The new cholesterol target

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A new cholesterol target, which is better at predicting risk of cardiovascular events than LDL-cholesterol targets and does not require fasting, has recently been introduced into Australian guidelines for the primary prevention of cardiovascular disease.

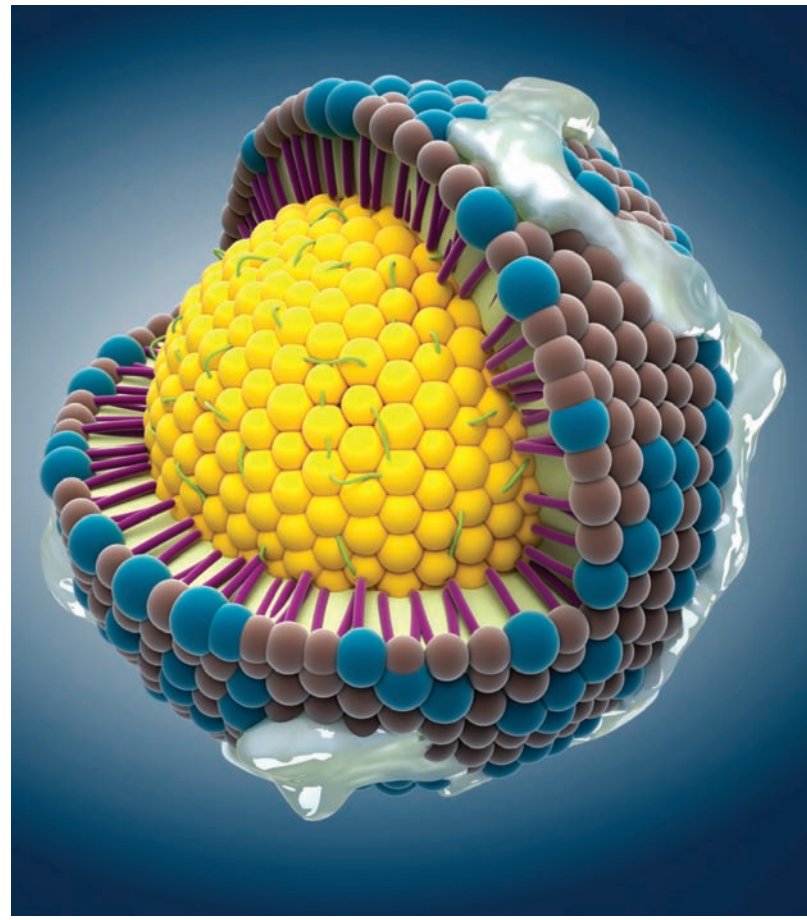
In 2012, the National Vascular Disease Prevention Alliance published its new management guidelines for primary prevention of cardiovascular disease (CVD) and introduced a new cholesterol target: non-HDL-cholesterol (non-HDL-C; target level <2.5 mmol/L; see the Table).[1] Non-HDL-C comprises total cholesterol minus HDL-cholesterol (HDL-C). Using non-HDL-C, clinicians can rapidly assess cardiovascular risk and adequacy of treatment. Non-HDL-C appears to be superior to LDL-cholesterol (LDL-C) as a CVD risk marker because it includes cholesterol in all atherogenic lipoprotein subclasses, including LDL.

In the current US guidelines, target levels of non-HDL-C are used for patients with triglyceride levels of 2.3 mmol/L or more, and are 0.8 mmol/L higher than target levels of LDL-C.

What is non-HDL-cholesterol and why is it important?

Non-HDL-C is plasma cholesterol present in all lipoproteins except HDL (see the Figure).[2] It is simply calculated by subtracting HDL-C from total cholesterol (see the box on page 27). Non-HDL-C includes cholesterol in LDL, very-low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and chylomicron remnants, all of which are mainly atherogenic. This is in contrast to the cholesterol in HDL, which is mainly antiatherogenic.[2]

Non-HDL-C is important because it represents in a single value the plasma cholesterol concentration within atherogenic lipoproteins (LDL, IDL, VLDL and chylomicron remnants), which have the apoliprotein B (apoB) isoform apoB-100 as their major protein.



