SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 4: CARDIOVASCULAR
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the complete chapter for cardiovascular conditions.
Note: This primary healthcare chapter has been updated to align to previous NEMLC recommendations as well as the recent NEMLC-approved Adult Hospital Level STGs and EML, 2019 edition and Paediatric Hospital Level cardiovascular chapter (2020 draft).

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/AMENDED
3.1 Ischaemic heart disease and atherosclerosis, prevention		
- primary prevention	HMGCoA reductase inhibitors (statins), oral	Added as a therapeutic class
	Simvastatin, oral – 10 mg	Retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database
- secondary prevention	HMGCoA reductase inhibitors (statins), oral	Added as a therapeutic class
	Simvastatin, oral – 40 mg	Retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database
- statin drug-interaction with amlodipine	Simvastatin, oral	Dose amended
- myalgia associated with statins	HMGCoA reductase inhibitors (statins), oral	Added as a therapeutic class
	Simvastatin, oral – 10 to 20 mg	Retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database
4.2 Angina pectoris, stable *- Long-term prophylaxis for thrombosis*	Aspirin, oral	Dose amended
- Relief of angina	Nitrates, short acting	Directions for use amended
	Isosorbide dinitrate, sublingual	Dosing amended
- Step 1: Beta-blockers	Beta-blockers, oral	Added as a therapeutic class
	Atenolol, oral	Retained 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)
- Step 3: Organic nitrates	Isosorbide dinitrate, oral	Retained and dose amended
	Isosorbide mononitrate, oral	Retained
- secondary prevention	Statins, oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
4.3 Angina pectoris, unstable/ Non ST elevation myocardial infarction (NSTEMI)	Aspirin, oral	Dose amended
	Nitrates, short acting	Directions for use amended
	Isosorbide dinitrate, sublingual	Dosing amended
	Statins, oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
4.4 Myocardial infarction, acute (AMI)/ ST elevation myocardial infarction (STEMI)		
- emergency treatment	Aspirin, oral	Dose amended
	Nitrates, short actinng	Directions for use amended
	Isosorbide dinitrate, sublingual	Dosing amended
	Streptokinase, IV	Thrombolytic time window amended
- continuation of aftercare treatment initiated at higher level of care	Aspirin, oral	Dose amended
	Statins, oral	Aligned to section 3.1 Ischaemic heart disease and atherosclerosis, prevention
4.6.1 Cardiac failure, congestive (CCF), adults		
- STEP 1: Diuretic plus ACE-inhibitor - Mild volume overload (mild CCF) and normal renal function:	Hydrochlorothiazide, oral:	Directions for use amended

4.7.1 Hypertension in adults	Lifestyle modification	Guidance amended
- *Management of hypertension*	Stepped care approach management	Guidance expanded
	Hydrochlorothiazide, oral	Cautionary added
	Spironolactone, oral	Caution amended
	ACE-inhibitor, oral	Directions for use & contra-indications amended
	Calcium channel blocker, oral	Directions for use amended
	Medicine formulations	Fixed dose combinations encouraged if available and affordable

4.1 ISCHAEMIC HEART DISEASE AND ATHEROSCLEROSIS, PREVENTION

Primary prevention

HMGCoA reductase inhibitors (statins), oral – low dose: *added as a therapeutic class*

Simvastatin, oral 10 mg: *retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database*

Aligned with Adult Hospital Level STGs and EML, 2019; and therapeutic interchange databases (Primary Health Care, 2018; Adult Hospital Level, 2019).

Secondary prevention

HMGCoA reductase inhibitors (statins), oral – intermediate dose: *added as a therapeutic class*

Simvastatin, oral 40 mg: *retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database*

Drug interaction of statins with amlodipine

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

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. Amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin.[1] 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.[2] 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.[3]

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

Myalgia assicated with statins

HMGCoA reductase inhibitors (statins), oral: *added as a therapeutic class*

Simvastatin, oral 10-20 mg: *retained as an example of class (listed in STG); therapeutic alternatives listed in interchange database*

Aligned with Adult Hospital Level STGs and EML, 2019; and Adult Hospital Level, 2019 therapeutic interchange database.

[1] 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.

[2] 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.

[3] SAMF, 2016

The Primary Health Care STGs and EML, 2018 edition recommended that if myalgia develops whilst on a statin, then to reduce the dose to simvastatin 10 mg. Provision has now been made for therapeutic alternatives and also for 20 mg simvastatin or equivalent (with alternatives listed in the therapeutic interchange database).

4.2 ANGINA PECTORIS, STABLE

Long-term prophylaxis for thrombosis:

Aspirin, oral: *dose amended*

Given that the current tender price of "100 mg" is more expensive than the "150 mg"[4], the dose was aligned with the recommendations of NEMLC that aspirin be used as a daily dose of 150 mg throughout the STGs, until such time that there is price parity.

Level of Evidence: I Meta-analysis, Expert opinion

Relief of angina:

Nitrates, short acting: *directions for use amended*

Isosorbide dinitrate, sublingual: *dosing amended*

Amended for clarity and correctness as follows, aligned with SAMF 2016 and Adult Hospital Level STGs and EML, 2019, as follows:

- Nitrates, short acting e.g.:
- Isosorbide dinitrate, sublingual, 5 mg.
  - ~~May be repeated if required at 5–10 minute intervals for 3 doses.~~
  - 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, Expert opinion[5]

STEP 1:

Beta-blockers

Beta-blockers, oral: *added as a therapeutic 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)*

Acebutolol, oral: *added as an example of class (listed in therapeutic interchange database)*

Aligned with SAMF, 2016.

