supplier consumption data for January to December 2017 is as follows:

Medicine	Number of units
Enalapril 5 mg	0
Enalapril 10 mg	17 383 109
Enalapril 20 mg	3 140 783
Total number of units (1 month supply)	**20 523 892**

The number of ADRs reported to MCC/SAHPRA is best reviewed in the context of the consumption data above. Fatalities due to angioedema associated with laryngeal oedema or tongue oedema have very rarely been reported[97].

NOTE: The Adult Hospital Level Committee had requested additional information from the PV Committee at MCC/SAHPRA to inform decision-making: "For the ADRs of angioedema associated with enalapril, which ADRs were further associated with mortality (where there was a possible/ probable causal link of angioedema-associated mortality with the suspect medicine, enalapril)". The Director of the Pharmacovigilance Unit of MCC/SAHPRA acknowledged the query via email on 28 November 2018, but to date, no official response has been received.

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 management of blood pressure. Small observational study (n=20) [98] 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[99] and cost are additional considerations.
Level of Evidence: III Observational studies (low quality)[95] [100], Expert opinion

[92] Minutes of the NEMLC meeting of 6 December 2018 – of note is that this meeting was not quorate, and the minutes were reviewed and corrected for final ratification at the NEMLC meeting of 21 February 2019.
[93] Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. J Am Acad Dermatol. 2018 Apr;78(4):673-681.e9. https://www.ncbi.nlm.nih.gov/pubmed/29217346
[94] Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 2017 Oct;282(4):322-331. https://www.ncbi.nlm.nih.gov/pubmed/28480532
[95] National Department of Health, Essential Drugs Programme: Updated Notice: Risk of skin cancer associated with hydrochlorothiazide, 6 March 2019. http://www.health.gov.za
[96] WHO Vigibase. [Internet] [Accessed 25 November 2018] Available at: http://www.vigiaccess.org/
- For the period 1968 to 25 Nov 2018, reports: *Basal cell carcinoma 0.06; Skin cancer 0.03%; Squamous cell carcinoma (0.03%); Squamous cell carcinoma of skin (0.02%).*
[97] Banerji A, Clark S, Blanda M, LoVecchio F, Snyder B, Camargo CA Jr. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. Ann Allergy Asthma Immunol. 2008 Apr;100(4):327-32. https://www.ncbi.nlm.nih.gov/pubmed/18450117
[98] 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
[99] SAMF, 2016
[100] 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

Spironolactone, oral: *added*
Spironolactone was added to the algorithm to manage hypertension, aligned with the PHC STG (approved by NEMLC[101]):
Efficacy: Evidence provided (PATHWAY study[102] - a double-blind, placebo-controlled cross over RCT) showed that spironolactone was the most effective in reducing systolic blood pressure compared to placebo (–8·70 mm Hg, 95% CI –9·72 to –7·69; p<0·0001), bisoprolol (–4·48 mm Hg, 95% CI –5·50 to –3·46];p<0·0001) and doxazosin (–4·03 mm Hg, 95% CI–5·04 to –3·02; p<0·0001), in resistant hypertension.
Safety: The study reported that "In six of the 285 patients who received spironolactone, serum potassium exceeded 6·0 mmol/L on one occasion".

Hyperkalaemia caution: Caution regarding use of spironolactone found in the "front" of the Adult Hospital Level STGs and EML was updated as follows to provide practical guidance, "Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. *Check potassium levels within one month of starting therapy and as per clinical need thereafter.* Avoid if eGFR < 30 mL/minute".
Rationale: Evidence of superior efficacy of spironolactone to beta-blocker in resistant hypertension.
Level of Evidence: I RCT, Expert opinion

Atenolol, oral: *retained*
Atenolol, oral retained as last line therapy for refractory hypertension, after addition of spironolactone.
Level of Evidence: III Expert opinion

Angiotensin II receptor blockers (ARBs): *directions for use not amended*
Novartis had submitted comment that the option of "ACE or ARB" be considered throughout this chapter. However, ACE-inhibitors are 1st line option, and only where an ACE-inhibitor is not tolerated, e.g. intractable cough, are ARBs considered.

