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Invited commentary

HDL function and cardiovascular risk: Debate continues…

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Measurement of high-density lipoprotein (HDL) cholesterol is highly relevant in the context of estimating global cardiovascular risk based on SCORE [1]. Based on animal models showing that HDL have a number of properties that are potentially atheroprotective, it has been suggested that assessment of HDL function may offer advantages over measurement of plasma concentration of HDL cholesterol. However, given the complexity of HDL biology, there are still uncertainties about what assays of HDL function represent.

The ability of HDL to promote cholesterol efflux from cells, including lipid-laden macrophages in the arterial wall, is the best known of the potentially atheroprotective effects of HDL, and is therefore a logical focus for study. Recent work has shown cholesterol efflux capacity to be inversely associated with prevalent coronary artery disease (CAD), independent of HDL cholesterol concentration. Each 1-standard deviation increase in cholesterol efflux capacity was associated with 30% decrease (95% CI 17–41%) in risk of prevalent CAD ($p < 0.001$) [2]. However, a recent report questions whether cholesterol efflux capacity is predictive for risk of cardiovascular events [3].

This study aimed to confirm previous findings of the relationship between cholesterol efflux capacity and prevalent coronary artery disease (CAD). Another important objective of the study was to provide information about the potential association between cholesterol efflux capacity and risk of incident major cardiovascular events (death, myocardial infarction and stroke). Thus, the study aimed to bridge a gap in knowledge about the clinical relevance of cholesterol efflux capacity as a prognostic indicator of cardiovascular risk.

The investigators measured cholesterol efflux capacity from free cholesterol-enriched macrophages to apolipoprotein B (apoB)-depleted serum as the cholesterol acceptor, in two case–control cohorts: one cohort (A) included subjects with stable CAD undergoing elective coronary angiography (871 with angiographic CAD versus 279 controls), and the second (B) included an outpatient cohort (146 with CAD versus 431 controls). As anticipated, the prevalence of diabetes, hypertension, smoking and obesity was higher in subjects with CAD than in controls. Additionally, in each cohort, subjects with CAD had lower plasma HDL cholesterol concentration than controls (median 33 mg/dL versus 39 mg/dL in Cohort A, and 44 mg/dL versus 53 mg/dL in cohort B).

In each cohort, ATP-binding cassette transporter A1 (ABCA1)-stimulated cholesterol efflux capacity was inversely associated with prevalent CAD (Table 1). Adjustment for conventional cardiovascular risk factors attenuated this association in cohort A but not in cohort B. Thus, subjects with the highest cholesterol efflux capacity had the lowest risk of prevalent CAD, consistent with previous findings [2].

In contrast, the reverse was shown for the association between cholesterol efflux capacity and incident risk of major cardiovascular events over 3 years. In cohort A, subjects with the highest cholesterol efflux capacity also had the highest risk (unadjusted hazard ratio 1.66, 95% CI 1.07–2.58, $p < 0.05$ versus subjects in the lowest tertile). Furthermore, this association was strengthened after adjustment for conventional cardiovascular risk factors (hazard ratio 1.85, 95% CI 1.11–3.06, $p < 0.05$). There were also issues as to what this assay was measuring, as most of the radiolabelled cholesterol from macrophages was not detected in HDL particles, although 75% did interact with apoA-I as the cholesterol acceptor.

The authors of this report suggest that their paradoxical findings might relate to the ABCA1-dependent cholesterol efflux pathway. Lipid-poor pre-beta1 HDL particles are known to be primary

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Table 1
Association between cholesterol efflux capacity and risk of prevalent CAD.

Cohort	Unadjusted odds ratio (95% CI)[a]	*p*-value
A (angiographic CAD versus control)	0.60 (0.42–0.85)	<0.01
B (outpatients with CAD versus control)	0.11 (0.06–0.20)	<0.01

[a] Comparing tertiles with the lowest versus highest cholesterol efflux capacity.

acceptors of cholesterol from the ABCA1 transporter in macrophages [4,5]. Previous studies report that ABCA1-dependent cholesterol efflux is correlated with the concentration of pre-beta HDL [6], and further, that pre-beta-HDL is positively correlated with coronary heart disease [7].

HDL biology is still inadequately understood. The changing focus of HDL measurement, from HDL cholesterol to HDL function, is an evolving area. Additionally, it needs to be recognised that potentially atheroprotective properties of HDL are actually conferred by other molecules that HDL transports. Therefore, further understanding of HDL biology is clearly indicated before such assays can be used as a predictive tool for cardiovascular risk.

