Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis

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Abstract

Background and objectives Multiple meta-analyses of lipid-lowering therapies for cardiovascular primary prevention in the general population have been performed. Other meta-analyses of lipid-lowering therapies in CKD have also been performed, but not for primary prevention. This meta-analysis assesses lipid-lowering therapies for cardiovascular primary prevention in CKD.

Design, setting, participants, & measurements A systematic review and meta-analysis using a random-effects model was performed. MEDLINE was searched between January 2012 and September 2013 for new studies using predefined search criteria without language restrictions. A number of other sources including previously published meta-analyses were also reviewed. Inclusion criteria were randomized control trials of primary prevention with lipid-lowering therapy in non–end stage CKD.

Results Six trials were identified, five including patients with stage 3 CKD only. These studies included 8834 participants and 32,846 person-years of follow-up. All trials were post hoc subgroup analyses of statins in the general population. Statins reduced the risk of cardiovascular disease (the prespecified primary outcome) by 41% in stages 1–3 CKD compared with placebo (pooled risk ratio, 0.59; 95% confidence interval [95% CI], 0.48 to 0.72). For the secondary outcomes, the risk ratios were 0.66 (95% CI, 0.49 to 0.88) for total mortality, 0.55 (95% CI, 0.42 to 0.72) for coronary heart disease events, and 0.56 (95% CI, 0.28 to 1.13) for stroke. In study participants with stage 3 CKD specifically, the results were similar.

Conclusions This meta-analysis suggests that the use of statins in CKD for primary prevention of cardiovascular disease is effective. These findings are consistent with recent guidance for the use of statins in all patients with CKD.


Introduction

CKD is an independent risk factor for cardiovascular morbidity and mortality (1). Previous research has suggested that 5%–10% of the adult population has CKD (2). The role of statins in cardiovascular primary prevention for the general population is well defined (3,4). However, the most recent Cochrane review of statins and primary prevention of cardiovascular disease (3) made no mention of CKD, possibly because most cardiovascular primary prevention trials of statins were performed more than a decade before a standard CKD definition was agreed. Therefore, limited data exist specifically for cardiovascular primary prevention in CKD.

Meta-analyses (5,6) suggest that lipid lowering, predominantly using statins but also statin/fibrate combinations, produced a relative risk reduction of 0.81 (95% confidence interval, 0.74–0.88) for all-cause mortality and relative risk 0.78 (confidence interval, 0.68–0.89) for cardiovascular mortality in non–end stage renal failure CKD, mostly stage 3 CKD. These data were subsequently used to suggest that low-cost generic statins may be cost-effective for cardiovascular primary prevention in CKD (7). These findings are reflected in guidance from Kidney Disease Improving Global Outcomes (KDIGO) (8). Although the Study of Heart and Renal Protection (SHARP) (9) examined benefits of lipid lowering in patients with CKD in secondary care, most of the participants were at high risk of experiencing renal disease progression or requiring RRT. By contrast, the majority of primary care patients with CKD have a significantly increased risk of cardiovascular disease, but do not require secondary care nephrology referral and will not experience progressive renal impairment.

We aimed to assess the evidence for using lipid-lowering therapy in patients with CKD typically encountered in primary care, who lack both pre-existing cardiovascular disease and risk factors associated with progressive worsening of renal function such as proteinuria and/or well phenotyped primary renal disease.

Materials and Methods

MEDLINE was searched for randomized controlled trials of lipid-lowering therapies including patients with CKD using predefined search criteria (see the
Supplemental Material), without language restrictions. In addition, Cochrane databases (10–12) and the National Institutes of Health’s database of clinical trials (13) were searched. All trials included in recent meta-analyses of lipid-lowering therapy and cardiovascular outcomes in general patients with CKD (5,6) and for general population primary prevention (3,4) were reviewed. Because these were high-quality contemporary studies, we limited our search for new studies from January 2012 to September 2013. Authors who had previously published in a similar area were contacted to ask whether they were aware of any unpublished studies. The review protocol is available on request. All identified abstracts were independently assessed by two of the current authors. Each assessor made a shortlist of potential studies for further consideration. The full text of these articles was then reviewed to identify suitable studies. Randomized controlled trials of cardiovascular primary prevention in adults with CKD were included. Either statins or other lipid-lowering treatments were considered as interventions. Studies were included if they provided cardiovascular events, including mortality, or all-cause mortality. A minimum follow-up of 6 months was preset. Studies were included if they did not report renal-related outcomes, but were excluded if they incorporated RRT patients at study commencement. Furthermore, studies including participants with primary renal pathology or high cardiovascular risk categories such as macroalbuminuria (urine albumin/creatinine ratio [ACR] >300 mg/mmol) were also excluded. No minimum was set for the number of study participants. The final list of studies was then discussed by the reviewers and one further author and was unanimously agreed.

