Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

Summary

Background Statin therapy is effective for the prevention of coronary heart disease and stroke in patients with mild-to-moderate chronic kidney disease, but its effects in individuals with more advanced disease, particularly those undergoing dialysis, are uncertain.

Methods We did a meta-analysis of individual participant data from 28 trials (n=183 419), examining effects of statin-based therapy on major vascular events (major coronary event [non-fatal myocardial infarction or coronary death], stroke, or coronary revascularisation) and cause-specific mortality. Participants were subdivided into categories of estimated glomerular filtration rate (eGFR) at baseline. Treatment effects were estimated with rate ratio (RR) per mmol/L reduction in LDL cholesterol.

Findings Overall, statin-based therapy reduced the risk of a first major vascular event by 21% (RR 0·79, 95% CI 0·77–0·81; p<0·0001) per mmol/L reduction in LDL cholesterol. Smaller relative effects on major vascular events were observed as eGFR declined (p=0·008 for trend; RR 0·78, 99% CI 0·75–0·82 for eGFR ≥60 mL/min per 1·73 m²; 0·76, 0·70–0·81 for eGFR 45 to <60 mL/min per 1·73 m²; 0·85, 0·75–0·96 for eGFR 30 to <45 mL/min per 1·73 m²; 0·85, 0·71–1·02 for eGFR <30 mL/min per 1·73 m² and not on dialysis; and 0·94, 0·79–1·11 for patients on dialysis). Analogous trends by baseline renal function were seen for major coronary events (p=0·01 for trend) and vascular mortality (p=0·03 for trend), but there was no significant trend for coronary revascularisation (p=0·90). Reducing LDL cholesterol with statin-based therapy had no effect on non-vascular mortality, irrespective of eGFR.

Interpretation Even after allowing for the smaller reductions in LDL cholesterol achieved by patients with more advanced chronic kidney disease, and for differences in outcome definitions between dialysis trials, the relative reductions in major vascular events observed with statin-based treatment became smaller as eGFR declined, with little evidence of benefit in patients on dialysis. In patients with chronic kidney disease, statin-based regimens should be chosen to maximise the absolute reduction in LDL cholesterol to achieve the largest treatment benefits.

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Introduction

Statin-based therapy is widely used among patients with chronic kidney disease to reduce the risk of atherosclerotic events (myocardial infarction and ischaemic stroke), but there is uncertainty about the effects of such treatment among patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min per 1·73 m². In particular, controversy exists over whether patients undergoing maintenance dialysis benefit from statins.[1] The findings of the 4D[2] and AURORA[3] trials did not show substantial benefits of statins on cardiac disease or stroke among patients undergoing haemodialysis, and no independently significant benefit was observed among the subgroup of patients undergoing dialysis treatment in the SHARP study.[4] Systematic reviews and meta-analyses of trials among patients with chronic kidney disease have reached conflicting conclusions about the effects of statin therapy among individuals on dialysis.[5–14] The Kidney Disease Improving Global Outcomes (KDIGO) lipid management guidelines currently suggest that statin-based therapy should be prescribed for selected high-risk patients with chronic kidney disease, but should not be initiated in individuals who already need dialysis.[15]

Meta-analyses published up to now have several limitations.[5–14] First, in a meta-analysis of individual participant data from large trials of statins,[16] the relative effects of statin therapy on major vascular events in a wide range of patients were proportional to the absolute magnitude of the reduction in LDL cholesterol. Smaller relative decreases in risk among people on dialysis might occur if the absolute reduction in LDL cholesterol achieved among them was smaller than the equivalent reduction among those not on dialysis. Indeed, in the SHARP trial,[4] smaller relative reductions in risk were reported in patients on dialysis as a result of diminished compliance and lower baseline LDL cholesterol. However, the extent to which

Research in context

Evidence before this study

Systematic reviews and tabular meta-analyses to investigate the effects of statin-based therapy on vascular risk among patients with chronic kidney disease, have reached conflicting conclusions about the effects of statins in patients on dialysis. These studies have not taken into account between-trial differences in achieved LDL cholesterol reduction and variations in the definition of coronary death.

Added value of this study

Individual participant data for our meta-analysis were available from the Cholesterol Treatment Trialists' Collaboration database, which has near-complete information on baseline renal function, LDL cholesterol measurements, and subtypes of major vascular events. Furthermore, we included data from the SHARP trial and readjudicated deaths from the AURORA trial. Our meta-analysis provides a more reliable summary than previous tabular meta-analyses of the effects of statin-based therapy on vascular risk among people with different stages of chronic kidney disease.

Implications of all the available evidence

Lowering LDL cholesterol with a statin-based regimen effectively reduces vascular risk among patients with mild-to-moderate chronic kidney disease. However, even after allowing for both outcome adjudication differences and smaller reductions in LDL cholesterol as the estimated glomerular filtration rate declines, there is a trend towards smaller relative risk reductions for a given absolute reduction in LDL cholesterol in both major coronary events and strokes in patients with more advanced chronic kidney disease (with little evidence of benefit in patients on dialysis). In patients with chronic kidney disease, statin-based regimens achieving larger reductions in LDL cholesterol are likely to achieve larger reductions in cardiovascular risk.

variations in absolute reductions in LDL cholesterol account for the results of trials in patients on dialysis has not been investigated. Second, trial findings show that statin therapy does not reduce the risk of non-atherosclerotic cardiac mortality (eg, cardiac arrhythmia, heart failure);[17,18] therefore, an apparent lack of efficacy in patients on dialysis might have arisen if some non-atherosclerotic deaths were mistakenly attributed to coronary heart disease. Differences were recorded in the definitions used in the primary outcomes in the 4D, AURORA, and SHARP trials,[2–4] and the proportions of patients on dialysis who were coded as dying from a coronary cause also varied (appendix p 2). Thus, further investigation is needed to assess the extent to which these differences affected the findings of previous meta-analyses.

