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AMPATHCHAT

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# LIPID UPDATE: Changes to South African Dyslipidaemia Guidelines 2018 and new markers for assessing lipid status

In 2016 the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) revised guidelines for the management of Dyslipidaemia. The South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA) officially adopted these guidelines to ensure that the guidelines are based on the most recent and best available data. The 2018 South African update aims to ensure and promote current best management of dyslipidaemias in South Africa.

## Screening

**Recommended age of screening for dyslipidaemia**
The revised recommended screening age is 40 years in patients without cardiovascular risk-factors. However earlier screening is indicated for certain individuals, depending on genetics, family history and other cardiac risk factors (Table 1).[1]

**Table 1: The recommended age of screening for dyslipidaemia**

| From 8 years of age | From 20 years of age | From 40 years of age |
|---|---|---|
| 1. Family history of severe dyslipidaemia.<br>2. Relative of subject with FH (if both parents have FH, testing should be undertaken within the first six months of life to identify infants with homozygous FH). | Presence of CV risk factors:<br>1. Hypertension and/or on antihypertensive medication.<br>2. Smoking: Any smoking.<br>3. Family history of premature CVD in first degree relative (male ≤55 years of age; female ≤65 years of age).<br>4. BMI ≥30 or waist circumference >94 cm (men) or >80 cm (women).<br>5. Autoimmune chronic inflammatory disease, e.g. rheumatoid arthritis, systemic lupus erythematosus, psoriasis.<br>6. Chronic Kidney Disease (CKD). | All other individuals (asymptomatic adults without evidence of CVD, diabetes, CKD or FH). |

***BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; FH = familial hypercholesterolaemia***

## Evaluation of laboratory lipid and apolipoprotein parameters

**Timing of testing at diagnosis**
Traditionally, a full 12-hour fasting lipogram, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), has been recommended for initial diagnosis of dyslipidaemia. **Fasting lipograms** have always been the standard because many randomised lipid-lowering trials used fasting lipid measurements. Secondly, the calculated LDL-C using Friedewald equation might underestimate the LDL-C when chylomicrons are present in a non-fasting sample.[1, 2]

To improve compliance with lipid testing, in 2009, the Danish Society for Clinical Biochemistry (DSCB) recommended the use of random **non-fasting lipograms**.

The recommendation was based on recent evidence, which demonstrated that fasting and non-fasting blood samples yielded similar results for TC, LDL-C and HDL-C, and also have comparable cardiovascular risk estimation prediction.[2] Triglycerides were shown to be affected by food intake, causing an average increase of 0.3 mmol/ℓ higher in plasma. This is highly dependent on the composition and time of the last meal.[3] Thus, the DSCB offered clinicians the option of remeasuring TG in the fasting state if the non-fasting TG concentration was above 4 mmol/ℓ. In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines were amended, which do not require a fasting lipogram for estimating cardiovascular disease risk. They do, however, recommend a fasting lipogram before statin initiation for individuals with non-HDL-C >5.7 mmol/ℓ or TG >5.7 mmol/ℓ as this may be indicative of genetic and/or secondary hypertriglyceridaemia. In 2014, the UK NICE guidelines further endorsed the use of non-fasting lipogram testing. [2, 3]

**Lipids measurement**
Total cholesterol and LDL-C are the robust traditional markers used for CV risk estimation based on research evidence and clinical drug trials.[3, 4] Calculated LDL-C (using the Friedewald equation) is still widely used, despite having direct methods of measuring LDL. Ampath prefers to use direct LDL methods due to the limitations of calculating LDL, including that the formula cannot be used in non-fasting samples. Direct LDL is more reliable than the calculated LDL in a number of frequently encountered clinical situations, e.g. metabolic syndrome and diabetes mellitus. Studies have demonstrated that, in patients where the conventional lipid parameters (TG, HDL-C, LDL-C and TC) remain apparently normal, lipid ratios can be diagnostic alternatives in predicting the risk of developing cardiovascular events.[5]

**Non-HDL cholesterol**
Non-HDL-C is a calculated parameter: TC minus HDL-C. It provides an estimation of the total number of atherogenic particles in plasma, including LDL, VLDL, IDL and Lipo(a) and it relates to Apo B levels. Non-HDL-C is recommended as secondary treatment target, especially in patients with diabetes, metabolic syndrome and chronic kidney disease, where hypertriglyceridaemia/mixed hyperlipidaemia is commonly found. In the abovementioned patients, non-HDL-C ≥3.7 mmol/ℓ has been shown to provide a better cardiovascular risk estimation compared to LDL-C, thus it is considered an alternative risk marker. These findings are supported by recent meta-analysis from 14-statin trials, seven fibrate trials and six nicotinic acid trials.[3, 6] When used as an alternative treatment target to LDL-C, the target should be <2.6 mmol/ℓ and <3.3 mmol/ℓ in those at very high and high CV risk respectively.[3]