These additional studies were assessed for quality, including bias and how CKD subgroups were identified in the individual trials. Two authors independently assessed nonblinded versions of all studies for risk of bias using a standardized proforma based on the Cochrane Handbook for Systematic Reviews and Interventions (14). Comparisons of assessments were made and any discrepancies were discussed until a consensus was achieved. Study authors were contacted for any available, additional relevant information. Results from the identified studies were extracted and statistical analysis was performed using RevMan 5.2 software (15).

All risk ratios (RRs) were calculated from original studies using the published dichotomous data for each treatment group; where unavailable, the RR was used to back-calculate events. Where no events were reported, a correction factor of 0.5 was used to allow an effect size to be calculated (14). Where an event was not reported in an individual trial, the corresponding author was contacted. Pooled RRs with 95% confidence intervals (95% CIs) and P values were calculated using the Mantel–Haenszel method, both by CKD stage and overall. Because heterogeneity of the results was expected, random-effects models were used. Heterogeneity was assessed using the I² and Q statistics.

We calculated absolute risk reductions per 100 person-years and number needed to treat (NNT) for 5 years to prevent one event. We based our calculations on the risk difference

![Figure 1. Flow chart showing the number of studies identified and reason for inclusion or exclusion in meta-analysis. RCT, randomized controlled trial.](image-url)
<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of Main Cohort with CKD, %</th>
<th>Statin</th>
<th>LDL Reduction in Treatment Group, %</th>
<th>Mean/Median Follow-Up, mo</th>
<th>Mean/Median (SD) Age of Participants, yr</th>
<th>CKD Definition</th>
<th>eGFR Formula</th>
<th>Mean/Median Subgroup eGFR (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS</td>
<td>4.8</td>
<td>Lovastatin</td>
<td>27.0</td>
<td>61.2</td>
<td>62 (8)</td>
<td>eGFR &lt;60 (1 excluded due to eGFR &lt;15)</td>
<td>MDRD</td>
<td>53 (6.0)</td>
</tr>
<tr>
<td>CARDs</td>
<td>34.2</td>
<td>Atorvastatin</td>
<td>40.8</td>
<td>46.8</td>
<td>65 (6.7)</td>
<td>eGFR &lt;60 (n=1 for eGFR &lt;30)</td>
<td>MDRD</td>
<td>Placebo 54.1 (5.4), statin 53.5 (5.3)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>18.4</td>
<td>Rosuvastatin</td>
<td>51.4</td>
<td>22.8</td>
<td>70 (IQR 65–75)</td>
<td>eGFR &lt;60 (n=14 for eGFR &lt;30)</td>
<td>MDRD</td>
<td>56 (IQR 51–58)</td>
</tr>
<tr>
<td>MEGA</td>
<td>41.4</td>
<td>Pravastatin</td>
<td>18.9</td>
<td>63.6</td>
<td>60 (.)</td>
<td>eGFR &lt;60 (Sr &gt;1.5 mg/dl excluded from original study, 16 excluded from subanalysis due to eGFR &lt;30)</td>
<td>MDRD equation for Japanese patients</td>
<td>Placebo 52.5 (5.6), statin 52.6 (5.7)</td>
</tr>
<tr>
<td>PREVEND IT</td>
<td>100</td>
<td>Pravastatin</td>
<td>24.4</td>
<td>46.0</td>
<td>51 (12)</td>
<td>Excluded if creatinine clearance &lt;60%, CKD defined by proteinuria</td>
<td>Creatinine clearance</td>
<td>eGFR not given; mean Sr placebo 90 µmol/L (14), statin 91 µmol/L (14)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>7.6</td>
<td>Pravastatin</td>
<td>31.5</td>
<td>60.0</td>
<td>65.7 (5.6)</td>
<td>Defined by both CG-eGFR and MDRD-eGFR 30–99.99, 27 excluded due to CG-eGFR &lt;30</td>
<td>MDRD and CG</td>
<td>MDRD 55.0 (8.2), CG 51.8 (6.3)</td>
</tr>
</tbody>
</table>

AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARDs, Collaborative Atorvastatin Diabetes Study; JUPITER, Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; WOSCOPS, West of Scotland Coronary Prevention Study; IQR, interquartile range; Sr, serum creatinine; CG, Cockcroft–Gault; MDRD, Modification of Diet in Renal Disease. (.), the MEGA study did not provide an SD or IQR.

*WOSCOPS mean age value refers to mean age across whole CKD Prospective Pravastatin Pooling Project analysis. Mean age of all WOSCOPS participants, including those with no CKD, was 55.2 years (SD 5.5). No specific published value was available for the WOSCOPS’s CKD cohort’s mean age.
Results

Altogether 603 unique manuscripts were reviewed. Figure 1 depicts the screening process and the studies identified, including reasons for inclusion or exclusion. Explanations of the rationale for inclusion/exclusion are available on request. The search identified six trials (16–21). Table 1 describes their key characteristics. For individual trial definitions of events, see the Supplemental Material. These trials included 8834 participants with stages 1–3 CKD. Median follow-up was 46.4 months (range, 22.8–63.6) and all trial results were published in peer-reviewed journals. Three trials (16–18) were terminated early due to interim analysis showing prespecified termination end points having been met. The risk of bias assessment is available in the Supplemental Material.

Five studies reported eGFR based on the Modification of Diet in Renal Disease (MDRD) equation using a single serum creatinine measurement. One study also reported eGFR using the Cockcroft–Gault formula. MDRD results were used for all calculations in the meta-analysis. One study, the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) (20), used albuminuria as a study entry criterion. PREVEND IT recorded both spot and 24-hour measurements of urinary albumin and the threshold for study inclusion required both a morning urinary albumin concentration of >10 mg/L and 24-hour albumin excretion of 15–300 mg in at least one of two collections. This study excluded participants with a creatinine clearance <60 ml/min per 1.73 m² (equivalent to stages 3–5 CKD at study onset). None of the trials prespecified a CKD subanalysis, with the exception of PREVEND IT, which was specifically a trial of screening in proteinuria with preserved renal function.

Table 2 presents a summary of the overall results of the random-effects models for the pooled RR. Table 3 shows a summary of absolute risk reductions and NNT over 5 years to prevent one event in stage 3 CKD. The only data not in the original study publications related to total mortality in the PREVEND IT trial (20). Data for this category have been published in other meta-analyses (4,21) and their accuracy was confirmed by the corresponding author for PREVEND IT (20). All six trials reported data relating to major cardiovascular events for stages 1–3 CKD, with 409 events occurring in 8834 participants (4.5%) over a total of 32,846 person-years. Lipid-lowering therapy reduced the risk of major cardiovascular events by 41% (RR, 0.59; 95% CI, 0.48 to 0.72; P<0.001), and there was no statistical heterogeneity (I²=0%; P=0.46).

The results for CKD 3 only were similar (RR, 0.56; 95% CI, 0.45 to 0.69; P<0.001; I²=0%; P=0.66 for Q test). Figure 2 shows the forest plot for cardiovascular events.

Five trials reported all-cause mortality data. Overall, 225 events occurred in 8530 participants (3.0%) over a total of 31,588 person-years. Lipid-lowering therapy reduced the risk of mortality by 34% (RR, 0.66; 95% CI, 0.49 to 0.88; P=0.01), and there was a low-level heterogeneity (I²=22%; P=0.54). For stage 3 CKD only, mortality was reduced by 38% (RR, 0.62; 95% CI, 0.47 to 0.82; P<0.001). Heterogeneity was lower than for stages 1–3 CKD (I²=10%; P=0.34 for Q test). Figure 3 shows the forest plot for total mortality. Two trials reported cardiovascular mortality data, five trials reported coronary heart disease event data, and four trials reported stroke data. No unpublished data were available.