See Online for appendix

The Cholesterol Treatment Trialists' (CTT) Collaboration database incorporates individual participant data from trials of statin regimens into which at least 1000 participants were recruited and followed up for at least 2 years.[16] The database includes two trials of statin therapy among patients on dialysis (4D and AURORA) and one among individuals who had a renal transplant (ALERT).[2,3,19] To this database, we added individual participant data from the SHARP trial of simvastatin plus ezetimibe versus placebo among 9270 patients with chronic kidney disease (including 3025 patients on dialysis).[4] By applying consistent outcome categorisation across these renal trials,[3] we aimed to compare the effects of statin-based therapy on major vascular events at different levels of renal function more reliably than has previously been possible.

Methods

Study design and patients

The methods of the CTT Collaboration have been described previously.[16,20–22] In brief, in 1994, we established a collaborative meta-analysis of individual participant data from all trials of statin-based regimens in which at least 1000 patients were followed up for 2 years or longer. We achieved data completeness through electronic literature searches and regular enquiry of researchers and statin manufacturers, with data requested promptly when we identified new trials.

Procedures

During the planning of the analyses, we identified major differences in the proportions of cardiac deaths attributed to coronary heart disease in the AURORA trial[3] compared with other trials of statin-based regimens among patients on dialysis.[2,4] On further enquiry with the AURORA investigators, we established that the outcome adjudication rules in that trial differed substantially from those used in the 4D and SHARP trials. In particular, in AURORA, a death of uncertain cause was attributed to coronary heart disease if, as was frequently the case, there was a previous history of coronary heart disease, whereas in 4D and SHARP, which had broadly similar adjudication rules, deaths were attributed to coronary heart disease only if there was strong evidence that coronary atherosclerosis was the cause (appendix p 3). To ensure that deaths were coded as uniformly as possible within this meta-analysis, we readjudicated all deaths in the AURORA trial before analysis of the combined data. The SHARP trial coding rules for deaths were applied by independent clinicians (MDS, PBM, and AGJ) at the University of Glasgow's Institute of Cardiovascular and Medical Sciences (Glasgow, UK), who had full access to the AURORA trial source data and, for all participants, were unaware of both the original adjudicated outcome and the treatment allocation. The result of this process was that the proportion of deaths attributed to coronary heart disease in patients on dialysis in the AURORA trial fell from 32%

to 8% (compared with 11% in 4D and 8% in SHARP), and the proportion of other cardiac deaths in patients on dialysis rose from 5% to 23% (compared with 33% in 4D and 19% in SHARP; appendix p 2).

Outcomes and statistical analysis

The main outcomes of our meta-analysis are major vascular events, defined as major coronary events (ie, non-fatal myocardial infarction or death from coronary heart disease), coronary revascularisation, or stroke; and mortality, subdivided into vascular and non-vascular causes. We subdivided all participants, including those with a functioning kidney transplant, by baseline renal function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[23] equation for eGFR. We used the following categories of eGFR: 60 mL/min per 1·73 m² or greater; 45 mL/min per 1·73 m² to less than 60 mL/min per 1·73 m²; 30 mL/min per 1·73 m² to less than 45 mL/min per 1·73 m²; less than 30 mL/min per 1·73 m² and not on dialysis; or receiving dialysis (haemodialysis or peritoneal dialysis) at randomisation. We used Cox proportional-hazard models analogous to those reported previously,[21] but using the readjudicated AURORA data and categories of baseline renal function as an additional independent variable, to model the 5-year baseline risk of major vascular events among patients allocated to either control or less intensive statin therapy (appendix pp 4–6). On the basis of these risk prediction models, we categorised participants into one of three baseline 5-year risk categories for major vascular events (<20%, 20% to <30%, or ≥30%).

Analyses of treatment effect were done according to the intention-to-treat principle—ie, they included all participants, irrespective of whether they received their allocated treatment. Analyses of the effects of statin-based regimens on outcome rates within each included trial were derived from the log-rank (o–e) statistic and its variance (v) for first events. Findings of a previous CTT meta-analysis showed that the principal source of between-trial heterogeneity in the effects of statins on major vascular events is the size of the differences in the achieved absolute LDL cholesterol reduction at 1 year (d).[16] Therefore, as previously described,[16,20,21] we first standardised the average log event rate ratio (RR) for each trial (derived from the o–e statistic and v) to correspond to an effect per 1·0 mmol/L (39 mg/dL) reduction in LDL cholesterol, and then we combined the standardised results in a meta-analysis, with weights proportional to the amount of statistical information (ie, inverse-variance weighting). Specifically, we calculated the log RR per mmol/L as S/V with variance 1/V (yielding a 95% CI $S/V \pm 1{\cdot}96/\sqrt{V}$), where S is the sum over all trials of $d(o–e)$ and V is the sum over all trials of d^2v. For subgroup analyses in different categories of baseline renal function, the weight for each trial was generally the absolute difference in LDL cholesterol recorded for the whole trial, apart from in SHARP (the only trial to enrol patients with chronic kidney disease both on dialysis and not on dialysis), for which separate dialysis and non-dialysis subgroup-specific weights were used, since the LDL cholesterol difference differed substantially between these subgroups (appendix p 7).[4]

