Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Wanyin Hou1, Jicheng Lv1*, Vlado Perkovic2, Lihong Yang3, Na Zhao1, Meg J. Jardine2, Alan Cass2, Hong Zhang1, and Haiyan Wang1

1Renal Division, Peking University First Hospital, Institute of Nephrology, Peking University and Key Laboratory of Renal Disease, Ministry of Health of China, No. 8, Xishiku Street, Xicheng District, Beijing, China; 2The George Institute for Global Health, University of Sydney, New South Wales, Australia; and 3Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, Guangdong, China

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Aims
The effects of statin therapy in patients with chronic kidney disease (CKD) remain uncertain. We undertook a systematic review and meta-analysis to investigate the effects of statin on major clinical outcomes.

Methods and results
We systematically searched MEDLINE, Embase, and the Cochrane Library for trials published between 1970 and November 2011. We included prospective, randomized, controlled trials assessing the effects of statins on cardiovascular outcomes in people with kidney disease. Summary estimates of relative risk (RR) reductions were calculated with a random effects model. Thirty-one trials that include at least one event were identified, providing data for 48,429 patients with CKD, including 6,690 major cardiovascular events and 6,653 deaths. Statin therapy produced a 23% RR reduction (16–30) for major cardiovascular events (P<0.001), an 18% RR reduction (8–27) for coronary events, and 9% (1–16) reduction in cardiovascular or all-cause deaths, but had no significantly effect on stroke (21%, −12 to 44) or no clear effect on kidney failure events (5%, −21 to 10). Adverse events were not significantly increased by statins, including hepatic (RR 1.13, 95% CI 0.92–1.39) or muscular disorders (RR 1.02, 95% CI 0.95–1.09). Subgroup analysis demonstrated the relative effects of statin therapy in CKD were significantly reduced in people with advanced CKD (P<0.001) but that the absolute risk reductions were comparable.

Conclusion
Statin therapy reduces the risk of major cardiovascular events in patients with chronic kidney disease including those receiving dialysis.

Keywords
Cardiovascular events • Statin • Chronic kidney disease • Meta-analysis

Introduction
Chronic kidney disease (CKD) is a major public health problem.1 Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality among people with CKD worldwide, with rates of cardiovascular events and mortality consistently increasing as kidney function declines.2,3 Dialysis patients have mortality rates up to 40-fold higher than the general population, with CVD being responsible for up to 50% of these deaths.3 Patients with CKD have higher prevalence of a number of risk factors for CVD, including lipid abnormalities, hypertension, obesity, and diabetes. Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines have recommended statin therapy for the prevention of CVD in patients with CKD and high-LDL cholesterol (LDL-C) levels.5 However, the value of this approach continues to be debated, particularly in those with the most advanced kidney dysfunction. Levels of cholesterol in patients with kidney disease do not always have the same log-linear relationship with cardiovascular events observed in the general population.6 Indeed, a ‘U’-shaped or inverse relationship has been described in cohort studies of dialysis patients where people with the lowest levels of LDL-C have the worst outcomes. The burden of CVD may not be predominantly due to atherosclerotic disease.
in people with severely decreased GFR when compared with people with normal renal function. Emerging data suggest the pattern of cardiovascular pathology may be different in advanced CKD, with vascular stiffness and calcification, structural heart disease, and sympathetic overactivity contributing to an increasing risk of cardiac arrhythmia and heart failure.7 Thus, the effect of statin therapy may be less compared with the general population. In the past few years, several large-scale trials of statin therapy in people with CKD have been completed, including the recent large SHARP (Study of Heart and Renal Protection) trial.8 Although some of these trials have shown benefit,9 others have shown no effect,9,10 leading to uncertainty about the presence and magnitude of cardiovascular protective effects and therefore difficulties for clinicians in the interpretation of the results.