Differences in RRs were compared, tested for interaction, and then a RRR (the additional relative risk reduction of statins in CKD compared with the risk reduction in the general population) (22) was calculated. The RRR of a cardiovascular event was not statistically significantly lower (RRR, 0.78; 95% CI, 0.61 to 1.01; P=0.06) in stage 3 CKD than in the general population. The RR for all other outcomes was of a similar size and none were statistically significant (total mortality RRR, 0.75; 95% CI, 0.55 to 1.03; P=0.08; Table 4). Limited or no information was published in relation to adverse events for most trials. Three trials reported biochemical abnormalities, none of which reported excess abnormalities for statins. Two trials reported serious adverse events, neither describing excess events associated with statins (see the Supplemental Material for details). Limited information was available from the identified studies in relation to CKD progression, manifesting either as rising creatinine, proteinuria, or progression to end stage renal failure.

Although our original protocol excluded the SHARP study (9), by virtue of its participants’ characteristics, we repeated the meta-analysis including SHARP. Using

<table>
<thead>
<tr>
<th>Table 2. Summary results of random-effects models</th>
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<tbody>
<tr>
<td><strong>Outcome Event</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Total mortality</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
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<td>Total mortality</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Stroke</td>
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</tbody>
</table>

RR, risk ratio; 95% CI, 95% confidence interval.
published data, we compared our meta-analysis primary outcome with SHARP’s primary outcome, also major cardiovascular events, for nondialysis participants. There was no significant difference ($P$ value for interaction, $P=0.46$) between our original result (RR, 0.56; 95% CI, 0.45 to 0.69) and the result including the SHARP subgroup (RR, 0.63; 95% CI, 0.50 to 0.79). However, when the SHARP subgroup was directly compared with our original result, heterogeneity was observed ($I^2=86.6\%$; $P=0.01$). We also tested for heterogeneity in relation to the type of statin used. Three studies (19–21) used pravastatin and three studies used different statins. Doses of pravastatin varied from trial to trial. Testing for subgroup differences for the primary outcome between pravastatin versus all other statins did not show any heterogeneity ($I^2=0\%$; $P=0.49$).

**Discussion**

Previous meta-analyses of lipid lowering in nondialysis CKD (5,6) have shown RR reductions for cardiovascular events. However, there has been little consideration of the heterogeneous pathophysiology, including cardiovascular disease, within this diverse group. The current meta-analysis focuses on individuals with CKD but without known cardiovascular disease. This group, comprising mainly individuals with stage 3 CKD but without well clinically phenotyped primary renal diseases, represents the bulk of patients with CKD seen by general practitioners, in which cardiovascular disease prevention may be a more pertinent issue than progression of renal disease.

The prespecified primary outcome of the present meta-analysis showed a 41% reduction in cardiovascular events for participants with stages 1–3 CKD. All secondary outcomes also showed highly significant reductions in events, including a 34% reduction in total mortality. Current KDIGO guidance recommends a statin or a statin/ezetimibe combination for all individuals aged ≥50 years with stages 3–5 CKD, if not receiving dialysis or transplanted (8). For those aged <50 years, KDIGO recommends a statin if another cardiovascular risk factor is present, or if 10-year risk of a coronary heart disease event exceeds 10%. The data presented in this meta-analysis support this guidance. The American Heart Association guidance (23) recommends a statin when the 10-year risk of atherosclerotic cardiovascular disease is $>7.5\%$. In addition, the guidance introduced a new risk assessment tool. However, this guidance does not refer to CKD and cardiovascular primary prevention. The QRisk2 score (24) does provide a fixed CKD adjustment without consideration of staging. Furthermore, the QRisk2 cohort only contained 0.15% of participants with CKD. The commonly used Framingham Risk Score has poor discrimination in CKD (25).

Previous studies suggest that generic statins may be cost-effective for primary prevention in all patients with CKD (7). This article presents the first CKD primary prevention meta-analysis, and these more refined risk reductions are likely to show improved cost-effectiveness. On the basis of the current findings as well as a recent analysis of the effect of CKD on the English National Health Service (26), it is estimated that universal statin use in CKD could prevent 10,750 myocardial infarctions, 7300 strokes, and 14,900 deaths over 5 years (see the Supplemental Material). However, cautious interpretation of these figures is warranted.
due to the limits of extrapolating RRs from clinical trials to observational prevalence data, particularly in meta-analyses in which baseline event risk varies between trials. Indeed, the most suitable method for NNT calculation is open to debate (27–29).

