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Department:
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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 4: CARDIOVASCULAR CONDITIONS
NEMLC RECOMMENDATIONS ON MEDICINE AMENDMENTS (2016 – 2018)

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

SECTION	MEDICINE	ADDED/DELETED/AMENDED/ RETAINED
4.1 Prevention of ischaemic heart disease and atherosclerosis		
- Primary prevention of ischaemic events	Simvastatin, oral	Dose retained as 10 mg
- Secondary prevention of ischaemic events	Simvastatin, oral	Dose amended from low 10 mg dose to intermediate 40 mg dose
- Secondary prevention of ischaemic events: i) Drug-drug interaction with amlodipine	Simvastatin, oral 10 mg	Added
- Secondary prevention of ischaemic events: ii) Drug-drug interaction with protease inhibitors	Atorvastatin, oral, 10 mg	Added
- Secondary prevention of ischaemic events: iii) Managing ADRs associated with intermediate dose statins	Simvastatin, oral, 10 mg	Added
- CVD risk assessment	Screening of IHD risk using BMI	Added
	Screening of IHD risk using Framingham tables	Retained
4.2 Angina pectoris, stable		
	Aspirin, oral	Dose amended
	Isosorbide dinitrate, oral	Retained and dose amended
	Isosorbide mononitrate, oral	Retained
4.3 Angina pectoris, unstable/ non ST elevation myocardial infarction (NSTEMI)		
	Aspirin, oral	Dose amended
- Continuation of aftercare treatment initiated at higher level of care:	Aspirin, oral	Added
	Atenolol, oral	Added
	Simvastatin, oral (10 and 40 mg)	Added
	Atorvastatin, oral (10 mg)	Added
	Enalapril, oral	Added
4.3 Angina pectoris, unstable / non ST elevation myocardial infarction (NSTEMI)		
- Emergency treatment : Before transfer	Aspirin, oral	Dose amended
	Thrombolytics	Added as therapeutic group
	Streptokinase, IV	Retained and listed in the STG as an example of therapeutic class
	Altepase, IV	Medicine in therapeutic group
	Tenectaplse, IV	Medicine in therapeutic group
	Heparin	Not added
	LMWH	Not added
- Continuation of aftercare treatment initiated at higher level of care:	Aspirin, oral	Added
	Atenolol, oral	Added
	Simvastatin, oral (10 and 40 mg)	Added
	Atorvastatin, oral (10 mg)	Added
	Enalapril, oral	Added
	Aspirin, oral	Added
4.7.1 Hypertension in adults		
- BP target	Screening and treatment target	Not amended (review deferred)
-Stroke	Amlodipine, oral	Not added as a pre-referral dose

- *Moderate hypertension*	Initiation of combination anti-hypertensive therapy	Not added
- *Step 2*	Hydrochlorothiazide, oral	Retained as 1st line option
	Calcium channel blocker, oral	Not amended to 1st line option
- *Step 7*	Spironolactone, oral	Added
	Atenolol, oral	Deleted
	Enalapril, oral	Dosing not amended
- *Contraindications to individual medicines*	Spironolactone, oral	A contra-indications added
4.9 Rheumatic fever, acute		
- *Eradication of streptococci in throat*	Amoxicillin, oral	Dosing amended
- *Severe penicillin allergy*	Azithromycin, oral	Added

4.1 PREVENTION OF ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS

Primary prevention of ischaemic events

Simvastatin, oral: *dose retained as 10 mg*

Secondary prevention of ischaemic events

Simvastatin, oral: *dose amended from low 10 mg dose to intermediate 40 mg dose*

Cost-effectiveness analysis was done, based on the Cholesterol Treatment Trialists' Collaboration meta-analysis[1] that showed a linear relationship between statin dose and prevention of ischaemic events) to inform a decision on the dose of the statin to be recommended. Previously, a meta-regression[2] had informed the previous PHC ERC's recommendation to retain simvastatin at a dose of 10 mg that showed a ceiling on the dose-response curve with no benefit beyond a decrease of 1 mmol of low-density (LDL) cholesterol.

Budget impact assessment: The author of the report recommended that from a public sector provider perspective, simvastatin 40 mg is a cost-effective intervention for the secondary prevention of cardiovascular disease, but that a budget impact assessment should be done to further inform recommendations. However, local prevalence data is not available and using contract estimates and/or consumption data was unreliable.

Guideline recommendations: Guidelines[3] [4] recommend fixed dose (or intensity) of statin for each risk category (with intended LDL-C reductions of 30% to 49% and ≥ 50% for moderate- and high-intensity statins, respectively) as opposed to the previous treat-to-target approach. High-intensity statins are recommended for secondary prevention.