Key points

- This study reported a direct association between cholesterol efflux capacity and prospective risk of major cardiovascular events. This contrasts with evidence of an inverse association between cholesterol efflux capacity and prevalent CAD.
- These paradoxical findings underline the fact that HDL biology is complex and not fully understood. Further study is needed before such research tools can be adapted as prognostic markers in clinical trials or beyond.

1. Statin confers benefit across the spectrum of CKD

Chronic kidney disease (CKD) is a major public health problem. Individuals with CKD are known to be at high risk of cardiovascular events; independent of other risk factors, the risk of cardiovascular death is 2–4-fold higher in individuals with stage 4–5 CKD than the general population [8]. Moreover, CKD has a substantial economic impact, highly relevant when resources for healthcare are increasingly finite. Diabetes is a key driver of end-stage renal disease; consequently, the escalation in diabetes prevalence will undoubtedly impact the socioeconomic cost of CKD.

Low-density lipoprotein (LDL) cholesterol lowering with a statin is recommended by guidelines as the cornerstone for dyslipidaemia management [1]. However, there is uncertainty about the role of statin therapy in patients with severe CKD. This uncertainty is reflected by recent meta-analyses, with one concluding that benefit was confined to individuals with earlier stages of disease [9,10]. There are also emerging data that the underlying pathology of cardiovascular disease may differ in individuals with and without severe CKD [11]. Furthermore, trials in CKD patients have shown conflicting results [12–14].

A recent meta-analysis [15] of 31 randomised, controlled trials of 48,429 patients with CKD (mean age 42–73 years) treated with a statin (atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin and lovastatin) aimed to resolve this controversy. Ten of these trials ($n = 4503$) were solely in dialysis patients, 18 were in non-dialysis patients ($n = 33{,}252$) and three included both dialysis and non-dialysis patients. The database included 6690 major cardiovascular events and 6653 deaths.

Table 2
Effect of statin therapy according to CKD stage.

CKD stage	Statin-treated no. with event/Total N	Placebo no. with event/Total N	Relative risk (95% CI) of major CV event
Stage 5 − dialysis	866/3639	934/3650	0.93 (0.86–1.00)
Stage 5 − no dialysis	67/614	81/607	0.82 (0.60–1.11)
Stage 4	134/1263	179/1335	0.78 (0.63–0.96)
Stage 2–3	504/6194	764/6211	0.69 (0.63–0.77)

Overall, statin therapy was associated with a 23% (95% CI 15–30%) reduction in the risk of major cardiovascular events, comparable to risk reductions reported by the Cholesterol Treatment Trialists' Collaboration [16]. Consistent with findings in patients without CKD, there was greater reduction in risk with intensive versus less intensive regimens. The benefit of statin therapy was modified by renal function, with greater reduction in risk in individuals with less severe CKD than those with more severe disease (Table 2). In patients not receiving dialysis, there was a 27% (95% CI 17–35%, $p < 0.001$) reduction in the risk of cardiovascular events per 1 mmol/L reduction in LDL cholesterol.

Similarly, statin therapy reduced the risk of major coronary events by 22% (95% CI 12–31%), cardiovascular mortality by 9% (95% CI 1–16%) and all-cause mortality by 8% (95% CI 1–15%).

There was no clear evidence that statin treatment reduced the risk of renal failure events, defined as a 25% reduction in estimated glomerular filtration rate, doubling of serum creatinine, or end-stage renal disease (relative risk 0.95, 95% CI 0.90–1.01).

In conclusion, the results of this meta-analysis reaffirm the benefit of statin therapy across a broad spectrum of renal impairment. Kidney function was an important modifier of the benefit derived from statin therapy. Thus, consistent with previous analysis [10], the magnitude of benefit was lower in patients with the most severe disease (CKD stage 5 on dialysis treatment). Despite this, there were clinically meaningful reductions in cardiovascular events in every stage of renal disease. These findings therefore support guideline recommendations for statin therapy to reduce cardiovascular risk in patients with CKD [1].

Key points

- This meta-analysis reaffirms the value of LDL lowering with a statin as the cornerstone of dyslipidaemia management in CKD, as recommended by the joint European Society of Cardiology/European Atherosclerosis Society guidelines for dyslipidaemia management.
- Although renal function is a modifier of this benefit, there are clinically meaningful reductions in cardiovascular risk across the spectrum of renal dysfunction.
- Statin therapy had no benefit on renal events.

2. Lifestyle: potential benefit comparable to statins?

Current guidelines clearly focus on lifestyle as the important first step in preventing cardiovascular disease. Considering the evolution of atherosclerosis it is clearly more relevant to target intervention to an earlier pre-clinical stage rather than the later