Although this study contributes additional information to this area, we acknowledge several limitations. All studies were post hoc analyses of general population studies, a study type that is open to bias, including selection bias. Unsurprisingly, given their post hoc nature, there is limited information on other CKD cardiovascular risk stratifying factors, such as proteinuria. However, data suggest (2) that of individuals with stage 3 CKD, approximately 25% have persistent urine ACR \( \geq 3 \text{ mg/mL} \) and only 6.5% have ACR \( \geq 30 \text{ mg/mL} \).

Figure 2. | Forest plot of risk ratios for stages 1–3 CKD cardiovascular events using a random-effects model and the Mantel–Haenszel method. M–H, Mantel–Haenszel; 95% CI, 95% confidence interval; AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARDS, Collaborative Atorvastatin Diabetes Study; JUPITER, Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; WOSCOPS, West of Scotland Coronary Prevention Study.

Figure 3. | Forest plot of risk ratios for stages 1–3 CKD total mortality using a random-effects model and the Mantel–Haenszel method. M–H, Mantel–Haenszel; 95% CI, 95% confidence interval; CARDS, Collaborative Atorvastatin Diabetes Study; JUPITER, Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; WOSCOPS, West of Scotland Coronary Prevention Study.
Because the trials presented here were recruited from mainly primary care populations, and not secondary care nephrology services, it is likely that the proportions of micro- and macroalbuminuria are less than the KDIGO proportions (2). This hypothesis is supported by the only included trial to report detailed quantification of proteinuria (17). Within the CKD subgroup of this diabetic nephropathy trial, <3.5% had nephrotic-range proteinuria. The limited information available in relation to adverse events did not raise any safety concerns. Previous data (5,6) have shown no excess adverse events with statins, or other lipid-lowering medications, compared with placebo in CKD. Furthermore, limited data were available in relation to renal outcomes; therefore, no conclusion can be made regarding statin-mediated changes to CKD progression.

We did not formally consider publication bias because all included studies were post hoc analyses. Not all general population primary prevention studies have published such analyses and therefore publication bias may exist. However, of the 13 trials with total mortality data included in the most recent Cochrane meta-analysis for primary prevention (3), the five largest trials have published CKD-related data and are included in this meta-analysis. eGFR measurement is suboptimal in all included studies. A diagnosis of CKD requires two serum creatinine measurements >3 months apart (2), something that occurred in none of the included studies. Use of the MDRD equation (30), utilized to calculate the eGFR in all included studies, has been challenged by the Chronic Kidney Disease Epidemiology Collaboration equation (31) due to the former’s propensity to overdiagnose stage 3 CKD, particularly stage 3A CKD. No study prespecified a CKD-related subanalysis, but we reflected this in our analysis of bias.

Limited published information exists from the studies in relationship to noncholesterol-lowering effects of statins. Only Justification for the Use of Statins in Prevention–An Intervention Trial Evaluating Rosuvastatin (18) provided information relating to the potential role of inflammation. Hazard ratios were similar between the CKD and non-CKD groups, as were relative reductions in both LDL cholesterol and C-reactive protein from baseline. Thus, it is not possible to attribute the benefit of statins to either lipid-lowering properties or pleiotropic effects in CKD.

The five trials reporting stage 3 CKD outcomes had mean/median eGFRs between 53 and 56 ml/min per 1.73 m² with SDs of 5–6 ml/min per 1.73 m². Two trials specifically excluded participants with an eGFR<30 ml/min per 1.73 m². The remaining trials had a minimal number (<1%) of participants with stage 4 CKD. The results including these trials are therefore only likely to be applicable to individuals with stage 3 CKD.