Two recent overviews have investigated the effect of statin in patients with CKD. However, both have not evaluated the effect of kidney function on the statin therapy.11,12 In this systematic review, we sought to synthesize all the available clinical trial data and define better the balance of risks and benefits of statin in patients with CKD and also the effect of kidney function on statin use.

Methods

Data sources, search strategy, and selection criteria

We performed a systematic review of the published literature according to the approach recommended by the statement for the conduct of meta-analyses of intervention studies. We included data from randomized, controlled trials in which statin was given for at least 6 months to patients with CKD. These data were extracted either from studies conducted solely in people with kidney disease, or from subsets of other trials where data on the CKD population could be obtained.

Relevant studies were identified by searching the following data sources: MEDLINE via Ovid (from 1950 to November 2011), Embase (from 1966 to November 2011), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction), with relevant text words and medical subject headings that included all spellings of ‘kidney disease’, ‘dyslipidemia’, ‘hypercholesterolemia’, ‘cardiovascular disease’, ‘myocardial infarction’, ‘revascularisation’, ‘stroke’, ‘simvastatin’, ‘atorvastatin’, ‘rosuvastatin’, ‘pravastatin’ (see Supplementary material online). Trials were considered without language restriction. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. The ClinicalTrials.gov website was also searched for randomized trials that were registered as completed but not yet published.

The literature search, data extraction, and quality assessment were undertaken independently by two authors (W.H. and L.Y.) using a standardized approach. All completed randomized, controlled trials assessing the effects of statin compared with placebo and/or compared with conventional therapy in CKD, and that reported one or more of the primary or secondary outcomes, were eligible for inclusion. Trials that recruited patients with kidney transplants were not included in this study.

Data extraction, quality assessment, and outcome estimation

Published reports were obtained for each eligible trial, and relevant information was extracted into a spreadsheet. The data sought included baseline patient characteristics (age, sex, history of diabetes, history of CVD, mean systolic and diastolic blood pressure values, lipid concentrations), statin used, dose of drug, follow-up duration, change in LDL-C concentrations, outcome events, and adverse events. Study quality was judged by the proper conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, the provision of a description of the eligibility criteria, completeness of follow-up, and the use of an intention-to-treat analysis, and was quantified with the Jadad scale.13 Any disagreement in the abstracted data was adjudicated by a third reviewer (J.L.).

We collected data for major cardiovascular events (defined as a composite including fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, revascularization procedures, cardiovascular death, and heart failure, or comparable definitions used by individual authors), cardiovascular mortality, all-cause death, new onset cancer, and other drug-related adverse events. We listed all cardiovascular events for each included studies in Supplementary material online, Table S2. Trials that compare high- vs. low-dose statin therapy met the inclusion criteria but in a separate analysis. Kidney failure events were defined as a 25% decrease in the estimated GFR, doubling of serum creatinine, or end stage renal disease (ESRD) as defined by the authors of each study.

When required quantitative data were not provided in the relevant article from the text, we use the g3 data software (http://www.frantz.fi/software/g3data.php) to extract exact numbers from published figures.

Statistical analysis

Individual patient data were not available from the studies in this analysis, so tabular data were used. Individual study relative risks (RRs) and 95% CIs were calculated from event numbers and total population at risk extracted from each trial, using a standard method14 before data pooling. In the calculation of risk ratios, the total number of patients randomly assigned in each group was used as the denominator. Summary estimates of risk ratios were obtained with a random

