Cholesterol, a spherical steroid molecule, is instrumental in steroid hormone and bile acid synthesis and forms an integral part of cell membranes. Cholesterol is transported as part of specific proteins (lipoproteins) due to their insolubility in aqueous media. These lipoproteins can be divided into different classes based on their composition, associated apoproteins and size. Apolipoproteins play a functional role in the structural integrity and metabolism of lipoproteins, whilst acting as ligands for lipoprotein receptors. Lipoproteins include, amongst others, high-density lipoprotein (HDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and lipoprotein (a) (Lp(a)). Hypercholesterolaemia is defined as "the presence of high plasma cholesterol levels, with normal plasma triglycerides, as a consequence of the rise of cholesterol and apolipoprotein B (apoB)-rich lipoproteins, called low-density lipoprotein (LDL)." Hypercholesterolaemia forms part of a group of disorders called dyslipidaemias that also include hypertriglyceridaemia. This mini-review will only focus on hypercholesterolaemia.

Burden of disease

The WHO reported cardiovascular disease (which includes ischaemic heart disease and cerebrovascular disease) to be responsible for approximately a third (31%) of deaths worldwide. In South African Asian Indian, White and Coloured populations, ischaemic heart disease and cerebrovascular disease combined are the leading cause of death at 32.3%, 26.7% and 17.9%, respectively. In the Black population both cerebrovascular disease (7.4%) and ischaemic heart disease (2.5%) are amongst the top ten causes of mortality. More people in South Africa die from cardiovascular disease (CVD) than all the cancers combined with almost one in six deaths in South Africa attributed to CVD. The high disease burden in South Africa is ascribed to the high prevalence of familial hypercholesterolaemia (FH) – up to one in every 80 people – in Afrikaner, Jewish and South Asian Indian origin due to the founder effect. This is a reduction in genetic variation due to colonisation of a new area by a small subset of a population. Hypercholesterolaemia is one of the leading causes of atherosclerosis 4 contributing to an increase in the risk for developing CVD. South Africa is further burdened by a high incidence of obesity, undiagnosed diabetes mellitus, renal disease, hyperthyroidism and smoking, which are all secondary risk factors for CVD.10

Genetic basis of familial hypercholesterolaemia

Primary hypercholesterolaemia is an autosomal dominant inherited genetic disorder, also known as familial hypercholesterolaemia or familial hyperlipoproteinaemia type 2 (Fredrickson class 2a hyperlipidaemia), which can be either heterozygous or homozygous.11,12 The disorder is mainly (> 90%) as a consequence of a monogenic loss-of-function mutation in the LDL-receptor gene,13,14 but also includes genetic variants of the apolipoprotein (apo) B gene, gain-of-function mutations in the proprotein convertase subtilisin/kexin 9 (PCSK9) gene,15 and very rarely due to mutations in the LDL receptor adaptor protein (LDLRAP). The latter causes autosomal recessive hypercholesterolaemia.16 Excellent reviews of cholesterol metabolism and the role of the LDL receptor within the context of FH, discussing the genetic disorders and resultant phenotype, have been published by South African experts in the field.17,18

South African dyslipidaemia guideline consensus statement

A high correlation has been established between cardiovascular risk and hypercholesterolaemia19 and studies have shown that populations with low cholesterol have a low risk of coronary heart disease.20 The South African dyslipidaemia guideline consensus statement was updated in 2018, taking into account...
the multi-ethnicity and heterogeneity of the population, following the 2016 update of the adopted Cardiology (ESC)/European Society of Atherosclerosis (EAS) Guideline for the Management of Dyslipidaemias.² The aim of this comprehensive guideline is to advocate best-practice treatment and appropriate management of dyslipidaemias in a South African context. For this mini-review, the focus was on the primary prevention and clinical treatment recommendations for hypercholesterolaemia and a short summary is given in Figure 1.

Clinical treatment decisions are based on an estimate of the total cardiovascular 10-year risk for having a fatal or non-fatal cardiac event. This CVD risk score is calculated based on gender, age, total cholesterol and HDL-cholesterol (preferably obtained from a lipogram), systolic blood pressure and smoking status and patients are then classified as having a low, moderate, high or very high risk. It is important to note that this guideline excludes those individuals with established cardiovascular diseases (including atherosclerotic diseases such as coronary artery disease, unstable angina, previous MI and previous cerebrovascular event) from the multi-ethnicity and heterogeneity of the population, following the 2016 update of the adopted Cardiology (ESC)/European Society of Atherosclerosis (EAS) Guideline for the Management of Dyslipidaemias.² The aim of this comprehensive guideline is to advocate best-practice treatment and appropriate management of dyslipidaemias in a South African context. For this mini-review, the focus was on the primary prevention and clinical treatment recommendations for hypercholesterolaemia and a short summary is given in Figure 1.

