LDL-cholesterol is the only clinically relevant biomarker for ASCVD risk

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Conflict of interest

SZ reports past participation in advisory boards and/or receiving honoraria from AstraZeneca/Bristol-Myers Squibb Australia; Janssen-Cilag; Merck, Sharp, and Dohme (Australia); Novartis Australia; Novo Nordisk; Sanofi and Servier Laboratories for work unrelated to this study. DL reports past participation in advisory boards and/or receiving honoraria from Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi and Shire for work unrelated to this study.

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Introduction

Recent years have witnessed the emergence of promising novel lipid and non-lipid biomarkers for atherosclerotic cardiovascular disease, with suggestions that some of these may be superior to low-density lipoprotein cholesterol (LDL-C). In the present viewpoint, we compare LDL-C and other biomarkers against the three key criteria for the clinical utility of a biomarker: accuracy, reliability and therapeutic relevance. We conclude that the available data support LDL-C as the most clinically relevant biomarker for ASCVD risk.

Despite declining mortality, atherosclerotic cardiovascular disease (ASCVD) remains the most common cause of morbidity and mortality worldwide. Furthermore, the burden of disease is projected to rise due to population ageing and an increasing prevalence of risk factors, notably in developing countries.

Optimal primary and secondary prevention of ASCVD is dependent on accurate estimation of the risk of future incident or recurrent ASCVD using demographic, clinical and biomarker information.

Despite the title of this manuscript, we do not support the premise that low-density lipoprotein cholesterol (LDL-C) is the "*only* clinically relevant biomarker for ASCVD" risk. Cardiovascular risk is the consequence of the complex interplay of multiple genetic and somatic factors and its evaluation should consider multiple cardiovascular biomarkers, including indicators of glycaemic control, haemostasis, myocardial damage and inflammation, as well as other risk factors including smoking, hypertension, obesity and physical inactivity. Rather, in the present viewpoint, we argue that LDL-C is the "*most* clinically relevant biomarker for ASCVD risk". LDL-C has been the primary biomarker for ASCVD risk prediction and goal-directed therapy for decades. However, recent years have witnessed the emergence of many novel biomarkers, including those outside of lipid metabolic pathways, and there remains scepticism of the 'LDL hypothesis'.

To support our argument, we will first summarise data for LDL-C drawn from laboratory studies, prospective cohort studies, genetic epidemiology and randomised controlled trials, assessing these against the three key criteria for the clinical utility of a biomarker: i) accuracy (able to identify persons at risk); ii) reliability (able to be measured consistently); and iii) therapeutic relevance (able to help guide therapy) (1). Then, we will evaluate the currently most promising other lipid, and novel, biomarkers against the same criteria.

Criterion 1: Accuracy of LDL-C

The capacity of LDL-C to identify persons at risk of ASCVD has now been established, with supporting evidence drawn from a vast body of research.

More than a century of laboratory research points to cholesterol-carrying low-density lipoprotein being the principal causative factor in ASCVD. Low-density lipoprotein (as well as other apolipoprotein B-containing lipoproteins) delivers cholesterol to peripheral cells, and is thus directly implicated in the initiation and progression of atherosclerosis (2). In addition, experimentally-induced elevations in LDL-C have led to atherogenesis in all mammalian species studied.

Data showing a positive relationship between LDL-C levels and risk of ASCVD have accumulated from prospective cohort studies over the last 30 years. Indeed, over 200 studies involving more than 2 million participants, 20 million person-years of follow-up and more than 150,000 cardiovascular

events have confirmed a dose-dependent, log-linear and independent association between magnitude of exposure to LDL-C and risk of ASCVD (3) in both males and females, as well as across different age-groups and ethnicities. Elevated LDL-C is also predictive of cardiovascular events post-acute coronary syndrome (ACS). Furthermore, variations in more than 50 genes associated with LDL-C levels (but not otherwise associated with ASCVD) also predict risk of ASCVD, and among people within each LDL-C variant, the relationship between LDL-C level and risk is preserved. The accumulated observational data regarding LDL-C and risk of ASCVD is remarkable for its consistency and coherence, and is arguably unrivalled by any other cardiovascular risk factor.