Statin dose: Simvastatin 40 mg was shown to be the most cost-effective for secondary prevention, the intermediate intensity statin was proposed for use in secondary prevention:

Costs, outcomes and cost-effectiveness ratios of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease:

	Cost	Life years	ICER
Simvastatin 10mg	42829.40	4.31	Dominated
Simvastatin 20 mg	42024.12	4.32	Dominated
Atorvastatin 40 mg	40500.50	4.34	Dominated
Simvastatin 40 mg	39773.00	4.34	

[1] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78. Epub 2005 Sep 27. Erratum in: Lancet. 2008 Jun 21;371(9630):2084. Lancet. 2005 Oct 15-21;366(9494):1358. http://www.ncbi.nlm.nih.gov/pubmed/16214597

[2] Takagi H, Umemoto T; for the ALICE (All-Literature Investigation ofCardiovascular Evidence) Group. Limit to Benefits of Large Reductions in Low-Density Lipoprotein Cholesterol Levels: Use of Fractional Polynomials to Assess the Effect of Low-Density Lipoprotein Cholesterol Level Reduction in Metaregression of Large Statin Randomized Trials. *JAMA Intern Med.* 2013 Apr 29:1-2.http://www.ncbi.nlm.nih.gov/pubmed/23700132

[3] American College of Cardiology/American Heart Association Guidelines, 201

[4] NICE Guidelines, Cardiovascular disease, 2014.

Atorvastatin 80 mg	40737.80	4.34	128142.33

ICER: incremental cost effectiveness ratio

(Refer to the cost effectiveness analysis report for detailed information).

StatinsForSecondar
y PreventOfCVD evei

Recommendations:

- Simvastatin 40 mg be recommended for secondary prevention of ischaemic events in adults.

Secondary prevention of ischaemic events:

i) Drug-drug interaction with amlodipine

Simvastatin, oral: *10 mg added*

Pharmacokinetic studies indicated that concurrent administration of amlodipine and simvastatin, at a daily dose greater than 10 mg, increased the AUC and Cmax of simvastatin. Thus, the risk of myopathy and rhabdomyolysis is increased.

Recommendation: Guidance is provided to reduce simvastatin from 40 mg to 10 mg, with concomitant use of amlodipine.

Level of Evidence: III Pharmacokinetic studies[5]

NEMLC made further recommendations for dose reductions of statins (NEMLC Minutes of the meeting: 12 April 2018)

Amlodipine: The drug-drug interaction of intermediate to high dose statins and amlodipine results in a 10-fold increase in the area under the curve (AUC) with simvastatin and a 6-fold increase in AUC with atorvastatin.

Recommendation: The NEMLC recommended that the dose reduction for management of the drug-drug interaction with amlodipine as well as for ADRs associated with intermediate dose statins, be standardised to 10 mg simvastatin/atorvastatin for pragmatic purposes.

Secondary prevention of ischaemic events:

ii) Drug-drug interaction with protease inhibitors

Atorvastatin, oral: *10 mg added*

Network meta-analysis by Naci et al[6], suggests that simvastatin 40 mg has similar potency to atorvastatin 40 mg in reducing low density lipoprotein (LDL). Doses of 21 to 40 mg of atorvastatin and simvastatin reduced LDL by -1.41 (95% CI -1.83 to -0.99) and -1.42 (95% CI -1.91 to -1.03), respectively. However, atorvastatin is indicated for secondary prevention of ischaemic events in patients on protease inhibitors. Co-administration of atorvastatin with atazanavir may increase the risk of myopathy including rhabdomyolysis, as both agents are metabolised by CYP3A4. Thus, a lower dose of atorvastatin 10 mg[7], was recommended, with careful safety monitoring. Pharmacokinetic studies show an increase in plasma AUC of atorvastatin when used concomitantly with protease inhibitors.[8] [9] [10]

[5] Drug Interactions database. [Accessed 7 February 2018] Available at: https://www.uptodate.com/drug-interactions

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

[7] Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

[8] Lennernäs H. Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet. 2003;42(13):1141-60. https://www.ncbi.nlm.nih.gov/pubmed/14531725#

[9] Chauvin B, Drouot S, Barrail-Tran A, Taburet AM. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. Clin Pharmacokinet. 2013 Oct;52(10):815-31. https://www.ncbi.nlm.nih.gov/pubmed/23703578#

[10] Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Level of Evidence: III Guidelines[11]

Secondary prevention of ischaemic events:
iii) Managing ADRs associated with intermediate dose statins
Simvastatin, oral: *10 mg added*
Aligned with NICE Guidelines for the management of ADRs associated with intermediate dose statins
Level of Evidence: III Guidelines[12]

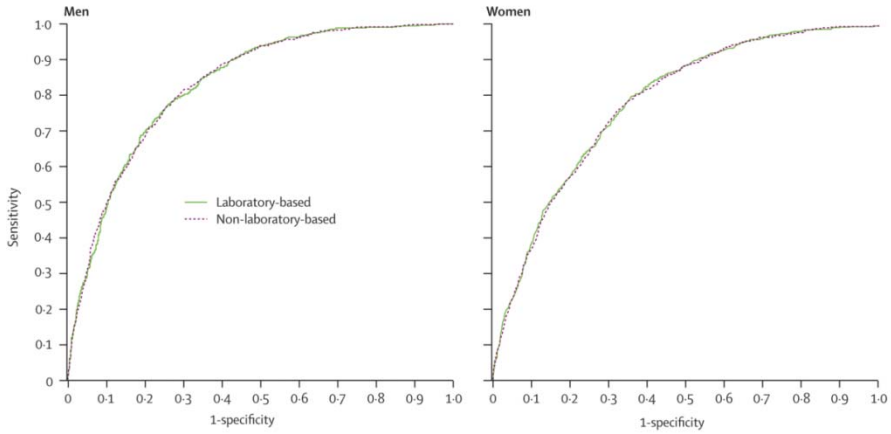
NEMLC made further recommendations for dose reductions of statins (NEMLC Minutes of the meeting: 12 April and 5 July 2018)
Recommendation: The NEMLC recommended that the dose reduction for management of the drug-drug interaction with amlodipine as well as for ADRs associated with intermediate dose statins, be standardised to 10 mg simvastatin for pragmatic purposes. Patients on protease inhibitors experiencing adverse effects on atorvastatin 10 mg to be referred to higher level of care, for further management.