### Table I: Treatment targets based on baseline LDL-C and associated risk

| Target LDL-C | Associated risk score |
|--------------|-----------------------|
| < 3 mmol/L   | Low- and moderate-risk cases |
| < 2.5 mmol/L | High-risk cases |
| < 1.8 mmol/L | Very high-risk cases |

### Diagnosing FH using the Simon Broome Criteria

- **Definite FH**: Severe elevated cholesterol and tendonous xanthomata in the patient or relative (1st°) or LDLR, APOB or PC SK9 gene mutations confirmed by genotyping.
- **Probable FH**: Severe high cholesterol and a family history of MI before 60 years is 1st° relative/50 years in 1st° relative or severely high cholesterol and a family history of elevated cholesterol >7.5 mmol/L in 1st°/2nd° relative.

### Medications

- Diuretics
- Glucocorticoids
- Cyclosporin
- Antiretroviral agents
- Retinoids
- Beta blockers
- Oestrogens

### Useful conversions:

- mmol/L = mg/dL x 0.0259
- mg/dL = mmol/L x 38.6

### Useful Apps for calculating CVD risk

ESV CVD Risk Calculation
S.A. Clinical guidelines and EML

### Clinical decisions based on total CVD risk score

- **Low risk (< 3%)**
  - (< 3%)
  - Lifestyle intervention, consider medication
  - Lifestyle intervention, consider medication

- **Moderate risk (3–15%)**
  - (3–15%)
  - Lifestyle intervention, consider medication
  - Lifestyle intervention, consider medication

- **High risk (15–30%)**
  - (15–30%)
  - Lifestyle intervention, consider medication
  - Lifestyle intervention, consider medication

- **Very high risk (> 30%)**
  - (> 30%)
  - Lifestyle and immediate medication intervention
  - Lifestyle and immediate medication intervention

**Figure 1**: Summary of the South African Consensus Statement guideline for primary prevention and treatment of hypercholesterolaemia¹

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¹ Screening requires a full lipogram and cascade screening is recommended; all potentially affected relatives of diagnosed FH patients or patients with severe dyslipidaemia should be screened. ² Familial hypercholesterolaemia is diagnosed based on genotype or phenotype of which the latter is more feasible in South Africa; ³ The CVD risk is calculated using the Framingham risk scoring algorithms are only used for primary prevention. ** Definite FH • Severely elevated cholesterol and tendonous xanthomata in the patient or relative (1st°) or LDLR, APOB or PC SK9 gene mutations confirmed by genotyping. *** The CVD risk is calculated using the Framingham Risk Assessment Score Charts; CVD – cardiovascular disease; FH – familial hypercholesterolaemia; 1st° – first degree, 2nd° – second degree, LDLR – low-density lipoprotein receptor, APOB – apolipoprotein B, PCSK9 – proprotein convertase subtilisin/kexin type 9.
artery disease and cerebrovascular disease and hypertension), severe dyslipidaemias related to familial hypercholesterolaemia and endocrine diseases such as hypothyroidism and diabetes mellitus. These patients are considered to have a high cardiovascular risk regardless of risk-scoring and are not subjected to Framingham risk-scoring. Treatment decisions are based on low-density lipoprotein (LDL-C) levels and the associated risk as shown in Figure 1.

Lifestyle modification is the foundation of treatment for all patients and the need for medication is determined by increased LDL-C measured at baseline and stratified by risk in individual patients. The LDL-C targets with medication are given in Table I.

Children with a genetic predisposition for FH or a family history of genetic or severe dyslipidaemia require special attention and should be screened for dyslipidaemia from eight years of age or before in cases where homozygous FH is suspected.

**Pharmacological treatment of familial hypercholesterolaemia**

The cornerstone treatment for the management of hypercholesterolaemia and the reduction of atherosclerosis and cardiovascular events is statins or HMG-CoA reductase inhibitors, with the dosage dependant on the LDL cholesterol target as well as its affordability and tolerability. Appropriate consideration should also be given to comorbidities and concomitant treatment. Studies have shown that treatment with statins in patients with heterozygous hypercholesterolaemia reduces the overall CVD risk by up to 76% and the CVD mortality by up to 48% as a result of a substantial reduction in LDL cholesterol levels. In patients with homozygous hypercholesterolaemia statin treatment, a reduction of 26% in LDL cholesterol delayed and prolonged the survival rate of CVD. Patients should understand the importance of adhering to treatment as failure in the efficacy of statins has been attributed to non-adherence.