Criterion 2: Reliability of LDL-C

Because direct measurement of LDL-C is costly, time-consuming and not widely available, it is often calculated using the Friedewald equation, which relies on the values of other lipid fractions. The main limitations of such a calculation are that patients must be fasting and the estimation is inaccurate in patients with triglyceride levels that exceed 4.5mmol/L. Interestingly, few large studies have validated the Friedewald equation against LDL-C measured by ultracentrifugation. A recent US study involving 15,917 people from an outpatient setting with fasting triglyceride concentrations <4.5mmol/L showed that the Friedewald equation tended to systematically under-estimate 'true' LDL-C (4). However, among patients with Friedewald-estimated LDL-C levels between above 1.8mmol/L, the extent of under-estimation was small, with a median difference of only 0.1mmol/L. At lower Friedewald-estimated LDL-C levels, the median difference was 0.3 mmol/L.

The clinical consequences of the above inaccuracies are attenuated by i) the Friedewald equation systematically under-estimating true LDL-C, rather than randomly misclassifying it; and ii) the extent of under-estimation being small among patients for whom LDL-C levels are clinically relevant (that is, high). It is important to further emphasise that LDL-C estimated via the Friedewald formula includes cholesterol contained in lipoprotein(a). This can be important when true LDL-C is low (e.g., with proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibition) and/or when Lp(a) levels are high.

Taken together, most of the epidemiological and clinical data that have linked LDL-C and risk of ASCVD have been based on measurement of LDL-C estimated via the Friedewald equation. Hence there is consistency between evidence from research regarding the role of LDL-C and the manner in which it is measured in clinical practice.

Criterion 3: Therapeutic relevance of LDL-C

To date, over 30 randomised clinical trials have evaluated the efficacy of LDL-C-lowering therapies (including statins, ezetimibe and PCSK9 inhibitors) in reducing the risk of ASCVD (3). Collectively, these studies have involved over 200,000 participants and 30,000 cardiovascular events, and all have shown that the reduction in the risk of ASCVD is proportional to the absolute reduction in LDL-C

achieved by therapy. Specifically with respect to statins, the most commonly used lipid-lowering agents, the Cholesterol Treatment Trialists Collaboration pooled data from 26 clinical trials involving 170,000 participants demonstrated a consistent relationship between LDL-C lowering and reduced cardiovascular risk. Their results suggest a 22% reduction in major cardiovascular events for every 1.0 mmol/L reduction in LDL-C (Figure 1) (5). For all-cause mortality, major coronary events and stroke, the reductions in relative risk for every 1.0 mmol/L reduction in LDL-C are 10%, 24% and 15% respectively. Notably, these effects are applicable across multiple patient sub-groups, and also agnostic to baseline (pre-treatment) LDL-C level. Even for LDL-C lowering via dietary interventions, use of bile acid sequestrants and ileal bypass surgery, the regression lines have been shown to be similar to those for statins (6).

As a reflection of its clinical relevance, LDL-C has been the focus of past and contemporary lipid management guidelines. In primary prevention, LDL-C is a core part of risk stratification (to estimate absolute risk) and used to guide lipid-lowering therapy, while in secondary prevention, statins are recommended to lower LDL-C, generally regardless of baseline levels. Hence both the clinical and the lay communities have become familiar with LDL-C ("bad cholesterol") such that measuring and interpreting LDL-C is part of established practice, as is the simple message to 'keep LDL-C low'. The importance of this cannot be under-estimated in an ever-changing, increasingly-complex clinical landscape.

Other lipid and novel ASCVD biomarkers (1, 7)

Table 1 summarises the evaluation of the most promising other cardiovascular biomarkers against the three key criteria for biomarker clinical utility. All are backed by reasonable evidence of association with ASCVD risk (Criterion 1), which is what has driven interest in these biomarkers. However, only a few are reliably measured (Criterion 2) and readily measured in clinical practice, and fewer have therapeutic relevance (Criterion 3). Nevertheless, three novel biomarkers warrant specific mention: HDL-C, non-HDL-C (total cholesterol minus HDL-C) and high sensitivity C-reactive protein (hsCRP).