We decided a priori not to calculate absolute treatment effects directly from available trials, since we noted that the underlying vascular risks in the trials contributing patients to each category of eGFR were determined principally by factors unrelated to kidney function and, hence, absolute risk reductions would not be generalisable. For example, trials contributing data for patients with mild or no chronic kidney disease were done mainly in patients with a previous history of coronary heart disease who were, therefore, at high risk, whereas data for patients with chronic kidney disease not on dialysis came mainly from the SHARP trial,[4] which excluded patients with previous coronary heart disease. Instead, we aimed to calculate RRs per 1·0 mmol/L at different levels of eGFR, which can be applied to contemporaneous and region-specific event rates to calculate the absolute effects of treatment.

In the forest plots, we show 95% CIs only with summary RRs; all other RRs are presented with 99% CIs to allow for multiple hypothesis testing in subgroup analyses. We compared RRs per mmol/L reduction in LDL cholesterol in different categories of baseline renal function and of risk of major vascular events using χ^2 tests for trend. In sensitivity analyses, we recalculated trend tests after excluding patients on dialysis, to assess whether any positive findings were dependent on results in this category. We did the statistical analyses using SAS version 9.3 and R version 2.11.1.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. WGH, JE, BM, LB, and CB had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

At the time of the present analysis (May 11, 2016), individual participant data had been provided from 28 trials with 183 419 participants,[2–4,17–19,24–45] including all trials in renal populations.[2–4,19] Data were unavailable for three trials: one trial of atorvastatin versus placebo in 4731 patients with a history of cerebrovascular disease;[46] one trial of atorvastatin versus usual care in 1600 patients with coronary heart disease;[47] and one trial of simvastatin plus ezetimibe versus placebo in 1873 patients with aortic stenosis.[48] Less than 1% of participants in these trials had a baseline eGFR below 30 mL/min per 1·73 m².[48–50]

In 23 trials, a statin-based regimen was compared with control (143 807 participants; mean baseline LDL cholesterol 3·64 [SD 0·92] mmol/L; mean difference

in LDL cholesterol at 1 year –1·08 mmol/L; median follow-up 4·8 years).[2–4,17–19,24–40] In the other five trials, an intensive statin regimen was assessed against a standard statin regimen (39 612 participants; mean baseline LDL cholesterol 2·53 [SD 0·63] mmol/L; mean difference in LDL cholesterol at 1 year –0·51 mmol/L; median follow-up 5·1 years).[41–45] Overall, the mean age of participants was 62·6 years (SD 9·6), 133 229 (73%) patients were men, 105 517 (58%) had vascular disease, and 35 781 (20%) had diabetes (table).

Data for baseline renal function were available for 181 032 (99%) participants: 123 560 (68%) people had an eGFR of 60 mL/min per 1·73 m² or greater; 34 417 (19%) had an eGFR of 45 mL/min per 1·73 m² to less than 60 mL/min per 1·73 m²; 10 634 (6%) had an eGFR of 30 mL/min per 1·73 m² to less than 45 mL/min per 1·73 m²; 5368 (3%) had an eGFR less than 30 mL/min per 1·73 m² and were not on dialysis; and 7053 (4%) were on dialysis (6557 haemodialysis and 496 peritoneal dialysis) at randomisation (table). Patients from the SHARP trial

