# Lowering LDL cholesterol reduces cardiovascular risk independently of presence of inflammation

OPEN

Benjamin C. Storey[1,2], Natalie Staplin[2], Richard Haynes[1,2], Christina Reith[2], Jonathan Emberson[1,2], William G. Herrington[2], David C. Wheeler[3], Robert Walker[4], Bengt Fellström[5], Christoph Wanner[6], Martin J. Landray[1,2,7,8] and Colin Baigent[1,2,8]; on behalf of The SHARP Collaborative Group

[1]*Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK;* [2]*Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK;* [3]*Centre for Nephrology, University College London, London, UK;* [4]*Department of Medicine, University of Otago, Dunedin, New Zealand;* [5]*Renal Unit, Department of Medicine, University of Uppsala, Uppsala, Sweden;* [6]*Division of Nephrology, University Hospital, Würzburg, Germany; and* [7]*Big Data Institute, Lia Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK*

**Markers of inflammation, including plasma C-reactive protein (CRP), are associated with an increased risk of cardiovascular disease, and it has been suggested that this association is causal. However, the relationship between inflammation and cardiovascular disease has not been extensively studied in patients with chronic kidney disease. To evaluate this, we used data from the Study of Heart and Renal Protection (SHARP) to assess associations between circulating CRP and LDL cholesterol levels and the risk of vascular and non-vascular outcomes. Major vascular events were defined as nonfatal myocardial infarction, cardiac death, stroke or arterial revascularization, with an expanded outcome of vascular events of any type. Higher baseline CRP was associated with an increased risk of major vascular events (hazard ratio per 3x increase 1.28; 95% confidence interval 1.19-1.38). Higher baseline LDL cholesterol was also associated with an increased risk of major vascular events (hazard ratio per 0.6 mmol/L higher LDL cholesterol; 1.14, 1.06-1.22). Higher baseline CRP was associated with an increased risk of a range of non-vascular events (1.16, 1.12-1.21), but there was a weak inverse association between baseline LDL cholesterol and non-vascular events (0.96, 0.92-0.99). The efficacy of lowering LDL cholesterol with simvastatin/ezetimibe on major vascular events, in the randomized comparison, was similar irrespective of CRP concentration at baseline. Thus, decisions to offer statin-based therapy to patients with chronic kidney disease should continue to be guided by their absolute risk of atherosclerotic events. Estimation of such risk may include plasma biomarkers of inflammation, but there is no evidence that the relative beneficial effects of reducing LDL cholesterol depends on plasma CRP concentration.**

**Correspondence:** *Colin Baigent, Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK. E-mail: colin.baigent@ndph.ox.ac.uk*

[8]MJL and CB are senior authors.

**Received 26 June 2017; revised 23 August 2017; accepted 7 September 2017**

*Kidney International* (2017) ■, ■–■; https://doi.org/10.1016/j.kint.2017.09.011

KEYWORDS: C-reactive protein; inflammation; LDL cholesterol; randomized trials; vascular disease



Inflammation has been implicated in the pathobiology of cardiovascular disease,[1,2] but it is unclear whether inflammation is a direct cause of disease or simply a marker of disease response. Among apparently healthy individuals, prospective cohort studies have shown that markers of inflammation, such as C-reactive protein (CRP)[3] and interleukin-6[4,5] (IL-6), are positively associated with an increased risk of cardiovascular events, and studies employing Mendelian randomization have suggested that the association between IL-6 and risk may be causal.[6] Prospective studies have also shown that low-density lipoprotein cholesterol (LDL-C) is positively associated with risk of major vascular events,[7,8] while randomized trials of statins[9] (and, more recently, of proprotein convertase subtilisin/kexin type 9 or PCSK-9 inhibitors[10]) have shown that lowering LDL-C reduces cardiovascular risk, confirming that LDL-C is a cause of atherosclerotic disease. It is unclear whether the presence of inflammation influences the relationship between LDL-C and cardiovascular disease. Some groups have suggested, based on experimental studies, that the presence of inflammation may reduce the efficacy of statin therapy,[11] but others have reported — albeit in nonrandomized analyses of randomized trials of statin therapy — that greater reductions in CRP with a statin are associated with larger reductions in cardiovascular risk.[12,13]