High-density lipoprotein is involved in delivery of cholesterol away from cells, and therefore it is not surprising that a strong inverse relationship between HDL-C levels and ASCVD risk has been demonstrated in observational studies, although not those involving genotypes which are expressed exclusively through HDL-C levels. The practical advantage of HDL-C is that it is directly measured rather than estimated and measurement accuracy is less susceptible to variations to the concentrations of other lipid sub-fractions, especially high triglycerides. However, at the present time, there is little evidence to support HDL-C as a specific therapeutic target. While early trials of fibrates, which modestly increase HDL-C and reduce LDL-C, suggested clinical benefit, they have not been supported by findings from recent larger studies of fibrate and niacin therapies. Furthermore, clinical

trials of two cholesterol ester transfer protein (CEPT) inhibitors, torcetrapib and dalcetrapib, which mainly increase HDL-C (but also decrease LDL-C), showed no benefit.

LDL is not the only lipoprotein involved in atherogenesis; other apolipoprotein B-containing lipoproteins (triglyceride-rich very low-density lipoprotein [VLDL], intermediate-density lipoprotein and lipoprotein(a)) are also atherogenic. It is therefore intuitive that non-HDL-C, which reflects cholesterol carried within *all* atherogenic particles, would be predictive of ASCVD risk. Also, like HDL-C, its measurement is direct. However, a large meta-analysis of prospective cohort studies showed that any regression model of ASCVD risk that included non-HDL-C or LDL-C produced similar results, affirming any lack of superiority of one over the other (8). Furthermore, there is limited evidence to support any additional utility of non-HDL-C over LDL-C as a therapeutic target, and it is currently not well appreciated by the clinical nor lay community.

It is now recognised that inflammation plays a significant role in atherogenesis. CRP is an acute-phase reactant synthesised primarily in the liver and released into the blood in response to injury or infection. While there is large body of evidence linking CRP concentration to ASCVD risk, Mendelian randomisation studies found that genes encoding for CRP were not associated with ASCVD risk, suggesting that the association is not causal. Nevertheless, hsCRP may still serve as a useful biomarker for therapy, as demonstrated by two clinical trials, one of rosuvastatin (9) and the other of the anti-inflammatory agent canakinumab (10). The main drawback of hsCRP as a biomarker is its lack of specificity; levels are increased in any condition involving injury or infection. hsCRP levels are thus highly variable. Furthermore, while CRP is routinely measured in clinical practice, hsCRP is not. Hence at the present time, the clinical relevance of hsCRP is limited.

Conclusions

There is ongoing debate as to whether LDL-C should be supplanted by other lipid or novel biomarkers in the evaluation of risk of ASCVD risk. The evidence to date suggests that despite that most of these other biomarkers have convincing associations with ASCVD and may provide incremental benefit in risk prediction, none rival LDL-C in terms of clinical relevance. Backed by decades of consistent research data, LDL-C is the only biomarker that definitively meets all three key criteria for clinical utility: accuracy, reliability and therapeutic relevance. It is also cheap to measure, widely available and entrenched in everyday clinical practice.

Table 1. Evaluation of LDL-C and novel cardiovascular biomarkers against the three key criteria for clinical utility: evidence categorised as none (-), weak (+), moderate (++) or strong (+++) (1, 7).

Figure 1. Meta-analysis of data from statin trials showing the relationship between reduction in LDL-C and reduction in risk of major cardiovascular events (5).

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Supplementary Reading List

Table 1. Evaluation of LDL-C and novel cardiovascular biomarkers against the three key criteria for clinical utility: evidence categorised as none (-), weak (+), moderate (++) or strong (+++) (1, 7).

Biomarker	Criterion 1: Accuracy	Criterion 2: Reliability	Criterion 3: Therapeutic relevance
LDL-C	+++	+++	+++
HDL-C	+++	+++	+
Non-HDL-C	+++	+++	++
apoB	++	+	+
apoAI	++	+	+
apoE	++	+	+
Lp(a)	++	+	-
hsCRP	++	+	++
IL6	++	+	+
Fibrinogen	++	+	-
NT-proBNP	++	+	+
hs troponin	++	+	+

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; apoB, apolipoprotein B; apoAI, apolipoprotein AI; apoE, apolipoprotein E; Lp(a), lipoprotein a; hsCRP, high sensitivity C-reactive protein; IL6, interleukin 6; NT-proBNP, N-terminal pro B-type natriuretic peptide; hs troponin, high sensitivity troponin (See **Supplementary Reading List** for key references which informed the qualitative scores assigned to each biomarker).

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