	Baseline renal function*					All patients (n=183 419)
	eGFR ≥60 mL/min per 1·73m² (n=123 560)	eGFR 45 to <60 mL/min per 1·73m² (n=34 417)	eGFR 30 to <45 mL/min per 1·73m² (n=10 634)	eGFR <30 mL/min per 1·73m², not on dialysis (n=5368)	On dialysis (n=7053)	
Demographic characteristics						
Age (years)	60·7 (9·0)	67·4 (8·1)	69·3 (10·1)	64·2 (12·3)	62·2 (10·5)	62·6 (9·6)
Men	94 770 (77%)	23 111 (67%)	6500 (61%)	3008 (56%)	4318 (61%)	133 229 (73%)
Women	28 790 (23%)	11 306 (33%)	4134 (39%)	2360 (44%)	2735 (39%)	50 190 (27%)
Current smokers	25 970 (21%)	5183 (15%)	1444 (14%)	641 (12%)	1009 (14%)	34 896 (19%)
Renal function						
eGFR (mL/min per 1·73 m²)	79 (13)	54 (4)	39 (4)	20 (7)	NA	69 (19)
Functioning kidney transplant†	500 (<1%)	668 (2%)	613 (6%)	247 (5%)	NA	2102 (1%)
Disease history						
Diabetes	22 306 (19%)	6599 (19%)	2444 (23%)	1265 (24%)	2654 (38%)	35 781 (20%)
Coronary heart disease	64 027 (52%)	19 650 (57%)	5518 (52%)	850 (16%)	1383 (20%)	92 591 (50%)
Other vascular disease	7396 (6%)	2559 (7%)	1134 (11%)	612 (11%)	1099 (16%)	12 926 (7%)
No history of vascular disease	52 137 (42%)	12 208 (35%)	3982 (37%)	3906 (73%)	4571 (65%)	77 902 (42%)
Blood pressure						
Treated hypertension	57 281 (47%)	20 390 (60%)	7609 (72%)	4491 (84%)	5357 (76%)	96 354 (53%)
Systolic blood pressure (mm Hg)	137·7 (20·6)	140·7 (21·9)	140·4 (22·8)	139·7 (21·9)	139·1 (24·0)	138·6 (21·2)
Diastolic blood pressure (mm Hg)	81·4 (11·2)	80·5 (11·3)	79·4 (11·9)	79·3 (12·5)	76·6 (12·7)	80·9 (11·4)
Physical measurements						
BMI (kg/m²)	27·7 (4·7)	27·7 (4·5)	27·6 (4·8)	27·2 (5·4)	26·2 (5·4)	27·6 (4·8)
Lipid measurements						
Total cholesterol (mmol/L)	5·38 (1·08)	5·33 (1·05)	5·43 (1·17)	5·56 (1·31)	4·89 (1·22)	5·36 (1·08)
LDL cholesterol (mmol/L)	3·36 (0·96)	3·30 (0·93)	3·33 (0·99)	2·98 (0·96)	2·70 (0·90)	3·31 (0·96)
HDL cholesterol (mmol/L)	1·17 (0·36)	1·17 (0·35)	1·16 (0·36)	1·14 (0·35)	1·08 (0·38)	1·17 (0·36)
Triglycerides (mmol/L)	1·78 (1·02)	1·83 (1·00)	2·03 (1·21)	2·24 (1·42)	2·21 (1·66)	1·83 (1·08)
Risk of major vascular event						
5-year risk <20%	86 273 (70%)	17 975 (52%)	4887 (46%)	3772 (70%)	3503 (50%)	117 900 (64%)
5-year risk 20% to <30%	26 971 (22%)	11 021 (32%)	2998 (28%)	888 (17%)	1511 (21%)	43 758 (24%)
5-year risk ≥30%	10 316 (8%)	5421 (16%)	2749 (26%)	708 (13%)	2039 (29%)	21 761 (12%)
Follow-up (years)						
Median (IQR) follow up among survivors‡	4·9 (4·5–5·3)	4·9 (4·5–5·4)	4·9 (4·5–5·4)	4·9 (4·5–5·4)	4·7 (3·9–5·4)	4·9 (4·4–5·3)

Data are mean (SD) for continuous variables and number of participants (%) for categorical variables, unless otherwise stated. eGFR=estimated glomerular filtration rate (calculated with the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula). NA=not applicable. BMI=body-mass index. *Data from 2387 participants without a baseline creatinine measurement contribute only to the All patients column. †All participants with a functioning transplant were from the ALERT trial (appendix p 8). ‡Median follow-up among survivors weighted by trial-specific variances of observed log-rank (*o–e*) for major vascular events.

Table: **Baseline characteristics of participants, by renal function**

accounted for about four-fifths of those with an eGFR less than 30 mL/min per 1·73 m² and not on dialysis at randomisation, but for only about a fifth of patients with an eGFR of 30 mL/min per 1·73 m² to less than 45 mL/min per 1·73 m², with trials among elderly people,[33] patients with heart failure,[17,18] and the Heart Protection Study[31] accounting for a large proportion of the remainder (appendix p 8).

Compared with patients with an eGFR of at least 60 mL/min per 1·73 m², a larger proportion of individuals with an eGFR less than 30 mL/min per 1·73 m² (whether on dialysis or not) had diabetes and a smaller proportion had vascular disease (mainly because people with a definite history of coronary heart disease were excluded from the SHARP trial). Compared with patients with an eGFR of at least 30 mL/min per 1·73 m², those with eGFR less than 30 mL/min per 1·73 m² (including those on dialysis) also had lower concentrations of LDL cholesterol and HDL cholesterol, and higher concentrations of triglycerides at randomisation (table; appendix p 8). After adjustment for the particular trial into which a patient had been recruited, and for other prognostic variables, decreased eGFR was associated independently with an increased risk of major vascular events (appendix pp 5, 6).

Overall, statin-based treatment reduced the risk of a first major vascular event by 21% (RR 0·79, 95% CI 0·77–0·81; p<0·0001) per mmol/L reduction in LDL cholesterol, including reduced risks of major coronary events (0·76, 0·73–0·79) and stroke (0·84, 0·80–0·89;