Cardiovascular disease risk assessment
Screening of IHD risk using BMI: *added*
Screening of IHD risk using Framingham tables: *retained*
An external comment with supporting evidence was received motivating for BMI based CVD risk-screening rather than Framingham risk score assessment, as the former was more pragmatic at primary level of care and would be cheaper (Total cost for cholesterol blood tests = R97.88).[13] It is noted that the Western Cape PACK guidelines uses the BMI-based risk assessment tool and no longer recommend cholesterol-based screening.

Evidence reviewed:
Gaziano et al (2008)[14] used a US cohort to compare cholesterol-based versus BMI-based models in terms for their ability to predict 5-year risk of a CVS event, in patients without existing atherosclerotic disease – i.e. a primary prevention population. (CVS event was a composite of death, MI, stroke, congestive heart failure, and coronary revascularisation; results were similar when restricted to CVS deaths only.) The primary outcome measure was the c-statistic: the area under the curve of a receiver operator characteristic (ROC) curve. (A ROC curve plots sensitivity (true positives) versus 1-specificity (false positives): the higher the c-statistic the better the prediction model.) The overall c-statistics for BMI- and cholesterol-based models respectively were 0.831 and 0.829 in women; and 0.783 and 0.784 in men. Models were similar to each other in terms of predictive ability across levels of risk (5–30% 5-year risk). Conclusion: the BMI-based model performed as well as the cholesterol-based model in terms of predicting CVS events.

Figure 1.: ROC curves for laboratory-based and non-laboratory-based methods for prediction of cardiovascular disease

[11] University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/
[12] NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181
[13] NHLS State Price List, 2017: Total cholesterol= R42.74; HDL cholesterol = R55.14. https://wwwhealth.gov.za
[14] Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet. 2008 Mar 15;371(9616):923-31. https://www.ncbi.nlm.nih.gov/pubmed/18342687