Figure 1 Identification process for eligible studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Inclusion criteria</th>
<th>Definition of CKD</th>
<th>Duration of time, year</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Mean age, years</th>
<th>LDL-C, mmol/L</th>
<th>eGFR, mL/min/1.73 m²</th>
<th>Number of patients</th>
<th>History of CVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2011</td>
<td>2011</td>
<td>PD &gt; 3 months</td>
<td>Dialysis</td>
<td>0.5</td>
<td>Rosuvastatin 10 mg/day + ARB 80 mg/day</td>
<td>Placebo + ARB 80 mg/day</td>
<td>49</td>
<td>4.83</td>
<td>NA</td>
<td>124</td>
<td>0</td>
</tr>
<tr>
<td>ATTEMP</td>
<td>2011</td>
<td>CKD stage 3 patients with metabolic syndrome, no CVD or DM</td>
<td>CKD stage 3, eGFR 30–59 mL/min/1.73 m²</td>
<td>3.5</td>
<td>Atorvastatin LDL-C target on 100 mg/L</td>
<td>Atorvastatin LDL-C target on 130 mg/dL</td>
<td>57</td>
<td>4.37</td>
<td>47.60</td>
<td>349</td>
<td>2</td>
</tr>
<tr>
<td>SHARP</td>
<td>2011</td>
<td>History of CKD, age &gt; 40, Scr: men &gt;150 μmol/L, women &gt;130 μmol/L</td>
<td>Increased Scr: men &gt;150 μmol/L, women &gt;130 μmol/L</td>
<td>4</td>
<td>Simvastatin + ezetimibe</td>
<td>Placebo</td>
<td>62</td>
<td>2.70</td>
<td>26.60</td>
<td>9438</td>
<td>15</td>
</tr>
<tr>
<td>Air Force/</td>
<td>2009</td>
<td>Hyperlipidaemia, no CVD or DM</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5.2</td>
<td>Lovastatin</td>
<td>Placebo</td>
<td>62</td>
<td>3.90</td>
<td>53.00</td>
<td>304</td>
<td>0</td>
</tr>
<tr>
<td>LORD</td>
<td>2008</td>
<td>History of CKD, Scr &gt; 120 μmol/L</td>
<td>Increased Scr 120 μmol/L</td>
<td>2.5</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>60</td>
<td>3.22</td>
<td>31.90</td>
<td>123</td>
<td>17</td>
</tr>
<tr>
<td>PANDA</td>
<td>2010</td>
<td>Type 2 DM</td>
<td>Urinary albumin creatinine &gt; 5 mg /mmol</td>
<td>2.1</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>64</td>
<td>3.06</td>
<td>71.70</td>
<td>119</td>
<td>28</td>
</tr>
<tr>
<td>MEGA</td>
<td>2009</td>
<td>No history of CHD and/or stroke</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5.3</td>
<td>Pravastatin</td>
<td>Diet therapy</td>
<td>NA</td>
<td>4.00</td>
<td>52.60</td>
<td>2978</td>
<td>0</td>
</tr>
<tr>
<td>AURORA</td>
<td>2009</td>
<td>ESRD patients, regular haemodialysis for at least 3 months</td>
<td>Dialysis</td>
<td>3.2</td>
<td>Rosuvastatin</td>
<td>Placebo</td>
<td>64</td>
<td>2.59</td>
<td>NA</td>
<td>2776</td>
<td>40</td>
</tr>
<tr>
<td>CARDS</td>
<td>2009</td>
<td>Type 2 DM or with risk factors such as hypertension, proteinuria, no CVD history</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>3.9</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>65</td>
<td>3.10</td>
<td>53.30</td>
<td>970</td>
<td>0</td>
</tr>
<tr>
<td>ALLIANCE</td>
<td>2009</td>
<td>With known CHD patients</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>4.53</td>
<td>Atorvastatin</td>
<td>Usual care (atorvastatin will not be excluded from the usual-care group)</td>
<td>66</td>
<td>3.83</td>
<td>51.30</td>
<td>579</td>
<td>100</td>
</tr>
<tr>
<td>4S</td>
<td>2008</td>
<td>With a history of MI and/or stable angina</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5.5</td>
<td>Simvastatin</td>
<td>Placebo</td>
<td>63</td>
<td>4.97</td>
<td>54.80</td>
<td>409</td>
<td>100</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>2008</td>
<td>Stage 1 or 2 hypertension with at least one additional CHD risk factor</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>4.8</td>
<td>Pravastatin</td>
<td>Usual care</td>
<td>71</td>
<td>3.79</td>
<td>50.80</td>
<td>1557</td>
<td>18</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Inclusion criteria</td>
<td>Definition of CKD</td>
<td>Duration of time, year</td>
<td>Treatment group</td>
<td>Control group</td>
<td>Mean age, years</td>
<td>Baseline LDL-C, mmol/L</td>
<td>eGFR, mL/min/1.73 m²</td>
<td>Number of patients</td>
<td>History of CVD (%)</td>
</tr>
<tr>
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</tr>
<tr>
<td>TNT 2008</td>
<td></td>
<td>With clinically evident CHD</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5</td>
<td>Atorvastatin 80 mg/day</td>
<td>Atorvastatin 10 mg/day</td>