**TC/HDL and LDL/HDL cholesterol ratios**
The TC/HDL-C ratio, also known as the atherogenic or Castelli Index, and the LDL/HDL-C ratio are important predictive indicators of vascular risk. Their predictive value has been found to be greater than the isolated parameters. The atherogenicity of these ratios is related to increase of TC, specifically LDL-C, which is an atherogenic marker, and reduced HDL-C, which is an anti-atherogenic marker. TC/HDL-C ≥3.5 has been associated with atherogenic dyslipidaemia and metabolic syndrome, and the ratio has also been shown to predict coronary heart disease and cardiovascular mortality. Since the TC/HDL-C ratio is considered a more sensitive and specific index of cardiovascular risk than TC, the Canadian working group has chosen this lipid ratio as a secondary goal of therapy.[5] The TC/HDL-C and LDL/HDL-C ratios have been found to give similar information to the Apo B/Apo A1 ratio.[3]

**TG/HDL cholesterol ratio**
Atherogenic dyslipidaemia, which is characterised by elevated TG, low HDL-C and elevated small dense LDL levels, has been reported to strongly predict CV morbidity, and especially coronary artery disease. Several studies have demonstrated a correlation between the TG/HDL-C ratio and the severity of insulin resistance and coronary atherosclerotic lesions.[7] The clinical application of the ratio is currently being assessed.

**Apo B/Apo A1 ratio**
Apolipoprotein B (Apo B) is a major apolipoprotein that provides a good estimate of atherogenic particles (VLDL, IDL and LDL) in plasma. This is important in patients with increased small dense LDL (sdLDL). Apo B has been shown to be equal to LDL-C in risk prediction. However, it has not been evaluated as a primary treatment target and is not included in algorithms for risk estimation. Apo B on its own does not provide better benefit than a traditional lipogram or non-HDL.[3, 8]

Apolipoprotein A1 (Apo A1) is the major apolipoprotein of HDL-C and provides a good estimate of HDL-C. The ratio between Apo B/Apo A1 reflects the balance of atherogenic and anti-atherogenic lipoproteins in plasma. The ratio has been used in prospective studies as an indicator of risk, and may be used as an alternative marker for risk screening. However, the ratio has not been evaluated as a target for treatment.[5]

## Novel biomarkers

**Small dense LDL-C (sdLDL-C)**
Low-density lipoprotein is involved in cholesterol and triglyceride transfer from the liver to peripheral tissues. Low-density lipoprotein consists of several subclasses of particles with different sizes and densities, including large buoyant, intermediate and small dense LDL. Small dense LDL-C (sdLDL-C) is known to possess atherogenic characteristics. This potential is related to the small particle having a lower affinity for the LDL receptor resulting in a longer plasma stay, and its small size facilitates entry into the arterial wall. It is also susceptible to oxidation due to decreased antioxidants in the core.[9]

The ARIC study has demonstrated that sdLDL-C levels are strongly correlated with an atherogenic lipid profile, and sdLDL-C levels were higher in patients with diabetes mellitus than in non-diabetics. The study also demonstrated that sdLDL-C is associated with incident cardiovascular events, even in patients with low cardiovascular risk based on LDL-C, indicating "residual risk". Small dense LDL can therefore be used for the risk prediction of future cardiovascular events.[10] Using the Randox method, sdLDL >0.90 mmol/ℓ can be used to predict cardiovascular risk.[11]

**Oxidised LDL**

Oxidised LDL (Ox-LDL) is the atherogenic form of LDL, which has been directly linked to the initiation and progression of the atherosclerotic disease process. Atherosclerosis is initiated by a macrophage-mediated immune response, leading to lipoprotein and cholesterol accumulation in arterial walls, where they are subjected to oxidation. The cells consider the oxidatively modified LDL particles to be foreign and the immune system is activated, which results in the formation of plaques.[12]

Several studies have identified Ox-LDL to be a predictive biomarker for the subclinical development of atherosclerosis and subsequent events (see Table 2). Holvoet et al. (1998) found elevated levels of circulating oxidised LDL in untreated patients with stable coronary artery disease (CAD), as well as in patients with acute coronary syndromes when compared to patients without coronary artery disease (see Figure 1).[13]

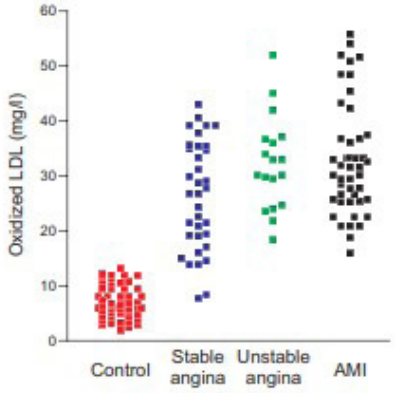


*Figure 1: Compared to controls, oxidised LDL levels are elevated in patients with stable angina, unstable angina and acute myocardial infarction(AMI) (Holvoet et al., 1998)*