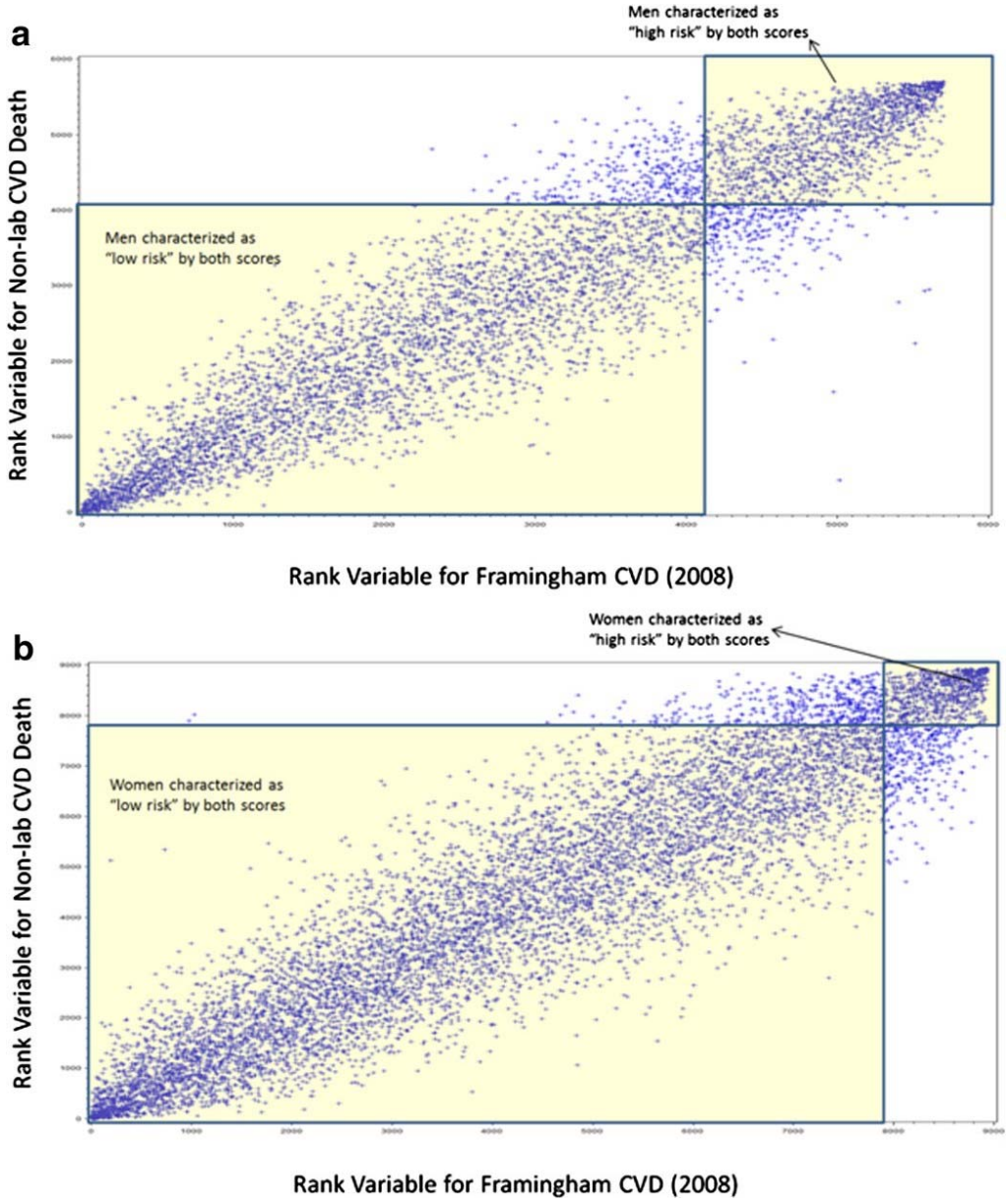


Gaziano et al (2013)[15], and Peer et al (2014)[16], used cross-sectional data only from South African populations to compare cholesterol- and BMI-based models (i.e. Framingham versus the Gaziano et al 2008 models) in terms of their classification of people into 10-year CVS event risk categories. They showed reasonable correlation. (Spearman correlation coefficients of around 0.9 for all risk categories in Gaziano 2013 study.)

Figure 1 Rank variables for the non-laboratory-based risk score are plotted against rank variables for the Framingham (2008) CVD score for adults 25 to 74 years old with complete data in the aggregate study population. Larger ranks indicate greater CVD risk. Based on a risk threshold that corresponds to 10-year Framingham (2008) CVD risk >20%, 92.3% of men (panel a, shaded regions) and 94.0% of women (panel b, shaded regions) would be similarly characterized as high or low risk by the non-laboratory-based and Framingham (2008) CVD risk scores.

[15] Gaziano TA, Pandya A, Steyn K, Levitt N, Mollentze W, Joubert G, Walsh CM, Motala AA, Kruger A, Schutte AE, Naidoo DP, Prakaschandra DR, Laubscher R. Comparative assessment of absolute cardiovascular disease risk characterization from non-laboratory-based risk assessment in South African populations. BMC Med. 2013 Jul 24;11:170. https://www.ncbi.nlm.nih.gov/pubmed/23880010

[16] Peer N, Lombard C, Steyn K, Gaziano T, Levitt N. Comparability of total cardiovascular disease risk estimates using laboratory and non-laboratory based assessments in urban-dwelling South Africans: the CRIBSA study. S Afr Med J. 2014 Aug 13;104(10):691-6. https://www.ncbi.nlm.nih.gov/pubmed/25363056



Pandya et al (2014, also Gaziano group)[17] used US data to show that it was relatively cost effective to use a 'multistage' screening model. They proposed an initial BMI-based screen, with cholesterol measured only in those with 'intermediate' risk.

Recommendations:
Screening for CVD risk and screening for familial hyperlipidaemia be separated.

i. *<u>CVD risk screening:</u>*

- No CVD risk screening for high risk patients (secondary prevention and many diabetics).
- BMI-based CVD risk screening for other patients, with management based on 10-year risk:
  - <10%: reassess every five years
  - 10-20%: lifestyle modification and reassess annually
  - >20%: lifestyle modification and statin

[17] [17] Pandya A, Weinstein MC, Salomon JA, Cutler D, Gaziano TA. Who needs laboratories and who needs statins?: comparative and cost-effectiveness analyses of non-laboratory-based, laboratory-based, and staged primary cardiovascular disease screening guidelines. CircCardiovascQual Outcomes. 2014 Jan;7(1):25-32. https://www.ncbi.nlm.nih.gov/pubmed/24425701

Rationale: Evidence that the BMI-based model performed as well as the cholesterol-based model in terms of predicting CVS events.
Level of Evidence: III Cross-sectional, Case control studies

ii. *Familial hyperlipidaemia screening:*

- Baseline total cholesterol in certain high-risk patients to screen for familial hyperlipidaemia (e.g. CVD at young age in patient or first-degree relative, tendon xanthomata etc.). These patients are referred to higher level of care for further management.

Practical issues with respect to implementation:
The Gaziano 2008 paper includes user-friendly tables to estimate CVD risk, without having to perform any calculations. However, these tables predict 5-year risk. The PHC Committee would like to include similar tables for 10-year CVD risk, using the Framingham BMI-based cardiovascular risk assessment[18].