Our results complement those of the SHARP trial (9), the only CKD-specific lipid-lowering trial. The SHARP trial showed an overall statistically significant 17% reduction in major cardiovascular events, as well as a nonstatistically significant reduction in mortality across a wide range of CKD stages, including dialysis. Our sensitivity analysis shows that inclusion of the SHARP data did not significantly change the overall results and conclusions of this meta-analysis. When the SHARP subgroup was considered individually against our meta-analysis, heterogeneity did exist. However, a number of factors may account for this heterogeneity. First, the participants’ characteristics in the SHARP trial contrast significantly with those in the studies included in our meta-analysis. The majority of SHARP participants had advanced (stage 4–5 CKD) renal disease, and SHARP was not specifically a primary prevention trial. Indeed, during the SHARP trial, approximately three times more participants progressed to end stage renal failure than had a major cardiovascular event. More advanced CKD may attenuate statin efficacy, as evidenced by negative statin trials in dialysis (5,6). Second, the SHARP trial used both simvastatin and ezetimibe, thus making the comparison of its 33.1% reduction in LDL cholesterol more difficult to interpret compared with the statin-only trials included in this meta-analysis. Considered alongside the SHARP results, the current meta-analysis supports an expansion of the range of patients with CKD for whom statins may be beneficial. The SHARP trial answered the question of the efficacy of statins in CKD from a nephrologist’s point of view. By identifying studies of patients with stages 1–3 CKD at low risk of CKD progression, the current meta-analysis answers a related question but from the prospective of primary care. Most patients in this group have nonprogressive stage 3 CKD and do not require nephrology referral, but instead need appropriate cardiovascular risk management.

The tools to assess cardiovascular risk in CKD currently remain undefined. Preexisting cardiovascular tools are of limited value, and even the most recent tool has no CKD adjustment. However, the more pertinent questions in primary prevention may be “What works?” and “In whom?” (32). This meta-analysis specifically answers these questions in relation to CKD and statins. Universal use of statins for

### Table 4. Cardiovascular disease RRs for participants in identified trials with CKD participants removed (without CKD) and RRRs for stage 1–3 CKD versus non-CKD and stage 3 CKD only versus non-CKD

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>RR without CKD (95% CI)</th>
<th>Stage 1–3 CKD</th>
<th>Stage 3 CKD Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P Value for Interaction</td>
<td>RRRs (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.71 (0.62 to 0.83)</td>
<td>0.83 (0.65 to 1.05)</td>
<td>0.12</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.82 (0.71 to 0.95)</td>
<td>0.81 (0.58 to 1.12)</td>
<td>0.19</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0.71 (0.62 to 0.81)</td>
<td>0.78 (0.57 to 1.05)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.67 (0.40 to 1.14)</td>
<td>0.84 (0.35 to 2.01)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

RR, risk ratio; RRR, ratio of risk ratios; 95% CI, 95% confidence interval.
cardiovascular disease primary prevention in all individuals with CKD, excluding dialysis, should be considered.

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Disclosures
None.

References

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Supplementary Material for ‘Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis’

Medline Literature Search Criteria

Database: Ovid MEDLINE(R) <2009 to September Week 2 2013>

Search Strategy:

1. ckd.tw. (5810)
2. exp Renal Insufficiency, Chronic/ (15734)
3. 'chronic kidney disease'.tw. (9308)
4. renal.tw. (65869)
5. nephro$.tw. (19522)
6. kidney*.tw. (55152)
7. 1 or 2 or 3 or 4 or 5 or 6 (106014)
8. exp Lipids/ (135671)
9. hyperlipid?emi*.tw. (3852)
10. lipid*.tw. (66958)
11. dyslipid?emi*.tw. (6235)
12. hypercholesterol?emia.tw. (3467)
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14. (ldl or vdl or hdl).tw. (15247)
15. (ldl or vdl or hdl).tw. (15247)
16. 8 or 9 or 11 or 12 or 13 or 14 or 15 (157387)
17. 'HMG CoA reductase inhibitor$.tw. (505)
18. 'hydroxymethylglutaryl-CoA reductase inhibitor$.tw. (20)
19. expHydroxymethylglutaryl-CoA Reductase Inhibitors/ (7986)
20. (cholesterol* adj2 lower*).tw. (2047)
21. (lipid* adj2 lowering*).tw. (2373)
22. 17 or 18 or 19 or 20 or 21 (10929)
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cerivastatin.tw.or 145599-86-6.rn. (33)
fluvasatin.tw.or 93957-54-1.rn. (307)
lovastatin.tw.or 75330-75-5.rn. (565)
mevastatin.tw.or 73573-88-3.rn. (49)
pitavastatin.tw.or 147511-69-1.rn. (221)
pravastatin.tw.or 81093-37-0.rn. (671)
rosuvastatin.tw.or 287714-41-4.rn. (985)
simvastatin.tw.or 79902-63-9.rn. (2097)
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Pravachol.tw. (2)
Selektine.tw. (0)
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Vytorin.tw. (7)
Advicor.tw. (0)
Caduet.tw. (11)
Simcor.tw. (3)
Inegy.tw. (3)
23 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (11146)
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colestitol.tw.or 50925-79-6.rn. (6)
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vitamin b3.tw. (47)
vitamin pp.tw. (2)
46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 (3245)
45 or 76 (13480)
ex Clinical Trials as Topic/ or exp Randomized Controlled Trials as Topic/ (54930)
ex Controlled Clinical Trial/ (7630)
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random$.tw. (168305)
trial$.tw. (154660)
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(double blind* or double-blind*).tw. (18207)
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exp Evaluation Studies/ (66930)
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'prospective stud*'.tw. (25368)
'cross-over stud*'.tw. (809)
'follow-up stud*'.tw. (5983)
78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 (378602)
16 or 22 or 77 (164760)
7 and 91 and 92 (1741)
limit 93 to yr="2012 -Current" (509)
Event Definitions