Observational studies previously suggested that cholesterol might not be associated with increased cardiovascular risk in patients with chronic kidney disease (CKD).[14–16] By contrast, the Study of Heart and Renal Protection (SHARP, which

randomized 9270 patients with CKD to simvastatin 20 mg plus ezetimibe 10 mg daily or matching placebo), reported that during a median follow-up of 4.9 years, a mean reduction of 0.85 mmol/l LDL-C reduced the risk of major atherosclerotic events (a composite of nonfatal myocardial infarction [MI], coronary death, nonhemorrhagic stroke, and arterial revascularization) by 17%, (rate ratio 0.83, 95% confidence interval [CI] 0.74–0.94). Furthermore, the strength of the causal association was comparable to that observed in trials among people without CKD.[9,17] The most likely explanation for the discrepancy between observational studies and SHARP is that nonrandomized studies in patients with CKD are subject to "reverse causality," whereby CKD (or comorbid disease) causes both lower LDL-C and an increased risk of death, thereby creating an apparent association between low cholesterol concentrations and death.[18,19]

In patients with CKD, inflammation is independently associated with an increased risk of cardiovascular disease.[20–22] It has been suggested that LDL-C may not be associated with cardiovascular disease among patients with evidence of inflammation. In one study of 823 incident dialysis patients, 77% of whom were defined as having evidence of inflammation (albumin $<$ 36 g/l, CRP $\geq$10 mg/l, or IL-6 $\geq$3.09 pg/ml), non–high-density lipoprotein cholesterol (non-HDL-C, a close correlate of LDL-C) was not associated with cardiovascular mortality overall (hazard ratio [HR] per 1 mmol/l higher non-HDL-C 0.97; 95% CI 0.86–1.10), but there was a significant association (HR 2.09; 95% CI 1.02–4.27) among patients without evidence of inflammation.[23]

The SHARP trial provides a further cohort in which to explore the associations of inflammation and LDL-C, because cardiovascular (and nonvascular) outcomes were systematically recorded and measures of lipid profile and CRP were taken at baseline and (in a subset of patients) at follow-up. This affords the opportunity to examine: (i) the association of CRP with risk of cardiovascular disease; (ii) the associations, in randomized and observational analyses, of LDL-C with risk of cardiovascular disease; (iii) whether the degree of underlying inflammation modified the strength of the association between LDL-C and cardiovascular risk in this population; and (iv) the separate associations of CRP and of LDL-C with nonvascular outcomes.

## RESULTS

Among 9270 patients randomized to simvastatin/ezetimibe versus placebo, 8603 had a plasma CRP concentration measured at baseline. Compared with patients with baseline CRP $<$3 mg/l, patients with CRP $\geq$3mg/l were older (63 vs. 61 years), more likely to be male, (64% vs. 61%), had a higher body mass index (28.3 vs. 25.8 kg/m$^2$), had more prior vascular disease (17% vs. 13%), and were more likely to be on dialysis (39% vs. 26%). Mean LDL-C was slightly lower among those with higher CRP (2.74 vs. 2.82 mmol/l) (Table 1).

During a median follow-up of 4.9 years, 2317 patients experienced at least 1 vascular event of any type; 1406 such events were adjudicated to be atherosclerotic and 1342 were nonatherosclerotic. Of 2317 vascular events of any type, 1515 met the definition of major vascular events.