NEMLC made further recommendations at the NEMLC meeting of 2 November 2017)
Screening of IHD risk using BMI: The NEMLC recommended that the Framingham risk scoring tables be retained in the text of the STG. A tool is available on the cellphone application to enable nurses to calculate CVS risk and intervention studies utilise Framingham risk scores; not BMI risk scores. NEMLC suggested that the PHC Committee consider developing a tool for the BMI risk scores to make this option available to healthcare workers.
Recommendations:

- STG retain Framingham risk scoring tables, as intervention studies use cholesterol risk scoring rather than BMI risk scoring to predict IHD events[19].
- PHC Committee considers development of a tool for the BMI risk scores for the EML Clinical Guide application.

At the meeting of 5 July 2018[20], NEMLC accepted the PHC recommendation to add the Framingham BMI-based CVD risk assessment, predicting 10-year CVD risk, as per risk algorithm recommended by D'Agostino et al (2008).

4.2 ANGINA PECTORIS, STABLE

Aspirin, oral: *dose amended*

Amended from "150 mg" to "75-100mg" daily, as the preferred dose and to use 150 mg only if the latter strengths are unavailable. Aligned with the NEMLC approved proposed Adult Hospital level STGs and EML, currently under review that is currently under review. Extract from the Adult Hospital Level NEMLC report for the cardiovascular chapter follows below:

Adult Hospital Level Committee NEMLC report, 2 November 2017:

3.2.1 ST elevation myocardial infarction (STEMI)
Aspirin, oral: dose amended (from "150 mg" to "100–150 mg", daily)
Berger et al[21] showed that "an initial dose of 162 mg aspirin may be as effective as and perhaps safer than 325 mg for the acute treatment of STEMI". Dose of 325 mg was associated with a significant increase in moderate/severe bleeding (adjusted OR, 1.14; 95% CI, 1.05 to 1.24; p=0.003).
***Recommendation**: Initial dose for acute STEMI with aspirin be recommended as "100-150 mg".*

[18] D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53. https://www.ncbi.nlm.nih.gov/pubmed/18212285
[19] NEMLC minutes of the meeting: 2 November 2017
[20] NEMLC minutes of the meeting: 5 July 2018
[21] 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

Rationale: RCT evidence suggests 100 mg aspirin with clopodigrel for acute STEMI. However, to ensure consistent availability, 150 mg likewise recommended. Currently, 300 mg dose of aspirin is available on tender as a scored tablet.
Level of Evidence: I RCTs, Expert opinion

4.3 Angina pectoris, unstable/ non st elevation myocardial infarction (NSTEMI)
Aspirin, oral: dose amended
Aligned with recommendations for management of STEMI, NSTEMI, UA and a meta-analysis[22] 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

Nitrates
Isosorbide dinitrate, oral: *retained and dose amended*
Isosorbide mononitrate, oral: *retained*
Aligned with the Adult Hospital Level Guidelines and dose amended to formulations that are currently available on the South African market[23].
Level of Evidence: III Guidelines, Expert opinion[24, 25]

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

Aspirin, oral: *dose amended*
Amended from "150 mg" to "75-100mg" daily, as the preferred dose and to use 150 mg only if the latter strengths are unavailable. Aligned with the NEMLC approved proposed Adult Hospital level STGs and EML, currently under review that is currently under review. See rationale above, in section 4.2: Angina pectoris, stable (page 6) for detailed information.

Continuation of aftercare treatment initiated at higher level of care:
Aspirin, oral: *added*
Atenolol, oral: *added*
Simvastatin, oral: *added*
Atorvastatin, oral: *added*
Enalapril, oral: *added*
The following text was added to the STG, aligned with the Adult Hospital level STG, 2015; though it was noted that management would be initiated at higher levels of care and then cases would be down referred for chronic management:

Continuation of aftercare treatment initiated at higher level of care
Continue therapy with appropriate lifestyle modification and adherence support.
- Aspirin, oral, 75–100 mg daily (continued indefinitely in absence of contraindications).

If unavailable:
- Aspirin, oral, 150 mg daily.

When clinically stable without signs of heart failure, hypotension, bradydysrhythmias or asthma:
- Cardio-selective β-blocker, e.g.:(Doctor prescribed)
- Atenolol, oral, 50 mg daily.

AND
- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 40 mg at night.

[22] 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
[23] SAMF, 2016
[24] 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
[25] 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

Patients on amlodipine and not on a protease inhibitor:

- Simvastatin, oral, 10 mg at night.

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night.

If patient complains of muscle pain:
Reduce dose to:

- Simvastatin, oral, 10 mg at night.

OR
Refer.

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

- ACE-inhibitor, e.g.:

Enalapril, oral, target dose 10 mg 12 hourly (usually titrated from 2.5 mg 12 hourly).

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

Level of Evidence: III Guidelines, Expert opinion

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

Emergency treatment
Before transfer
Aspirin, oral: *dose amended*

Amended from "150 mg" to "75-100mg" daily, as the preferred dose and to use 150 mg only if the latter strengths are unavailable. Aligned with the NEMLC approved proposed Adult Hospital level STGs and EML, currently under review that is currently under review. See rationale above, in section 4.2: Angina pectoris, stable (page 6) for detailed information.