In those small number of patients who are statin-resistant,

| Medicine class | Indication | Common adverse effects | Common drug interactions |
|----------------|------------|------------------------|-------------------------|
| **Statins:** | | | |
| Rosuvastatin 40 mg | Starting LDL-C of > 6.2; > 55–70% reduction is required; all VHRP with starting LDL-C of 3.9–6.2 | Gastrointestinal effects are common including: • Abdominal pain • Flatulence • Constipation • Diarrhoea • Nausea | Medicines that inhibit CYP3A4 metabolism and increase systemic exposure of statins and risk of myopathy and rhabdomyolysis: • Macrolide antibiotics • Antifungal azoles • Protease inhibitors |
| Atorvastatin 80 mg | VHRP with starting LDL-C 3.4–3.9 | Uncommon side-effects include: • Myalgia with associated muscle weakness • Elevated creatine kinase | Plasma digoxin concentration possibly increased by atorvastatin and simvastatin |
| LDL-C goal: VHRP < 1.8 mmol/L or HRP < 2.5 mmol/L | HRP with starting LDL-C 4.4–6.2 | Rare effects include: • Rhabdomyolysis • Headache • Insomnia • Angioedema | Anticoagulant effect of warfarin may be enhanced |
| Rosuvastatin 10 mg | HRP with starting LDL-C 3.9–4.4 | | |
| Atorvastatin 10 mg | | | |
| Rosuvastatin 10–20 mg | | | |
| Atorvastatin 20 mg | | | |
| Simvastatin 40 mg | | | |
| Rosuvastatin 5 mg | | | |
| Atorvastatin 10 mg | | | |
| Simvastatin 20 mg | | | |
| Lovastatin 40 mg | | | |
| Fluvastatin 80 mg | | | |
| **Fibrates:** | More effective for triglyceride disorders | Self-limiting gastrointestinal side-effects | Gemfibrozil inhibits glucuronidation leading to increased risk of rhabdomyolysis |
| Bezafibrate | | | |
| Fenofibrate | | | |
| Gemfibrozil | | | |
| **Bile acid sequestrants:** | Occasionally useful alone or in combo with statin therapy | Gastrointestinal side-effects especially constipation | Interferes with vitamin absorption Causes reduced absorption and possible therapeutic failure of: • Warfarin • Digoxin • Tetracyclines • Thyroxine • Thiazides |
| Colestyramine | | | |
| **Nicotinic acid derivatives:** | More effective for triglyceride disorders | Gastrointestinal side-effects, flushing | Risk of myopathy is increased with concomitant use of atorvastatin |
| Nicotinic acid | | | |
| Acipimox | | | |
| **Inh. of cholesterol absorption** | Second-line combo treatment to reduce LDL-C and incidence of MI and stroke Where statins are contraindicated | Headache, abdominal pain and diarrhea | Exposure of ezetimibe is decreased when given together with colestyramine Increased ezetimibe concentration with cyclosporin |
| Ezetimibe | | | |
| **PCSK9 inhibitors** | New class with restricted use | Flu-like symptoms such as cold, nausea, back and joint pain | No significant drug interactions are known to present date |
| Evolocumab | | | |
| Alirocumab | | | |
| LDL-C – low-density lipoprotein cholesterol, all in mmol/L, VHRP – very high-risk patients, HRP – high-risk patients, CYP3A4 – cytochrome P450 3A4 enzyme, combo – combination |
combination therapy is indicated.27,28 Table II gives an overview of the pharmacological classes with their indications, common drug interactions and adverse effects.

Conclusion

South Africa has a high burden of CVD due to both FH and secondary disease risk factors. As a result, all South Africans who are at a high risk for cardiovascular events should be on treatment with statins and primary prevention is essential in all other patients. Primary prevention includes screening of all citizens above the age of 40 years in order to ensure early detection and to guide clinical treatment decisions by implementing the South African consensus statement guideline.