Among 962 patients with measurements of CRP and LDL-C at both baseline and 2.5 years, allocation to simvastatin/ezetimibe produced an average 0.99 mmol/l (SE 0.06 mmol/l) reduction in LDL-C (or a 35% [SE 2.0] proportional

**Table 1 | Baseline characteristics by C-reactive protein group among all 9270 SHARP participants**

| Baseline characteristic | C-reactive protein (mg/l) <3 ($n$ = 4298) | ≥3 ($n$ = 4305) | Not available ($n$ = 667) |
|---|---|---|---|
| CRP (mg/l) (median, IQR) | 1.2 (0.7–2.0) | 7.1 (4.6–13.5) | - |
| Age at randomization (yrs) | 61 (12) | 63 (12) | 62 (12) |
| Men | 2630 (61%) | 2773 (64%) | 397 (60%) |
| Prior vascular disease | 576 (13%) | 733 (17%) | 84 (13%) |
| Diabetes | 917 (21%) | 1034 (24%) | 143 (21%) |
| Current smoker | 532 (12%) | 615 (14%) | 87 (13%) |
| Diastolic blood pressure (mm Hg) | 80 (12) | 78 (13) | 78 (13) |
| Systolic blood pressure (mm Hg) | 139 (21) | 139 (23) | 140 (22) |
| LDL cholesterol (mmol/l) | 2.82 (0.89) | 2.74 (0.86) | 2.70 (0.85) |
| HDL cholesterol (mmol/l) | 1.17 (0.35) | 1.06 (0.32) | 1.10 (0.26) |
| Apolipoprotein A1 (mg/dl) | 139 (29) | 128 (28) | 136 (30) |
| Apolipoprotein B (mg/dl) | 96 (26) | 97 (25) | 94 (25) |
| Albumin (g/l) | 40.7 (3.6) | 39.5 (3.7) | - |
| Body mass index (kg/m$^2$) | 25.8 (4.5) | 28.3 (6.1) | 27.3 (6.0) |
| Ethnicity | | | |
| White | 2944 (68%) | 3258 (76%) | 444 (67%) |
| Black | 88 (2%) | 120 (3%) | 56 (8%) |
| Asian | 1150 (27%) | 803 (19%) | 133 (20%) |
| Other/not specified | 116 (3%) | 124 (3%) | 34 (5%) |
| Co-medication | | | |
| Antiplatelet therapy | 852 (20%) | 1112 (26%) | 141 (21%) |
| ACE inhibitor or ARB | 2447 (57%) | 2263 (53%) | 320 (48%) |
| Beta blocker | 1620 (38%) | 1657 (38%) | 237 (36%) |
| Calcium channel blocker | 1891 (44%) | 1694 (39%) | 255 (38%) |
| Renal status | | | |
| Not on dialysis | 3188 (74%) | 2631 (61%) | 426 (64%) |
| On dialysis | 1110 (26%) | 1674 (39%) | 241 (36%) |
| MDRD-estimated GFR (ml/min per 1.73m$^2$)[a,b] | | | |
| Mean (SD) | 26.9 (13.7) | 26.2 (12.2) | 25.4 (12.4) |
| ≥60 | 61 (2%) | 26 (1%) | 1 (0%) |
| ≥30 to <60 | 1159 (36%) | 924 (35%) | 72 (34%) |
| ≥15 to <30 | 1315 (41%) | 1162 (44%) | 88 (42%) |
| <15 | 652 (20%) | 518 (20%) | 49 (23%) |
| Not available | 1 | 1 | 216 |
| Urinary albumin:creatinine ratio (mg/g)[a,b] | | | |
| Median (IQR) | 206 (50–725) | 206 (51–645) | 206 (206–206) |
| <30 | 584 (20%) | 481 (20%) | 42 (22%) |
| ≥30 to ≤300 | 1120 (38%) | 925 (39%) | 63 (32%) |
| >300 | 1280 (43%) | 987 (41%) | 90 (46%) |
| Not available | 204 | 238 | 231 |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CRP, C-reactive protein; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease Study.
Data are $n$ (%), mean (SD), or median (IQR).
[a]Among patients not on dialysis.
[b]Percentages exclude participants for whom data were not available for that category.