Thrombolytics: *added as a therapeutic class*
Streptokinase, IV: *retained as the example of thrombolytics therapeutic class*
Altepase, IV: *not added*
Tenectaplse, IV: *not added*

Streptokinase: Stock availability and access was confirmed with the pharmaceutical supplier[26]. A new application had been registered with the Medicines Control Council for a proprietary name change. However, the PHC Committee recommended that both streptokinase and alteplase be listed in the STG to address potential stock challenges, based on the NEMLC approved medicine review done by the previous Adult Hospital Level Committee (2014-2016), recommending the newer fibrinolytics as an alternative to streptokinase. Streptokinase is cheaper than the alternate fibrinolytics (alteplase and tenectaplase)[27] and is recommended as the first line option.

Alteplase vs tenectaplase: Cost minimisation (using direct medical costs only, modelled on a 70 kg adult using SEP prices[12]) suggests that altelpase is comparable to tenectaplase:

SEP (100% of price):	**Price of comparative dose:**
– Alteplase 50 mg = R 9310.65	– Alteplase dose: 100 mg = R 18621.30
– Tenectaplase 40mg = R 18551.13	– Tenectaplase dose: 40 mg = R 18551.13

Recommendation: For AMI/STEMI, the STG recommends thrombolytics (streptokinase, alteplase, tenectalpase) as a therapeutic class, with streptokinase cited as the example of the therapeutic group in

[26] Email communication from ActorPharma on file.
[27] SEP prices (SEP database, 2 May 2018):
- Streptokinase 1.5 MIU, 5mL:R 4718.93
- Alteplase 50mg/50mL: R 9310.65
-Tenectaplase 50mg/20mL: R 18,551.13

the STG (Alternate therapeutic options could then be accessed if there are challenges with the supply of streptokinase).
Rationale: Streptokinase is accessible. However, continuous supply is dependent on MCC registration processes. Alternative therapy, alteplase and tenectaplase, has been previously approved by NEMLC (Refer to medicine review: Thrombolytics (therapeutic class) for STEMI, July 2015[28].
Level of Evidence: I Metaanalysis, Expert opinion

Unfractionated heparin: *not added as adjunctive therapy with thrombyolytics*
Low molecular weight heparin: *not added as adjunctive therapy with thrombyolytics*

Adjunctive heparin: The alteplase package insert[29] mentions that alteplase is usually given with heparin, but specific dosing instructions are not provided. In most clinical trials, alteplase was given with heparin (as heparin was part of accepted standard of care). Most international guidelines recommend heparin as part of STEMI treatment, regardless of which thrombolytic is used (EML STGs currently do not).
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[30].

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[31].

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.[32]
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).[33]

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 only comparison that we could find of LMWH versus placebo with thrombolytics was with streptokinase. In clinical trials alteplase was generally given with standard of care, which included some form of heparin. The addition of low molecular weight heparin (LMWH) at primary level of care would have cost implications.
Recommendations:
- Adjunctive heparin not be recommended with thrombolytics for acute myocardial infarction at PHC.
- Adjunctive heparin could be considered at hospital level (all STEMI patients are referred urgently from primary level of care).

[28] Adult Hospital medicine review: Thrombolytics (therapeutic class) for STEMI, July 2015. www.health.gov.za
[29] Ingelheim Pharmaceuticals (Pty) Ltd. MCC registered package insert, Actilyse®, April 2008
[30] 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.
[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.
[32] 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.
[33] 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.

Rationale: There is uncertainty about the role of intravenous unfractionated heparin (UFH) and low molecular weight (LMWH) in patients with ST-elevation myocardial infarction (STEMI) treated with aspirin and thrombolysis.

Level of Evidence: I Meta-Analysis

Continuation of aftercare treatment initiated at higher level of care:
Aspirin, oral: *added*
Atenolol, oral: *added*
Simvastatin, oral: *added*
Atorvastatin, oral: *added*
Enalapril, oral: *added*
Aligned with section 4.3 Angina pectoris, unstable/ non ST elevation myocardial infarction (NSTEMI).
Level of Evidence: III Guidelines

4.7.1 HYPERTENSION IN ADULTS

Screening and treatment target for hypertension
The American College of Cardiology/American Heart Association had recently released updated hypertension guidelines (November 2017)[34] recommending that the target blood pressure be reduced from 140/90 mm Hg to 130/80 mm Hg.
Recommendation: The PHC Committee recommended that this be reviewed either by the Adult Hospital Level Committee or in the next PHC review cycle, as time constraints (current PHC review to be completed in the next month or two) prevents an in depth review regarding the ACC/AHA recommendation of reducing the target BP, which would have huge implications.

Stroke
Amlodipine, oral: *not added as a pre-referral dose*
Previously the PHC Committee (6 July 2017) had recommended that the text pertaining to management of stroke be reworded, in light of NEMLC's recommendation not to recommend a pre-referral dose of amlodipine for stroke at primary level of care (NEMLC was of the opinion that there are potential harms associated with this recommendation)[35].
The text was updated as follows:

BP is often elevated in acute stroke ~~and should only be treated if it persists >2days or is severely elevated. Diastolic BP >120 mmHg. Reduce BP gradually~~ Do not treat elevated BP at PHC, but refer patient urgently.