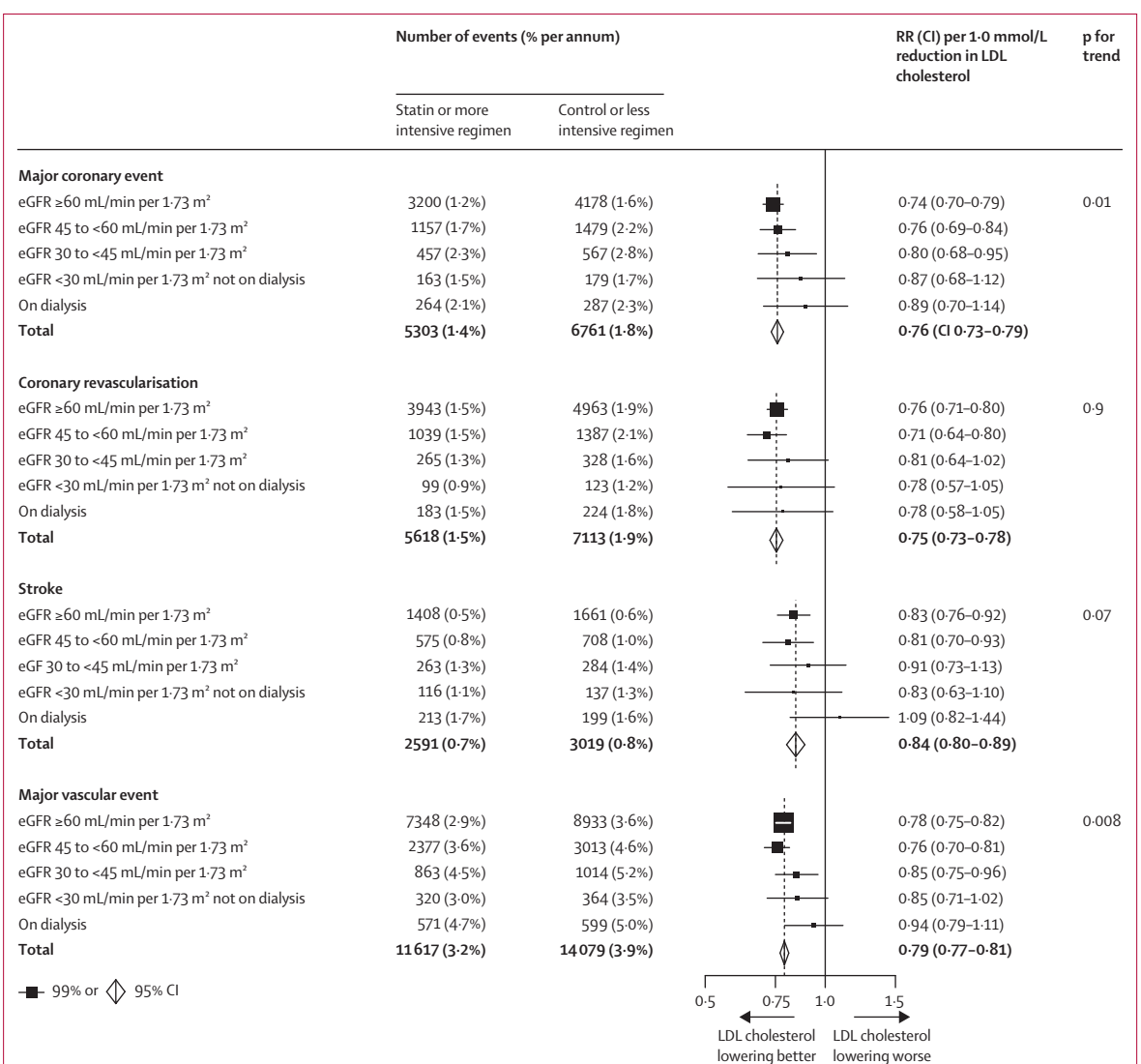

Figure 1: **Effects on major vascular events per mmol/L reduction in LDL cholesterol, by baseline renal function**
Data for participants with missing creatinine values at baseline are included in totals. Black squares and horizontal lines represent 99% CIs. White diamonds represent 95% CIs. Vertical dotted line represents overall RR for each outcome. eGFR=estimated glomerular filtration rate. RR=rate ratio.