Key points

- **The non-HDL cholesterol (non-HDL-C) measurement includes all potentially atherogenic lipoproteins.**
- **Non-HDL-C level is calculated by subtracting HDL-cholesterol level from total cholesterol level.**
- **The calculation of non-HDL-C does not require measurement of the lipid profile in the fasting state.**
- **Non-HDL-C allows for changes in lipoprotein composition, especially with raised triglyceride levels.**
- **Several studies have shown that non-HDL-C is superior to LDL-C as a marker of cardiovascular disease risk.**

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What are the problems with LDL-C as a target?

The problems with LDL-C as a cholesterol target include the following.

- Up to 50% of recurrent acute coronary syndromes occur in patients with 'normal' LDL-C levels, despite a six-fold increase in the control of LDL-C levels in patients with hypercholesterolaemia.[2]
- Coronary events still occur in patients with LDL-C at goal levels despite the aggressive use of statins.[2-5]
- Despite achieving target LDL-C levels, some patients still have an increased risk of CVD because of increased levels of triglyceride or small dense LDL and other particles containing apoB-100.[2]
- Targets of therapy other than LDL-C need to be considered because of the increasing prevalence of type 2 diabetes, obesity and the metabolic syndrome.[2,3,5,6] In patients with these conditions there is a preponderance of triglyceride-rich lipoproteins and small-dense LDL, which are better measured by non-HDL-C than by LDL-C.[2,5,6]

Why should non-HDL-C be used as a surrogate marker for CVD risk?

Possible reasons why non-HDL-C should be used as a surrogate marker for CVD risk include the following.

- The calculation of non-HDL-C does not require measurement of the lipid profile in the fasting state. In contrast, the calculation of LDL-C using the Friedewald formula (see the box on page 27) requires fasting.
- The Friedewald formula for calculating LDL-C is not valid when triglyceride levels are more than 4.5 mmol/L and LDL-C levels are less than 1.8 mmol/L, when direct methods for LDL measurement are required.[6,7] Calculation of non-HDL-C as a marker for CVD risk is particularly useful in patients with elevated triglyceride levels.
- The calculation of HDL-C involves only two potential sources of error versus the three potential sources of error for LDL-C: measurement of total cholesterol, HDL-C and triglyceride. These have inherent variation both within and between patients, especially triglyceride.
- Non-HDL-C is more reliable because total cholesterol levels vary little between the fasting and nonfasting state whereas triglyceride levels vary considerably, modifying the distribution of cholesterol between apoB-containing lipoproteins in the process. This reflects rapid clearance of chylomicrons and their remnants from the circulation. Chylomicron particles have very low cholesterol content, so contribute little to non-HDL-C in the nonfasting state. Clearance of these particles may be slow in

Table. Current Australian guidelines for lipid targets for CVD management[1]

Risk category	Lipid targets
High risk: clinically determined or five-year absolute risk of CVD events >15%	TC <4.0 mmol/L HDL-C ⩾1.0 mmol/L LDL-C <2.0 mmol/L Non-HDL-C <2.5 mmol/L TG <2.0 mmol/L
Moderate risk: five-year absolute risk of CVD events 10–15%	
Low risk: five-year absolute risk of CVD events <10%	
Note that decisions regarding management of risk are made according to the individual's absolute risk level, whereas response to treatment is monitored by measurement of individual risk factors.	

Abbreviations: CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

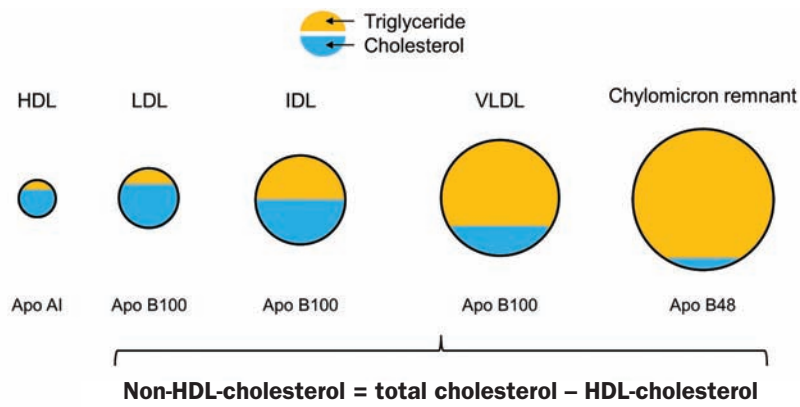

Figure. Plasma lipoproteins. The proportions of triglycerides (yellow) and cholesterol (blue) are shown for each lipoprotein particle.[2]