<td>66</td>
<td>2.49</td>
<td>53.00</td>
<td>3107</td>
<td>100</td>
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<tr>
<td>Melanie S. Joy, 2008</td>
<td></td>
<td>Hyperlipidaemia and CKD patients</td>
<td>Dialysis</td>
<td>0.69</td>
<td>Atorvastatin</td>
<td>No treatment</td>
<td>65</td>
<td>2.92</td>
<td>NA</td>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>4D 2005</td>
<td></td>
<td>Type 2 DM receiving maintenance haemodialysis for &lt;2 years</td>
<td>Dialysis</td>
<td>4</td>
<td>Atorvastatin</td>
<td>Matching placebo</td>
<td>66</td>
<td>3.23</td>
<td>NA</td>
<td>1255</td>
<td>29</td>
</tr>
<tr>
<td>Stegmayr, 2005</td>
<td></td>
<td>GFR &lt; 30 measured by clearance of either creatinine, Cr51-EDTA, or iohexol.</td>
<td>eGFR &lt; 30 mL/min/1.73 m²</td>
<td>2.58</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>68</td>
<td>3.56</td>
<td>NA</td>
<td>143</td>
<td>37</td>
</tr>
<tr>
<td>LIPS 2004</td>
<td></td>
<td>Successfully undergone their first PCI, mild renal impairment</td>
<td>Renal impairment, creatinine clearance &lt; 55.9 mL/min</td>
<td>3.8</td>
<td>Fluvastatin</td>
<td>Placebo</td>
<td>69</td>
<td>3.39</td>
<td>NA</td>
<td>310</td>
<td>100</td>
</tr>
<tr>
<td>Vincenzo Panichi, 2005</td>
<td></td>
<td>CRF with hypercholesterolaemia (LDL-C &gt; 100 mg/dL)</td>
<td>Mean creatinine clearance 45 mL/min</td>
<td>0.5</td>
<td>Simvastatin</td>
<td>Placebo</td>
<td>58</td>
<td>3.59</td>
<td>45.00</td>
<td>55</td>
<td>NA</td>
</tr>
<tr>
<td>Dornbrook, 2005</td>
<td></td>
<td>Hyperlipidaemia and undergoing long-term dialysis</td>
<td>Dialysis</td>
<td>1.67</td>
<td>Atorvastatin</td>
<td>No treatment</td>
<td>66</td>
<td>3.05</td>
<td>NA</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>Verma, 2005</td>
<td></td>
<td>GFR &lt; 60; no clinical evidence of acute renal failure</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>0.38</td>
<td>Rosuvastatin</td>
<td>No treatment</td>
<td>73</td>
<td>3.62</td>
<td>42.30</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>UK-HARP-I 2005</td>
<td></td>
<td>Scr ≥ 150 μmol/L</td>
<td>Scr ≥ 150 μmol/L</td>
<td>1</td>
<td>Simvastatin</td>
<td>Placebo</td>
<td>54</td>
<td>3.21</td>
<td>NA</td>
<td>448</td>
<td>9</td>
</tr>
<tr>
<td>PREVEND IT 2004</td>
<td></td>
<td>No antihypertension therapy and Tchol &lt; 8 mmol/L or Tchol &lt; 5 previous MI</td>
<td>Microalbuminuria with 15–300 mg/24 h</td>
<td>3.83</td>
<td>Pravastatin</td>
<td>Placebo</td>
<td>52</td>
<td>4.10</td>
<td>NA</td>
<td>864</td>
<td>3</td>
</tr>
<tr>
<td>Verglione, 2004</td>
<td></td>
<td>C-reactive protein ≥ 3 mg/L; undergo HD treatment for at least 6 months</td>
<td>Dialysis</td>
<td>0.5</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>65</td>
<td>NA</td>
<td>NA</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Tonelli, 2004 (PPP)</td>
<td></td>
<td>CKD subgroup of trials in WOSCOPS, LIPID, CARE</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5</td>
<td>Pravastatin</td>
<td>Placebo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>16824</td>
<td>NA</td>
</tr>
<tr>
<td>Lins, 2004</td>
<td></td>
<td>CRF treated with haemodialysis &gt;3 months and hyperlipidaemia</td>
<td>Dialysis</td>
<td>0.23</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>64</td>
<td>3.39</td>
<td>NA</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>CARE 2003</td>
<td></td>
<td>GFR &lt; 60, with AMI and hyperlipidaemia</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>5</td>
<td>Pravastatin</td>
<td>Placebo</td>
<td>63</td>
<td>3.61</td>
<td>53.20</td>
<td>690</td>
<td>11</td>
</tr>
</tbody>
</table>
effects model. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated with the $I^2$ statistic. For each trial, we calculated not only the average risk reduction, but also the average risk reduction per $1.0 \text{mmol/L} \text{LDL-C}$ reduction at the end of each trial where data were available (1 divided by the observed LDL reduction, for example, if the RR was 0.7 and the reduction in systolic blood pressure was 0.8 mmol/L, the standardized RR estimate was 0.7/0.8). Potential publication bias was assessed with the Egger test and represented graphically with Begg funnel plots of the natural log of the RR vs. its standard error.