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[103] 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.

[101] Minutes of the NEMLC meeting of 2 March 2017.
[102] Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015 Nov 21;386(10008):2059-68. http://www.ncbi.nlm.nih.gov/pubmed/26414968
[103] 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

- Meta-analysis by Ettehad et al[104] 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[105] – 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

MANAGEMENT OF HYPERTENSION

A number of comments and concerns were raised from external stakeholders that even with current guidelines, there remains a huge unmet need with regard to blood pressure management in South Africa. This would require intensive implementation strategies that falls outside NEMLC's mandate.

Stepped-care approach

However, the Adult Hospital Level Committee recommended that the following footnotes be added to the hypertension algorithm to further guide management on the stepped-care approach of hypertension:

Note:

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

» If BP control is suboptimal: Uptitrate treatment (maximise dose of current antihypertensive and/or add additional medicine). Evidence suggests that treatment inertia contributes to suboptimal BP control with patients remaining on monotherapy and/or suboptimal doses.

» Initiate combination medicine therapy in cases of severe hypertension (see section 3.6.1) and hypertension urgency (see section 3.6.2).

Level of Evidence: III Observational studies[106] [107]

Furthermore, additional guidance has been added to the STG (i.e. bedtime dosing, fixed dose combination for chronic BP management).

Bedtime dosing

ACE-inhibitor, oral: *directions of use amended*

Calcium channel blocker, oral: *directions of use amended*

Beta-blockers, oral: *directions of use amended*

There is emerging evidence[108] that taking the total daily dose of antihypertensive medication at bedtime rather than on awaking provides both better control of hypertension and a significant reduction in important cardiovascular

[104] 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

[105] 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

[106] Tiffe T, Wagner M, Rucker V, Morbach C, Gelbrich G, Stork S, Heuschmann PU. Control of cardiovascular risk factors and its determinants in the general population- findings from the STAAB cohort study. BMC Cardiovasc Disord 2017;17:276. https://www.ncbi.nlm.nih.gov/pubmed/29096615

[107] Berry KM, Parker WA, Mchiza ZJ, Sewpaul R, Labadarios D, Rosen S, Stokes A. Quantifying unmet need for hypertension care in South Africa through a care cascade: evidence from the SANHANES, 2011-2012. BMJ Glob Health. 2017 Aug 16;2(3):e000348. https://www.ncbi.nlm.nih.gov/pubmed/29082013

[108] Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. https://www.ncbi.nlm.nih.gov/pubmed/31641769

events. Dosing of these agents was amended to bedtime dosing; whilst daytime dosing may be preferred for diuretic monotherapy.
Level of Evidence: I RCT (PROBE study)

Fixed dose combinations
A late external comment was received regarding the use of fixed dose combination (FDC) medication for control of hypertension that provides greater adherence.[109] Antihypertensive FDC formulations may be used if they are available and shown to be affordable (when compared to single agents).
Level of Evidence: III Observational study[110]

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[109] Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, White CMJ, Petrák O, Gulsin GS, Patel V, Rosa J, Cole R, Zelinka T, Holaj R, Kinnell A, Smith PR, Thompson JR, Squire I, Widimský J Jr, Samani NJ, Williams B, Tomaszewski M. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension. 2017 Jun;69(6):1113-1120. https://www.ncbi.nlm.nih.gov/pubmed/28461599
[110] Dragomir A, Côté R, Roy L, Blais L, Lalonde L, Bérard A, Perreault S. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Med Care. 2010 May;48(5):418-25. https://www.ncbi.nlm.nih.gov/pubmed/20393367
(Note: *Observational data suggests that poor adherence may be associated with a higher risk of cardiovascular consequences;* ***NB:*** *this needs to be reviewed more extensively in the next review cycle).*