Abbreviations: ApoB = apoliprotein B; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Non-HDL = non-high-density lipoprotein; VLDL = very low-density lipoprotein.

patients with hypertriglyceridaemia, but non-HDL-C can still be measured accurately because chylomicron particles provide a quantitatively small contribution to total and non-HDL-C.
- Non-HDL-C calculation is quick and simple, requiring one subtraction step.
- Population norms for non-HDL-C have been published for the USA.[8,9] These are likely to be similar to those for Australia.
- Several research studies have shown that non-HDL-C is superior to LDL-C as a marker of CVD risk and also of subclinical atherosclerosis (see text below).
- It is possible that targeting non-HDL-C may produce superior CVD outcomes to targeting LDL-C, but further research is required to determine this.

Why is non-HDL-C superior to LDL-C as a CVD risk marker?

Non-HDL-C is a superior predictor of CVD because it is an accurate surrogate for apoB-100 levels, which in turn reflect the presence of atherogenic lipoproteins in plasma (LDL, IDL, VLDL and chylomicron remnants).

Several individual prospective studies have shown that non-HDL-C is a strong predictor of CVD risk. In most of these studies, non-HDL-C predicted risk more strongly than any other lipid fraction, including HDL-C and LDL-C.[5,10-23] Only the total cholesterol/HDL-C and apoB/apoA-1 ratios provide similar risk prediction to non-HDL-C in some studies.[13,24-26] Non-HDL-C has greater power than LDL-C in predicting CVD risk reduction, and has demonstrated dose-dependent effects in predictive models of CVD more consistently than LDL-C. [5,10-23]

Non-HDL-C as a therapeutic target

In patients receiving statin therapy, on-treatment levels of non-HDL-C were more closely associated with CVD outcome than levels of LDL-C, as shown in two secondary prevention trials.[10,14,15] A combined analysis of both of these trials assessed comparative on-treatment performance of apoB, LDL-C, and non-HDL-C levels.[10] Non-HDL-C and apoB levels were more closely associated with future major CVD outcomes than LDL-C levels.[10,14,15]

Non-HDL-C and subclinical atherosclerosis

In a study of 1611 consecutive asymptomatic individuals (67% men, mean age 53 years), their coronary artery calcium (CAC) was measured by single electron beam tomography. This study showed that non-HDL-C levels have a greater association with the severity of subclinical atherosclerosis than other lipid parameters, as measured by the CAC score.[27]

The pathological determinants of atherosclerosis in youth (PDAY) study included individuals aged 15 to 34 years who died of external causes and underwent autopsy.[23] The extent of fatty streaks and raised lesions in the thoracic aorta, abdominal aorta and right coronary arteries were assessed. Non-HDL-C was significantly associated with fatty streaks in all three sites, as well as with raised lesions in the abdominal and thoracic aorta. ApoB was not significantly associated with any raised lesions, and was less associated with fatty streaks compared with non-HDL-C.[23]

Calculation of non-HDL-C level

Non-HDL-C = TC – HDL-C

Abbreviations: HDL-C = high-density lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol.

The Friedewald formula to calculate LDL-C

The Friedewald formula, used to calculate LDL-C from fasting total cholesterol, HDL-C and TG levels (in mmol/L) is:

LDL-C = TC – (HDL-C + TG/2.2)

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

Summary

Non-HDL-C is now an important target of therapy for the prevention of coronary heart disease.[28-31] The recent National Vascular Disease Prevention Alliance guidelines recommend a target level of less than 2.5 mmol/L for non-HDL-C, in addition to target levels for triglyceride, HDL-C, total cholesterol and LDL-C (see the Table).[1]

Use of non-HDL-C as a marker for CVD risk is particularly useful in patients with elevated triglyceride levels (2.3 mmol/L or more). In addition, non-HDL-C is at least as powerful a risk marker as LDL-C in patients with all levels of triglycerides.[28-31] Australian clinicians now have the opportunity to familiarise themselves with non-HDL-C, especially as laboratories begin to include it routinely in their lipid reports. **CT**

References

A list of references is available on request to the editorial office.

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