We explored potential heterogeneity in the estimates of treatment effect with univariate meta-regression (for end-of-trial parameters such as achieved LDL-C concentrations) and by comparing summary results obtained from the subsets of studies grouped by number of patients, number of mortality events, publication year, statin used, diabetic status, stage of CKD, baseline morbidity, and study quality. A two-sided $P$-value, $0.05$ was regarded as significant for all analyses. All statistical analyses were done with STATA (version 12.0).

**Results**

The literature search yielded 2310 articles, of which 134 were reviewed in full text (Figure 1). Of these, 31 randomized, controlled trials met the inclusion criteria. These trials included a total of 48,429 patients with CKD, in whom 6690 major cardiovascular events were reported from 22 studies, and 6653 deaths from 23 studies. Study follow-up duration ranged from 6 months to 4.9 years. Thirteen trials were placebo-controlled and 18 trials used open-label designs. Ten trials reported post hoc analyses of the subgroup with CKD, four compared intensive lipid-lowering therapy to conventional or low-dose therapy. Formal statistical testing suggested the possibility of publication bias for the outcome of major cardiovascular outcomes with a borderline Egger test result ($P = 0.062$, see Supplementary material online, Figure S1).

Table 1 summarizes the characteristics of the included studies. Ten trials with 4503 participants were exclusively undertaken in dialysis patients; $^{9,10,16,18}$ 18 trials ($n = 33,252$) were in non-dialysis patients, and another 3 trials ($n = 10,029$) had a mixed population that included both dialysis and non-dialysis patients. Baseline estimated GFR levels for the participants in the trials were reported in the published paper or could be calculated or estimated from the inclusion criteria (Figure 2). Two trials were undertaken in people with diabetes and CKD.

The mean age of the study participants ranged between 42 and 73 years. Included studies were undertaken in Europe, North America, and in some part of Asia and Africa. The agents used in the studies varied: 12 studies assessed the effects of atorvastatin, 8 assessed simvastatin, 5 assessed pravastatin, 4 assessed rosuvastatin, where 1 assessed fluvastatin and 1 lovastatin.