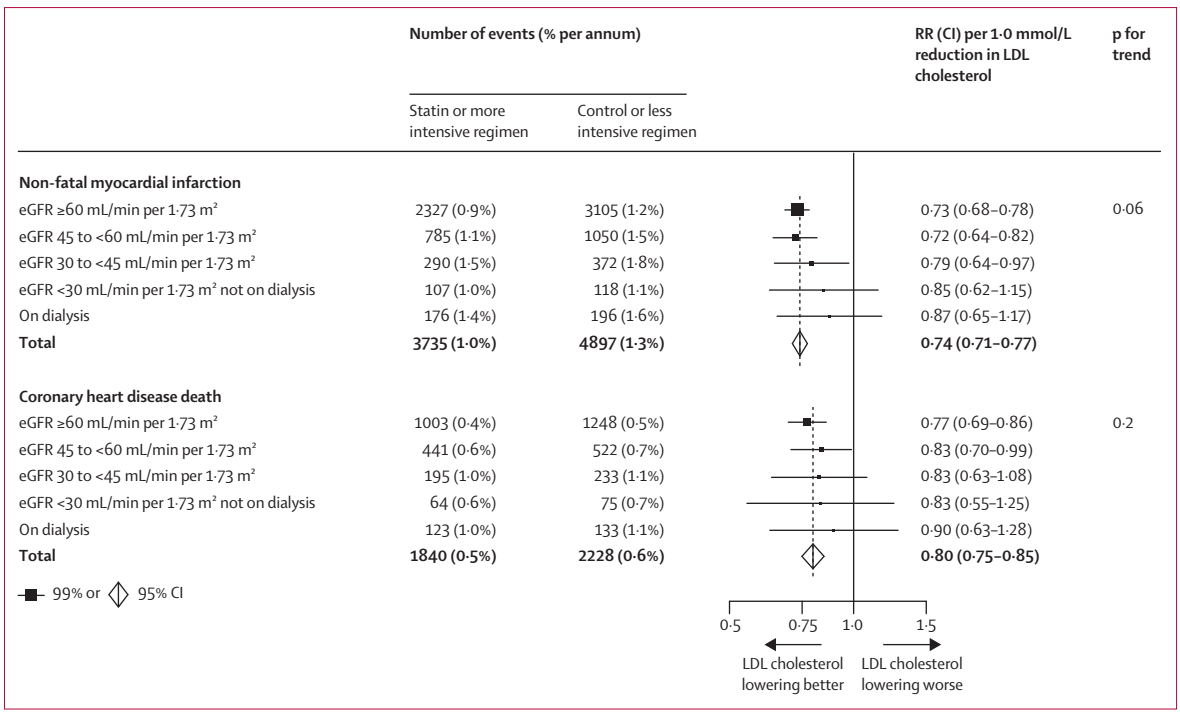

Figure 2: **Effects on major coronary events per mmol/L reduction in LDL cholesterol, by baseline renal function**
Data for participants with missing creatinine values at baseline are included in totals. Black squares and horizontal lines represent 99% CIs. White diamonds represent 95% CIs. Vertical dotted line represents overall RR for each outcome. eGFR=estimated glomerular filtration rate. RR=rate ratio.

figure 1). There was a significant trend towards smaller proportional effects on major vascular events with lower eGFR at randomisation (p=0·008 for trend). Within each baseline renal function category, the proportional reduction in major vascular events was similar, irrespective of estimated cardiovascular risk level (all trend p values >0·05; appendix p 9). The trend towards smaller proportional effects on major vascular events with lower eGFR was attributable chiefly to major coronary events (p=0·01 for trend) and stroke (p=0·07 for trend; figure 1). The trend in proportional effects observed for major coronary events resulted from combining non-fatal myocardial infarction (p=0·06 for trend) and coronary mortality (p=0·2 for trend; figure 2). Overall, statin-based treatment reduced the need for coronary revascularisation procedures by 25% (RR 0·75, 95% CI 0·73–0·78, p<0·0001) per mmol/L LDL cholesterol reduction (figure 1); however, no trend by baseline renal function was observed for this outcome (p=0·9 for trend).

The risk of vascular death was reduced overall by 12% (RR 0·88, 95% CI 0·85–0·91; p<0·0001) per mmol/L reduction in LDL cholesterol (figure 3), and there was a significant trend towards smaller proportional effects on vascular mortality with worse baseline renal function (p=0·03 for trend). However, reducing LDL cholesterol with statin-based therapy had no significant effect on non-vascular mortality at any level of renal function. A significant trend towards smaller effects on all-cause mortality was seen with lower eGFR (p=0·03 for trend; figure 3). In sensitivity analyses, in which we excluded patients undergoing dialysis at randomisation, no significant trends were recorded in RRs (per mmol/L LDL cholesterol reduction) for vascular outcomes (major coronary events, stroke, coronary revascularisation, major vascular events) or deaths across eGFR categories (all trend p values >0·05; appendix pp 10, 11).

Discussion

There has been considerable uncertainty about the cardiovascular effects of reducing LDL cholesterol in patients with advanced chronic kidney disease, particularly those on dialysis, with previous meta-analyses of published data reaching conflicting conclusions.[1,5–15] Availability of individual participant data from 28 trials of statin-based therapy in patients with various degrees of renal impairment, and readjudication of all deaths in the AURORA trial,[3] has allowed us to overcome many of the limitations of previous meta-analyses.[5–14] Our results show that, even after allowing for somewhat smaller reductions in LDL cholesterol as GFR declines, there is a trend towards smaller relative risk reductions for major coronary events and strokes. In particular, there was little evidence that statin-based therapy was effective in patients starting treatment after dialysis had been initiated.

Perhaps because several trials of statin-based therapy have been done solely among patients on dialysis,[2,3]