**Table 2: Studies demonstrating an association between oxidised low-density lipoprotein measurement and cardiovascular events**

| Study | Year | Findings |
|---|---|---|
| Hulthe | 2002 | Demonstrated association of circulating Ox-LDL with subclinical atherosclerosis (ultrasound-assessed atherosclerotic changes in the carotid and femoral arteries.)[14] |
| Wallenfeldt | 2004 | Identified Ox-LDL as prognostic biomarker in atherosclerosis development.[15] |
| Meisinger | 2005 | Demonstrated that increased Ox-LDL can predict future cardiovascular events.[16] |
| Johnston | 2006 | Demonstrated that increased Ox-LDL is an independent predictor of MI not mortality.[17] |
| MONICA/KORA Augsburg | 2011 | Demonstrated that increased Ox-LDL concentrations are associated with increased incidents of cardiovascular events.[18] |

Other causes of increased Ox-LDL levels include patients with kidney disease, polycystic ovary syndrome, and known autoimmune disorders.[19, 20, 21]

**Residual risk**

Although statins are highly effective, even patients who have achieved significant LDL-C reductions may still experience CV events, having "residual risk".[22] As shown in Figure 2, up to half of the patients admitted with CAD have reached their lipid treatment targets, which may indicate the presence of other background factors or the need to lower LDL treatment goals even further.[23]

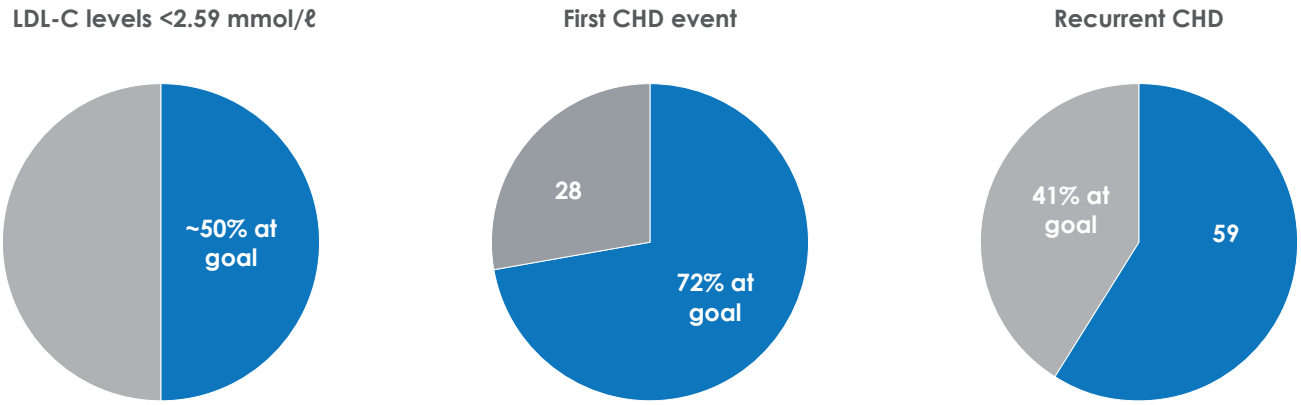


*Figure 2: Residual cardiovascular risk is still significant despite managing traditional risk factors[23]*

Studies show that LDL-C levels were often not predictive of coronary artery disease. In a population of over 200 000 patients hospitalised with CAD, almost half had LDL-C levels <2.59 mmol/ℓ. The AHA Get-With-The-Guidelines intiative analysis revealed that a substantial proportion of patients with CHD events were well within guideline-recommended targets for lipid panel values.

Although sdLDL and Ox-LDL have not been included in major societal algorithms for cardiovascular risk estimation or as treatment targets, they may have benefits in managing residual risk after statin therapy in specific patient populations, such as established CVD, hypertension, dyslipidaemia, diabetics and patients with metabolic syndrome.

**NB:** Ampath currently offers sdLDL testing. Ox-LDL has been validated and may be offered in future.

## Assessment of treatment goals and monitoring the effectiveness of therapy

Treatment goals in the 2018 guidelines are similar to the previous 2012 goals. After initiating lifestyle changes alone, lipid testing should be performed after six months.

In those who have initiated pharmacotherapy and those where dose or treatment has changed, lipid testing should be repeated at 8 (±4) weeks. In patients where the treatment goal is reached, testing should be performed six-monthly.[1]

## Genetic testing for familial hypercholesterolaemia

Ampath will soon be offering comprehensive genetic testing for FH, including testing for the most common loss of function mutations in the LDL-receptor and ApoB genes, and gain of function mutations in the PCSK9 (proprotein convertase subtilisin/kexin Type 9) gene. Recent studies from whole populations have estimated the frequency of heterozygous FH to be as high as 1/200 to 1/250.[4]

Genetic testing can be done as part of the cascade screening of family members of an index case with elevated total cholesterol levels (≥7.5 mmol/ℓ), and is especially useful when the causative mutation is known.[1, 4]

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