Moderate hypertension
Initiation of combination anti-hypertensive therapy: *not added*
The South African hypertension practice guideline, 2014[36] recommends that patients with BP ≥ 160/100 mmHg may either be initiated on lifestyle modification with either monotherapy or combination therapy. Progress to be monitored after 4-6 weeks for further step-up management or dose optimisation. The rationale provided is that initiating combination therapy is associated with better clinical outcomes and earlier achievement of goal BP. However, the evidence base for this recommendation is not generalisable to the South African setting[37], as the intervention (aliskiren, a

[34] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006.
[35] NEMLC minutes of the meeting: 29 June 2017
[36] Hypertension guideline working group, Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. Cardiovasc J Afr. 2014 Nov-Dec;25(6):288-94. https://www.ncbi.nlm.nih.gov/pubmed/25629715
[37] Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 2011 Jan 22;377(9762):312-20. doi: 10.1016/S0140-6736(10)62003-X.

direct-acting renin inhibitor) studied in one RCT is not available on the South African market. The second study[38] compared monotherapy (ACE-inhibitors, calcium channel blocker) vs combination therapy that included ACE-inhibitors with diuretic, angiotensin II receptor blocker and calcium channel blocker, or angiotensin II receptor blocker and diuretic, monitored over a period of 60 days. This differs from the STG, that recommends confirmation of diagnosis within 2 weeks; thereafter initiate treatment at Step 2 of the hypertension algorithm (i.e. hydrochlorothiazide and lifestyle modification). Failure to achieve BP targets within one month warrants add-on therapy in step 3.

Recommendation: Patient with moderate hypertension not be initiated on combination anti-hypertensive therapy.

Rationale: The PHC Committee was of the opinion that the step-wise hypertension algorithm was sufficient for management of moderate hypertension, with timely monitoring of BP.

Level of Evidence: III Expert opinion

Step 2

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[39] 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[40] 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[41], INSIGHT[42], STOP-HT2[43], CONVINCE[44]).

Furthermore the European (2013)[45] and the American (2014)[46] Hypertension Guidelines retain HCTZ

[38] Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension. 2013 Feb;61(2):309-18. doi: 10.1161/HYPERTENSIONAHA.112.201566.

[39]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

[40]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.

[41]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.

[42] 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.

[43]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.

[44] 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.

[45]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.

[46] 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

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

Step 7
Spironolactone, oral: *added*
Atenolol, oral: *deleted*
Motivation was submitted by the Western Cape PTC for spironolactone for resistant hypertension. Evidence provided (PATHWAY study[47] - 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.
It was proposed that concomitant spironolactone could possibly replace atenolol for management of resistant hypertension. However, the logistical implications for routine spironolactone monitoring at primary level of care needs consideration. The study reported that "In six of the 285 patients who received spironolactone, serum potassium exceeded 6·0 mmol/L on one occasion".
Spironolactone is currently listed in the primary healthcare STGs for cardiac failure as doctor initiated with the following caution: " *Spironolactone can cause severe hyperkalemia and should only be used when serum potassium can be monitored. Do not use together with potassium supplements. Do not use in kidney failure (Do not use if eGFR<30 mL/min)".*
Recommendation: Spironolactone be included in the STG for refractory hypertension as doctor initiated, with a caution emphasising routine potassium monitoring.
Rationale: Evidence of superior efficacy of spironolactone to beta-blocker in resistant hypertension.
Level of Evidence: I RCT

NEMLC recommendations at the meeting of 2 March 2017:
Recommendation: Spironolactone replace atenolol for resistant hypertension (doctor initiated with potassium monitoring).

Enalapril, oral: *dosing not amended*
In clinical practice, enalapril is dosed as 12 hourly. Available evidence found better compliance with once daily dosing, but no significant difference in blood pressure[48, 49](no RCT evidence could be found of superiority of the 12 hourly vs daily dosing of enalapril. Furthermore, enalapril 5 mg 12 hourly is more expensive than enalapril 10 mg daily (R6.00 vs R4.38, respectively for a 30 day treatment course[50]).
Level of evidence: III Observational studies (low quality), Expert opinion

The stepwise treatment algorithm was updated for clarity as follows:

STEPWISE TREATMENT WITHOUT COMPELLING INDICATIONS
STEP 1: Lifestyle modification.

Entry to Step 1	Treatment	Target

[47] 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
[48] 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
[49] 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
[50] Contract circular HP09-2016SD, average weighted prices used.

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

STEP 2: Add hydrochlorothiazide.

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

STEP3: Add a second antihypertensive medicine.

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

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

Entry to Step 4	**Treatment**	Target
» Failure of step 3 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 12.5 mg daily. **AND** Increase dose of antihypertensive started in Step 3: ▪ ACE-inhibitor, e.g.: • Enalapril, increase to 20 mg daily **OR** ▪ Long acting calcium channel blocker, e.g.: • Amlodipine, oral, increase to 10 mg daily.	» BP control within 1month to <140/90 mmHg, with no adverse reactions.