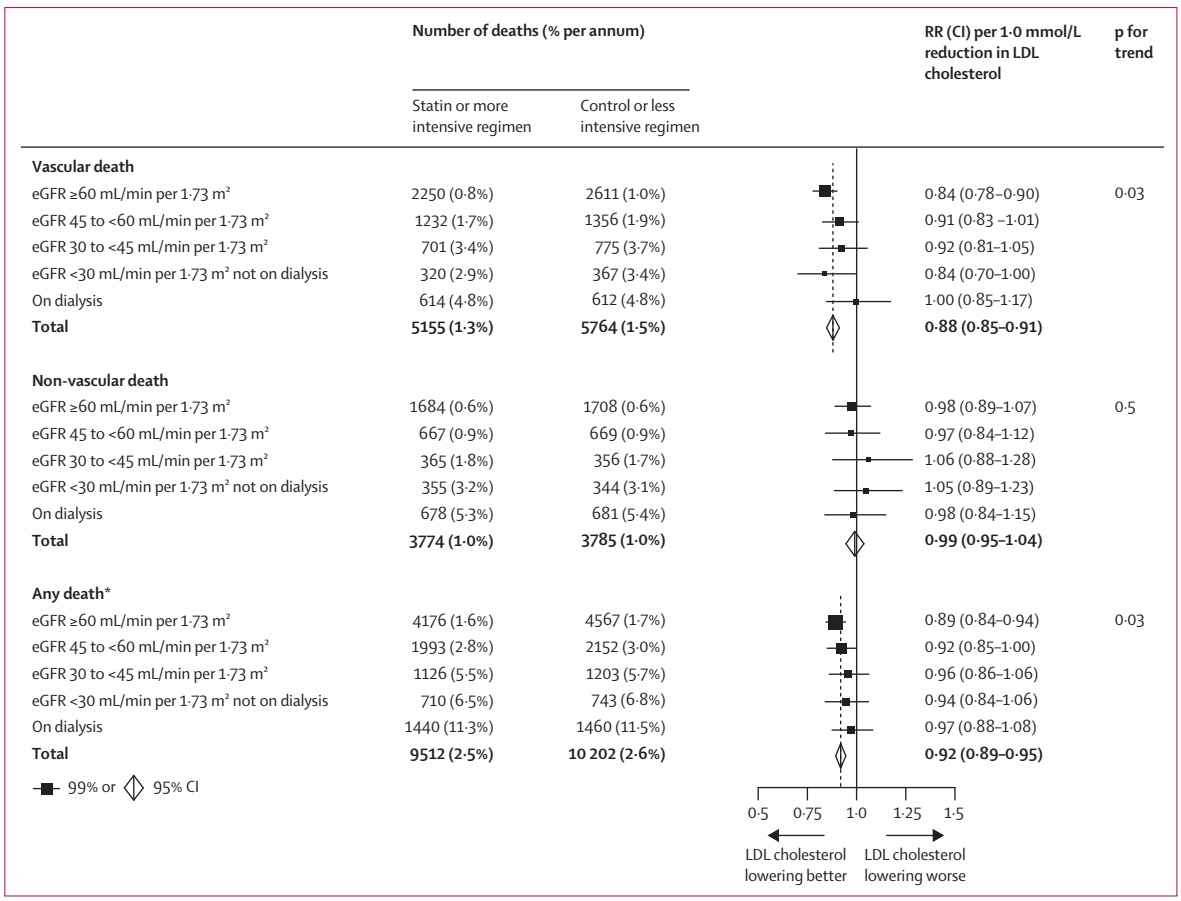

Figure 3: **Effects on cause-specific mortality per mmol/L reduction in LDL cholesterol, by baseline renal function**
Data for participants with missing creatinine values at baseline are included in totals. Black squares and horizontal lines represent 99% CIs. White diamonds represent 95% CIs. Vertical dotted line represents overall RR for each outcome. eGFR=estimated glomerular filtration rate. RR=rate ratio.*Includes 583 deaths from an unknown cause in the statin or more intensive regimen group and 653 deaths from an unknown cause in the control or less intensive regimen group.

treatment guidelines have generally considered the evidence among patients not on dialysis separately from those on dialysis.[15] In our meta-analysis, we looked at trends in treatment efficacy across all stages of chronic kidney disease, including patients on dialysis. Despite inclusion of all relevant large-scale trials of statin-based therapy among patients with chronic kidney disease, data were insufficient to be able to differentiate reliably between a gradual diminution of the relative reductions in risk of major vascular events with lower GFR (at least below about 30 mL/min per 1·73 m²) or a step-wise reduction in efficacy when a patient commences dialysis. Arguments can be made for either interpretation: a gradual diminution is predicted by findings of observational studies showing weaker associations between LDL cholesterol and myocardial infarction among people with impaired renal function,[51] but if data from dialysis trials were to be excluded from our analyses then the relative benefits of treatment would not differ significantly among the other categories of patients not on dialysis (appendix pp 10, 11).[2–4]

The pattern of diminished vascular benefit with lower renal function might result, at least partly, from the combination of two features that are peculiar to patients with chronic kidney disease. First, the proportion of cardiac deaths attributable to coronary heart disease—and, hence, potentially avoidable by reducing LDL cholesterol—becomes smaller as eGFR declines.[52,53] In our meta-analysis, for example, coronary heart disease was the attributed cause of 57% of cardiac deaths among individuals with an eGFR of 60 mL/min per 1·73 m² or greater, but was the cause of only 26% and 27% of such deaths among patients with an eGFR less than 30 mL/min per 1·73 m² not on dialysis and those on dialysis, respectively (appendix p 2). Second, the cause of cardiac deaths (and of non-fatal cardiac events) is subject to misclassification because of their frequently atypical clinical presentation[54] and the difficulty of interpreting raised biomarkers of cardiac damage in chronic kidney disease.[55,56]