Level of Evidence: III Guidelines[6]

STEP 3:

Organic nitrates

Isosorbide dinitrate, oral: *retained and dose amended*

Isosorbide mononitrate, oral: *retained*

These agents only offer symptomatic relief and long-term use is commonly associated with adverse drug reactions (e.g. headaches, etc). Isosorbide mononitrate was retained in 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[7].

Level of Evidence: III Guidelines, Expert opinion[8, 9]

[4] 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]

[5] 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

[6] SAMF, 2016

[7] SAMF, 2016

[8] 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

[9] 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

Secondary prevention
Statins, oral: *dosing and directions for use amended*
Aligned with section: 4.1 Ischaemic heart disease and atherosclerosis, prevention.

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

Aspirin, oral: *dose amended*
Nitrates, short acting: *directions for use amended*
Isosorbide dinitrate, sublingual: *dosing amended*
Aligned with section 4.2 Angina pectoris, stable.

Secondary prevention
Statins, oral: *dosing and directions for use amended*
Aligned with section: 4.1 Ischaemic heart disease and atherosclerosis, prevention.

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

Emergency treatment
Aspirin, oral: *dose amended*
Nitrates, short acting: *directions for use amended*
Isosorbide dinitrate, sublingual: *dosing amended*
Aligned with section 4.2 Angina pectoris, stable.

Streptokinase, IV: *thrombolytic time window amended*
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)[10]. 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[11], Expert opinion

Continuation of aftercare treatment initiated at higher level of care:
Aspirin, oral: *dose amended*
Aligned with section 4.2 Angina pectoris, stable.

Statins, oral: *dosing and directions for use amended*
Aligned with section: 4.1 Ischaemic heart disease and atherosclerosis, prevention.

4.6.1 CARDIAC FAILURE, CONGESTIVE (CCF), ADULTS

[10] 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
[11] 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

STEP 1: Diuretic plus ACE-inhibitor - Mild volume overload (mild CCF) and normal renal function:
Hydrochlorothiazide, oral: *directions for use amended*
Hydrochlorothiazide caution: Previously the NEMLC[12] reviewed the skin cancer risk of hydrochlorothiazide[13] [14] 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[15]. STG text was amended as follows:

- Hydrochlorothiazide, oral, 25–50 mg daily.
  - Caution in patients with gout.
  - Less effective in impaired renal function.
  - Caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

Level of Evidence: III Observational studies

4.7.1 HYPERTENSION IN ADULTS

Lifestyle modification: *guidance amended*
Aligned with Adult Hospital Level STGs and EML, 2019.

Hypertension without compelling indications
Stepped care approach management: *guidance* expanded
Aligned with the Adult Hospital Level STGs and EML, 2019 - the following footnotes were 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[16] [17]

Hydrochlorothiazide, oral: *cautionary added*
See section 4.6.1: Cardiac failure, congestive (ccf), adults. STG text was amended as follows:

Contraindications to individual medicines
Hydrochlorothiazide
» gout
» pregnancy
» severe liver impairment
» kidney impairment (eGFR < 30 mL/min)
» use with caution in patients with a history or family history of skin cancer; and counsel all patients on sun avoidance and sun protection.

Level of Evidence: III Observational studies

Spironolactone, oral: *caution amended*
Hyperkalaemia caution: Aligned with the Adult Hospital Level STGs and EML, 2019 edition, and the caution was also updated as follows to provide practical guidance:

[12] 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.
[13] 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
[14] 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
[15] National Department of Health, Essential Drugs Programme: Updated Notice: Risk of skin cancer associated with hydrochlorothiazide, 6 March 2019. http://www.health.gov.za
[16] 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
[17] 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

CAUTION

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

Level of Evidence: III Guidelines[18] [19]

Bedtime dosing

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

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

There is emerging evidence[20] that taking the total daily dose of antihypertensive medication at bedtime rather than on awaking provides both better control of hypertension and a significant reduction in important cardiovascular events. 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)

Contra-indications

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

As ACE-inhibitors may be used in renal impairment, the following text of the STG was amended for correctness:

ACE-inhibitors

- pregnancy
- bilateral renal artery stenosis or stenosis of an artery to a dominant/single kidney
- aortic valve stenosis
- history of angioedema
- hyperkalemia
- severe renal impairment (eGFR < 30 mL/min), unless dose-adjusted usage is recommended by a specialist – See Section 8.1:Chronic kidney disease (CKD)

Level of Evidence: III Guidelines[21] [22]

Thus, an additional referral criterion was added:

- Severe renal impairment (eGFR < 30 mL/min).

Fixed dose combinations

The use of fixed dose combination (FDC) medication for control of hypertension provides greater adherence.[23] 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[24]

[18] Adult Hospital Level STGs and EML, 2019

[19] SAMF, 2016

[20] 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

[21] SAMF, 2016

[22] Adult Hospital Level STGs and EML, 2019

[23] 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

[24] 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).*