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References
1. Smith LC, Pownall HJ, Gotto Jr AM. The plasma lipoproteins: structure and metabolism. Annu Rev Biochem. 1978;47(1):751-77. https://doi.org/10.1146/annurev.bi.47.070178.003353.
2. Mahley RW, Innerarity TL, Rall Jr SC, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1986;25(12):1277-94. https://doi.org/10.1194/jlr.25.12.1277.
3. Martinez-Hervas S, Ascaso JF. Hypercholesterolemia. In: Huhtaniemi I, Martin L, editors. Encyclopedia of endocrine diseases. 2nd ed. Oxford: Academic Press; 2019. p. 320-6. https://doi.org/10.1016/B978-0-12-801238-3.65340-0.
4. World Health Organization. Global status report on noncommunicable diseases. 2014.
5. Pillay-van Wyk V, Msemwari W, Laubscher R, et al. Mortality trends and differentials in South Africa from 1997 to 2012: second National Burden of Disease Study. Lancet Glob Health. 2016;4(9):e642-53. https://doi.org/10.1016/S2214-109X(16)30113-9.
6. Pillay-van Wyk V, Msemwari W, Laubscher R, et al. Second National Burden of Disease Study South Africa: national and subnational mortality trends, 1997-2007. Lancet. 2013;381:5113. https://doi.org/10.1016/S0140-6736(13)61367-7.
7. Mortality and causes of death in South Africa, 2014: Findings from death notification / Statistics South Africa. Pretoria: Statistics South Africa; 2015.
8. Rubinstein D, Van der Westhuizen D, Coetzee G. Monogenic primary hypercholesterolaemia in South Africa. S Afr Med J. 1994;84(6):339-44.
9. Steyn K, Goldberg YP, Kotze MJ, et al. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. Hum Genet. 1996;98(4):479-84. https://doi.org/10.1007/s004390050243.
10. Klug E, Raal F, Marais A, et al. South African dyslipidaemia guideline consensus statement: 2018 update A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). S Afr Med J. 2018;108(11b):973-1000.
11. Pejic RN. Familial hypercholesterolemia. Ochsner J. 2014;14(4):669-72.
12. Brunton LL, Knollmann BC, Hilal-Dandan RG, Gilman's the pharmacological basis of therapeutics. New York City, USA: McGraw-hill Education; 2018.
13. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986;232(4746):34-47. https://doi.org/10.1126/science.3513311.
14. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009;29(4):431-8. https://doi.org/10.1161/ATVBAHA.108.179564.
15. Abifadel M, Varret M, Rabès J-F, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34(2):154-6. https://doi.org/10.1038/ng1161.
16. Soutar AK, Naoumova RP, Traub LM. Genetics, clinical phenotype, and molecular cell biology of autosomal recessive hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2003;23(11):1963-70. https://doi.org/10.1161/01.ATV.0000094410.66558.9A.
17. Marais AD. Familial hypercholesterolaemia. Clin Biochem Rev. 2004;25(1):49-68.
18. Blom DJ. Familial hypercholesterolaemia. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2011;16(1):17-24. https://doi.org/10.1080/222010 09.2011.10822248.
19. Wong B, Kruse G, Kutikova L, et al. Cardiovascular disease risk associated with familial hypercholesterolemia: A systematic review of the literature. Clin Ther. 2016;38(7):1696-709. https://doi.org/10.1016/j.clinthera.2016.05.006.
20. Chen Z, Peto R, Collins R, et al. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ. 1991;303:6797(276-82. https://doi.org/10.1136/bmj.303.6797.276.
21. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;253:281-344. https://doi.org/10.1016/j.atherosclerosis.2016.08.018.
22. Vermeulen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolemia: a long term cohort study. BMJ. 2008;337:a2423. https://doi.org/10.1136/bmj.a2423.
23. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008;29(21):2625-33. https://doi.org/10.1093/eurheartj/ehn422.
24. Elias A, Zhou R, Stein EA. Effect of lipid-lowering treatment on natural history of heterozygous familial hypercholesterolemia in past three decades. Am J Cardiol. 2011;108(2):223-6. https://doi.org/10.1016/j.amjcard.2011.03.027.
25. Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation. 2011;124(20):2202-7. https://doi.org/10.1161/CIRCULATIONAHA.111.042523.
26. Galema-Boers J, Lenzen M, Van Domburg R, et al. Predicting non-adherence in patients with familial hypercholesterolemia. Eur J Clin Pharmacol. 2016;70(4):391-7. https://doi.org/10.1007/s00228-013-1640-3.
27. Reiner Z. Resistance and intolerance to statins. Nutr Metab Cardiovasc Dis. 2014;24(10):1057-66. https://doi.org/10.1016/j.numecd.2014.05.009.
28. Reiner Z. Combined therapy in the treatment of dyslipidemia. Fundam Clin Pharmacol. 2010;24(1):19-28. https://doi.org/10.1111/j.1472-8206.2009.00764.x.
29. Rossiter D, South African Medicines Formulary. Rondebosch, South Africa: Health and Medical Pub Group; 2010.
30. Reiner Z. Management of patients with familial hypercholesterolaemia. Nat Rev Cardiol. 2015;12(10):565-75. https://doi.org/10.1038/nrcardio.2015.92.
31. Turner L. Daily drug use: a guide for the health professional. Cape Western Branch of the Pharmaceutical Society of South Africa; 2010.