In our meta-analysis, because trial populations were highly selected, the event rates in each category of eGFR are not a reliable indication of the absolute levels of risks that would be seen in the clinic. For example, the SHARP study contributed 4201 (78%) of 5368 participants to the category with an eGFR less than 30 mL/min per 1·73 m²

and not on dialysis, but, patients with a previous history of coronary heart disease were excluded from the trial, so the mean risks of major vascular events were lower than would be seen in unselected patients with similar eGFRs. Conversely, 25 168 (56%) of 45 051 patients with an eGFR between 30 mL/min per 1·73 m² and 60 mL/min per 1·73 m² had a previous history of coronary heart disease (table); thus, the mean risks in these eGFR categories were higher than would be expected for unselected patients. Previous analyses of the CTT database have clearly shown that, across different statin regimens, the relative risk reduction is determined principally by the absolute reduction in LDL cholesterol achieved,[16] whereas the findings of the present analysis suggest that once GFR is reduced substantially the relative effects of statins might be smaller. Calculations of absolute effects on major vascular events are, therefore, derived most appropriately from applying GFR-specific RRs from our meta-analysis to absolute risks reported in unselected cohorts of people with chronic kidney disease. Results of cohort studies have shown that patients with chronic kidney disease are at high risk of atherosclerotic disease,[57] and in a meta-analysis of such cohorts, every 30% decrement in eGFR was associated with a 29% increase in risk of a major vascular event.[58] Therefore, a change from an eGFR of 60 mL/min per 1·73 m² to 10 mL/min per 1·73 m² (a notional threshold for commencing dialysis) would correspond to about four times the risk. Since there was also a fourfold difference in relative risk reductions in the corresponding categories in our meta-analysis (24% *vs* 6% per mmol/L reduction in LDL cholesterol), the absolute benefits of statin-based therapy might be of broadly comparable magnitude among the wide range of patients with chronic kidney disease, even with diminishing relative efficacy as eGFR falls. The absolute magnitude of any such benefit, however, can vary regionally—eg, there is substantial geographical variation in the prevalence of diabetes, a major risk factor for vascular disease,[59] as a cause of chronic kidney disease.[60]

Despite the relative absence of data from trials of statin-based therapy in advanced chronic kidney disease, such treatment has been shown to be safe with respect to adverse events.[2–4,13,61] As a result, many nephrologists might consider offering such treatment to their patients. If so, previous results from a CTT meta-analysis[16] suggest that any benefits of such treatment would be increased if larger absolute reductions in LDL cholesterol can be achieved. Since LDL cholesterol in patients with advanced chronic kidney disease is, on average, lower than in other high-risk populations (table),[62] achieving lower concentrations of LDL cholesterol would generally require higher-intensity regimens. However, renal impairment is a risk factor for myopathy with high-dose simvastatin,[63] and other high-dose statin regimens might also pose an unacceptable risk of myopathy in patients with advanced chronic kidney disease. Since trials have not established the safety of atorvastatin 40–80 mg in individuals with an eGFR less than 30 mL/min per 1·73 m², the UK's National Institute for Health and Care Excellence (NICE) currently recommends atorvastatin 20 mg once daily in populations with chronic kidney disease.[64] An alternative strategy to high-dose statins in patients with chronic kidney disease is the combination of a moderate-dose statin with the cholesterol absorption inhibitor ezetimibe, which was used successfully in the SHARP trial.[4]

Although our meta-analysis is strengthened by inclusion of near-complete information on the effects of statin-based therapy on major vascular events at different levels of renal function in large trials of statins, it has some limitations. The most important limitation is the relative paucity of evidence from randomised trials among patients with chronic kidney disease compared with other high-risk patients. A further limitation is that there is no agreed method for determining the precise cause or causes of vascular death among patients with more advanced chronic kidney disease. Lastly, the CTT Collaboration did not request information on adverse events other than vascular outcomes, deaths, and cancers (cancer data reported elsewhere[65]), so it is currently not possible to study the effects of statins on particular adverse events (eg, muscle pain) or to investigate statin adherence and discontinuations, beyond what has been reported by individual trials. The CTT Collaboration is, however, currently obtaining the necessary data to do this assessment.[66] Nevertheless, our meta-analysis does provide clear evidence that statin-based therapy was beneficial in a wide range of patients with chronic kidney disease and helps to reinforce the important point that the benefits could be enhanced by using treatments that achieve a large absolute reduction in LDL cholesterol in such patients.

In conclusion, previous tabular meta-analyses of randomised trials of statin therapy in patients with chronic kidney disease could not adjust for differences in the magnitude of reductions in LDL cholesterol and differences in the definitions of outcomes between trials in patients on dialysis. Even after allowing for smaller LDL cholesterol reductions achieved among patients with more severe chronic kidney disease (particularly those already on dialysis), and for outcome adjudication differences, there was a trend towards smaller reductions in major vascular events as eGFR declines.

Contributors

CB, AK, JS, and RC established the Cholesterol Treatment Trialists' (CTT) Collaboration. CB, WGH, and JE had the idea for this study. RC, MJL, CB, BF, CW, CR, WGH, JE, AGJ, HH, RH, AK, and JS contributed to data collection. MDS, PBM, WGH, AGJ, and BF readjudicated AURORA deaths. CR and WGH contributed to outcome categorisation. WGH, JE, BM, and CB contributed to analysis specification and interpretation. LB, JE, and BM contributed to statistical analyses and figures. WGH wrote the first draft of the manuscript and all authors revised the report. All collaborators had an opportunity to contribute to the interpretation of the results and to drafting of the report. WGH, JE, BM, LB, and CB had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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Declaration of interests

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