STEP 5: Add a third antihypertensive medicine

Entry to Step 5	**Treatment**	Target

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

STEP 6: Increase the dose of the third antihypertensive medicine

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

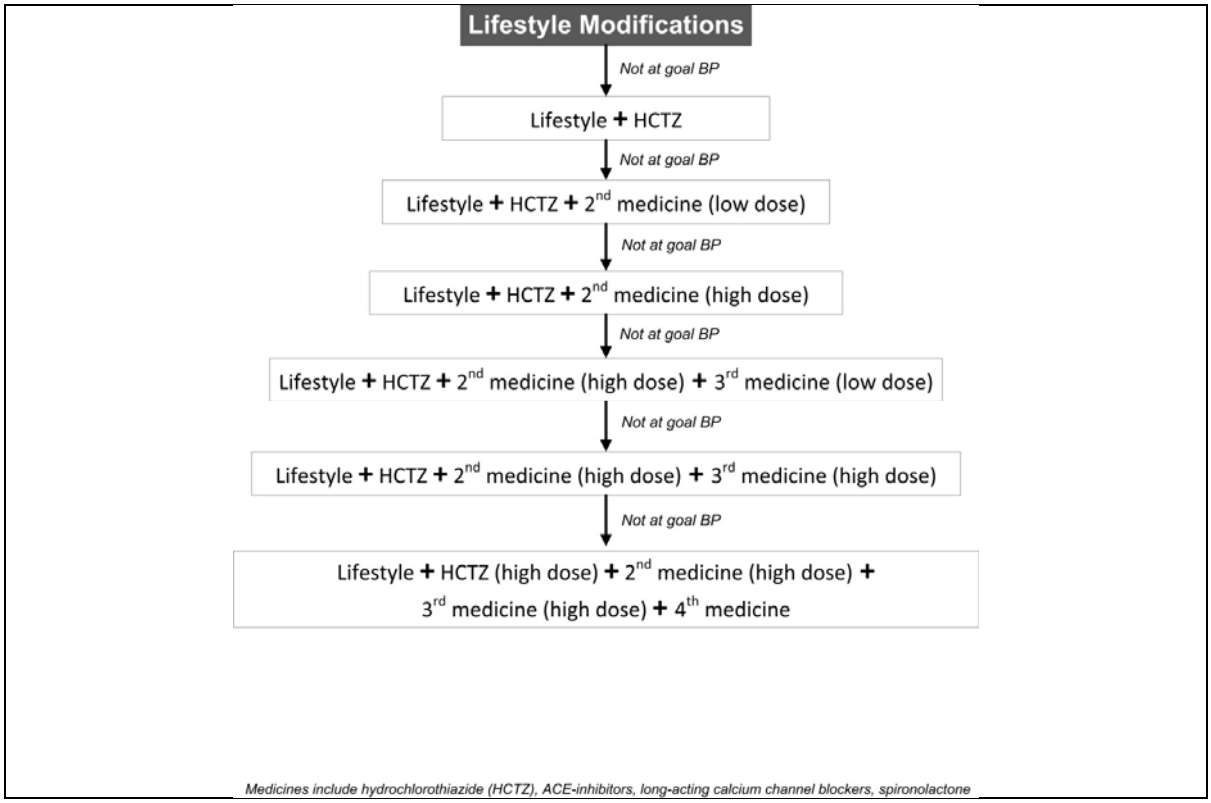
STEP 7: Add a fourth antihypertensive medicine

Entry to Step 8	**Treatment**	**Target**
» Failure of step 7 after 1 month of adherence.	» Lifestyle modification **AND** • Hydrochlorothiazide, oral, 25 mg daily. **AND** ▪ ACE-inhibitor, e.g.: • Enalapril, 20 mg daily. **AND** ▪ Long acting calcium channel blocker, e.g.: • Amlodipine, oral 10 mg daily. **AND ADD** • Spironolactone, oral, 25 mg daily. (Doctor initiated).	» BP control within 1 month to <140/90 mmHg, with no adverse medicine reactions.

CAUTION
Spironolactone can cause severe hyperkalemia and should only be used when serum potassium can be monitored.
Do not use together with potassium supplements.
Do not use in kidney failure(Do not use if eGFR<30 mL/min).

If not controlled on step 7 – refer.

Hypertension treatment algorithm for stepwise treatment without compelling indications



Contraindications to individual medicines

Spironolactone, oral: *contra-indications added*

Following NEMCL recommendation to replace atenolol with spironolactone as line therapy in the stepwise treatment algorithm for hypertension, text of the STG was updated as follows to include contra-indications for spironolactone.

Spironolactone » kidney impairment (eGFR<30 mL/min) » pregnancy

Level of Evidence: III Guidelines[51]

4.9 RHEUMATIC FEVER, ACUTE

Eradication of streptococci in throat:

Amoxicillin, oral: *dosing amended*

Dosing aligned with the PHC chapter 19: Ear, nose and throat conditions; Section 19.6: Tonsillitis and pharyngitis to ensure consistency throughout the PHC STGs and EML.

Severe penicillin allergy

Azithromycin, oral: *amended*

The macrolide of choice, azithromycin, was aligned with the Paediatric Hospital Level STG and EML, 2017 and the Adult Hospital Level STGs and EML, 2015 version.

Level of Evidence: III Guidelines

[51] SAMF, 2016