We also recorded key indicators of trial quality, in particular the process of randomization, concealment of allocation, and the use of intention-to-treat analysis techniques, blinding, withdraws and dropouts (see Supplementary material online, Table S1). Overall, 13 trials had a Jadad scale of 4, others scored $\leq 3$.

Data regarding the effects of statin on major cardiovascular events were available from 22 trials, including 44,096 participants and 66,953 events. Overall, statin therapy produced a 23% reduction...
Figure 2  Summary of the effects of statin therapy on major cardiovascular events stratified by kidney function. Only one trial and one subgroup (SHARP > 60 and Rayner, 1996) were in chronic kidney disease (CKD) 2 stage with few endpoints (4 cardiovascular events and 105 patients), and we combined chronic kidney disease stage 3 and chronic kidney disease stage 2 into one subgroup.
in the risk of cardiovascular events (RR 0.77, 95% CI 0.70–0.85, P < 0.001) (Figure 2A) or an 18% per 1 mmol/L LDL (RR 0.82, 95% CI 0.74–0.91, P < 0.001, see Supplementary material online, Figure S2) with evidence of heterogeneity in the results of individual trials. Subgroup analysis showed that statin effect was significantly modified by kidney function (Figure 2B). Four trials with 4154 participants that compared more vs. less intensive statin regimens showed that intensive statin therapy reduced cardiovascular events by 28% in people with CKD (see Supplementary material online, Figure S3).

Data for coronary events were available from 15 trials8 – 10,19 – 29 including 26,262 patients in whom 2516 events were recorded. Statin therapy reduced the risk of coronary events by 22% (RR 0.78, 95% CI 0.69–0.88) without evidence of heterogeneity (I^2 = 29.6%, P = 0.134) (Figure 3). Eight trials reported stroke, including 21,505 and 647 events. Overall, there was no effect of statin therapy on the risk of stroke (RR 0.79, 95% CI 0.56–1.12) with evidence of heterogeneity between trials (P-value for heterogeneity = 0.001).

Cardiovascular death was reported in 11 trials including 31,859 patients among whom 2123 events were observed. Nineteen trials reported all-cause death, including 39,722 patients and 6653 events. Statin therapy reduced all-cause death (RR 0.92, 95% CI 0.85–0.99) and also cardiovascular death (RR 0.91, 95% CI 0.84–0.99) without clear evidence of heterogeneity (Figure 3).

Kidney failure events defined as a 25% decrease in the estimated GFR, doubling of serum creatinine, or ESRD were reported in six trials8,20,23,26,30,31 including 11,924 participants and 2824 events. There was no clear evidence that statins reduced the risk of kidney failure (RR 0.95, 95% CI 0.90–1.01) (Figure 3).
The heterogeneity in the effect across the included studies was assessed by subgroup analysis and meta-regression. This revealed that the effect of statin therapy on major cardiovascular events was modified by the average baseline kidney function of the participants in the included trials ($P$-value for heterogeneity < 0.001), with a progressively smaller relative risk reduction (RRR) with a lower estimated GFR. The RRR for cardiovascular event in trials with CKD stage 5 including patients with dialysis (8 trials, with 7,987 participants) was 8% (95% CI 1–14, $I^2$ = 0%) and 22% (95% CI 4–37, $I^2$ = 0%) in stage 4 (2 trials or subgroups, with 2,598 patients) and 31% (95% CI 4–37, $I^2$ = 0%) in stage 3 or 2 (11 trials or subgroups with 12,330 participants). Only two small trials or subgroups included 107 participants with CKD stage 2, so meta-analysis was not separately done in this group. The RRR for cardiovascular event in trials with CKD stage 5 including patients with dialysis (8 trials, with 7,987 participants) was 8% (95% CI 1–14, $I^2$ = 0%) and 22% (95% CI 4–37, $I^2$ = 0%) in stage 4 (2 trials or subgroups, with 2,598 patients) and 31% (95% CI 4–37, $I^2$ = 0%) in stage 3 or 2 (11 trials or subgroups with 12,330 participants). Only two small trials or subgroups included 107 participants with CKD stage 2, so meta-analysis was not separately done in this group. The benefits of statin in patients not on dialysis (RR 0.90, 95% CI 0.83–0.97, $P$ = 0.01) in patients requiring dialysis (P-value for heterogeneity = 0.007) (see Supplementary material online, Figure S2). Similar findings were observed for coronary events (RR 0.69, 95% CI 0.58–0.83 in the non-dialysis population and RR 0.91, 95% CI 0.81–1.02 in the dialysis population, P-value for heterogeneity = 0.042) and stroke (RR 0.61, 95% CI 0.39–1.16 in non-dialysis patients and RR 0.91–1.47 in dialysis patients, P-value for heterogeneity = 0.001) (Figure 3).

As the risk of CVD increased as the kidney function deteriorated, but with the risk ratio lower, we calculated the absolute risk reduction among patients with different CKD stages (Table 2; we also provide three models for the number needed to treat (NNT), see Supplementary material online, Tables S3.1–S3.3). The NNT to reduce one major cardiovascular event was 46 in CKD stage 5 (25–257), 36 in CKD stage 4 (19–330), and 24 in CKD stages 2–3 (19–32).

Subgroup analysis was done for major cardiovascular events according to other baseline characteristics (Figure 4). The effect sizes were greater in trials that recorded a higher mean baseline LDL-C concentration (P-value for heterogeneity = 0.012). On univariate meta-regression, there was a trend for statin therapy not requiring dialysis compared with 10% (RR 0.90, 95% CI 0.83–0.97, $P$ = 0.01) in patients requiring dialysis (P-value for heterogeneity = 0.007).
to produce the greatest benefit when LDL-C concentrations were improved most (Figure 5, P = 0.062) in non-dialysis patients. In contrast, no clear relationship between LDL-C reduction and cardiovascular benefit was observed in patients receiving dialysis.

Key adverse outcomes were reported by few trials. For hepatic impairment,6,8,9,25,26,32,33 (RR 1.13, 95% CI 0.92–1.39), muscle pain,6,26–28,34–36 (RR 1.02, 95% CI 0.95–1.09), increased creatinine kinase level6,8,16,22,24,26,28,30,31,37,38 (RR 1.18, 95% CI 0.89–1.55), cancer morbidity6,8,24,39 (RR 0.95, 95% CI 0.87–1.05), and severe adverse event6,8,25,26,30,32,36 (RR 0.95, 95% CI 0.89–1.03) in the analysis (Figure 6), no significant difference in risk was observed in the statin-treated participants.

The conclusions were not changed after adjustment for publication bias with the trim-and-fill method (data not shown).

Discussion

The management of lipids in people with CKD has been an area of intense debate over recent years, particularly in those with more advanced kidney dysfunction. This large quantitative review, including 31 trials with more than 48,000 individuals, suggests that therapy with statin reduces the risk of cardiovascular events across different levels of kidney function. Major cardiovascular events are reduced by 23%, including a 22% reduction in coronary events, and 9% reduction in cardiovascular or all-cause death. No significant effect was observed on the risk of kidney failure, or on the risk of adverse events including cancer mortality.

The most important new finding of this study is the clear result that the effect of statin therapy is significantly modified by kidney function. The observed beneficial effects appear to be smaller in people with stage 5 kidney disease and those requiring dialysis. Similar findings were observed for coronary heart disease and stroke. Importantly, the absolute risk reductions and NNT were only slightly less in people with advanced kidney disease, suggesting that statin therapy still confers important benefits in these individuals. In this analysis, we did not find that the adverse events of statin were increased in the patients with CKD, which suggested the safety of using statin in this population. However, this is still needed to be cautious given many trials included in this meta-analysis are post hoc analysis, and adverse events are reported by only a few trials. For the effect on stroke risk in patients with dialysis, the risk ratio even goes in the opposite direction (RR 1.16, 95% CI 0.90–1.47), and more data are still needed to evaluate the safety of statin in dialysis patients.

The effects of LDL-lowering with statin therapy in patients without CKD have been described by the Cholesterol Treatment Trials’ (CTT) Collaboration, and shown that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one-fifth per mmol/L reduction in LDL-C.40 In this study, LDL-C-lowering with statin in CKD could yield 18% reduction per 1.0 mmol/L reduction in major cardiovascular events, which is close consistent with the effects seen in the CTT study. Our study is also consistent with the results from the SHARP study and supports statin use in patients with CKD, including dialysis patients. However, SHARP did not have sufficient power to assess the effects separately in dialysis and non-dialysis patients. This large meta-analysis with more than four times of participants strongly supports larger benefits in patients with less severe renal impairment. Further support comes from the meta-regression analysis that a linear association trend exists in patients with non-dialysis although not obvious in patients with dialysis.

The reason for the lesser RRR in patients with ESRD than those achieved in patients with less severe kidney disease may reflect differences in the distribution of CVD among these groups of patients. Cardiovascular disease may have different aetiological pathways in people with ESRD compared with those with better renal function, and indeed may have a different pathophysiology.39,41,42 Cardiovascular risk factors specific to ESRD include calcium and phosphorus dysregulation, anaemia, hyperhomocysteinaemia, increased levels of oxidant stress, and chronic inflammation.33,37–39,43–45 In addition, the burden of cardiovascular dysfunction may be further accelerated by haemodynamic instability in dialysis patients. It is postulated that statins may not impact the substantial proportion of cardiovascular events in ESRD populations resulting from non-ischaemic myocardial abnormalities, left ventricular hypertrophy, and fluctuations in electrolytes and fluid volumes.43 These may explain the more modest relative effect of statins than that seen in an earlier stage of kidney disease.
Trials including individuals with high average baseline LDL-C concentrations reported significantly greater proportional risk reductions, a finding that accords with the results in the general population. Importantly, we noted a significant relationship between the magnitude of LDL-C-lowering achieved with therapy and the reported risk reductions in patients with non-dialysis patients, although this phenomenon was not observed in patients with ESRD. This further supports the hypothesis that the excess of cardiovascular events observed in people with advanced kidney disease may not be atherosclerotic in nature, and therefore not able to be reduced with statins. However, in this analysis, given that the rates of cardiovascular events and mortality consistently increase as kidney function deteriorates, clinically meaningful absolute risk reductions can still be achieved in patients with severe kidney dysfunction. In the subgroup analysis, we also noted significant heterogeneity between trials only involving patients with kidney disease and trials in the general population where the subgroup with CKD was available. This difference may be due to different kidney functions among these trials. The trials with CKD are mostly studies involving patients with dialysis, whereas in the post hoc analysis, participants were mainly non-dialysis patients.

This meta-analysis benefits from a large volume of data available, and the resultant precision in the observed benefits across a broad range of kidney function. Our study does, however, have limitations mainly as a result of it being based on published data, which limits the capacity to fully explore effects in subgroups. The different definitions used by the contributing trials cannot be fully integrated, and the outcome definitions, in particular, required some grouping of event types. Also in the meta-regression assessing kidney function and the effect of statins, we were only able to use the mean baseline GFR of the included trials rather than individual patient kidney function.

In conclusion, this study has provided strong evidence that statin therapy reduces the risk of major vascular events, as well as cardiovascular and all-cause death in patients with CKD, across a broad range of kidney functions including patients with dialysis. Although the relative vascular protection of statins is significantly modified by kidney function, meaningful reductions in absolute risk would be expected to be achieved in every stage of CKD. Additional protective strategies are required to address the large excess of cardiovascular events in the population with ESRD.

**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

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References