**AFCAPS** - ‘fatal and nonfatal cardiovascular events’

**CARDS** - ‘major cardiovascular disease’

**JUPITER** - ‘cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization’

**MEGA** - ‘all cardiovascular events’

1. Definite fatal and nonfatal myocardial infarction (1 or more of the following criteria must be met):
   (a) Diagnostic ECG at the time of the event.
   (b) Ischemic cardiac pain (and/or unexplained acute left ventricular failure) and diagnostic enzymes.
   (c) Ischemic cardiac pain and/or unexplained acute left ventricular failure with both equivocal enzymes and equivocal ECG.
   (d) Diagnostic enzymes and equivocal ECG.
   (e) Angiographic evidence of occlusion of a major artery with appropriate ventriculographic wall motion abnormality where previous angiogram since randomization showed no such abnormality.
   (f) Postmortem examination.

2. Angina pectoris (stable or unstable, both of the following criteria must be met):
   (a) Ischemic cardiac pain, relieved by nitrates.
   (b) Equivocal ECG.

3. Ischemic stroke (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death plus evidence from neuroimaging (computed tomography or magnetic resonance imaging) showing cerebral/cerebellar infarction or no abnormality, or postmortem examination showing cerebral and/or cerebellar infarction).
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.

4. Primary intracerebral hemorrhage (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death, plus neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and cerebellar hemorrhage.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24 h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.
5. Transient ischemic attack:
   (a) Rapid onset of focal neurologic deficit or loss of monocular function lasting less than 24 h.
   (b) Negative neuroimaging.

6. ASO (atherosclerosis obliterans):
   (a) At least Fontaine Classification II.
   (b) Less than 0.9 (ankle brachial pressure index).
   (c) Positive vascular imaging.

PREVEND-IT - ‘Hospitalization for: Nonfatal myocardial infarction and/or myocardial ischemia, Heart failure, Peripheral vascular disease, Cerebrovascular accident’

- Nonfatal myocardial infarction was defined as all nonfatal events accompanied by at least 2 of 4 of the following, which should include either new Q waves or enzyme elevation: (1) presence or history of typical or atypical chest pain of at least 15 minutes’ duration; (2) ECG detection of ST-segment changes of at least 0.1 mV and/or T-wave inversion in at least 2 of 12 leads; (3) ECG detection of new significant Q waves in at least 2 of 12 leads; and (4) elevation of measurements of total creatine kinase (CK) and/or its isoenzyme CK-MB in at least 2 samples drawn within 48 hours of development of chest pain

- Myocardial ischemia was defined as all ischemic events accompanied by the appearance of an ST-segment change of 0.1 mV or T-wave inversion in at least 2 of 12 leads, objective evidence by means other than ECG, or a need for revascularization (PTCA/CABG) that was severe enough to justify immediate hospital admission.

- Heart failure was regarded as heart failure for which hospital admission (hospitalization or documented outpatient clinic visit) was necessary and for which there was objective evidence of left ventricular dysfunction or for which specific medication (diuretics and ACE inhibitors) was needed.

- Peripheral vascular disease was diagnosed when PTA or bypass operation was necessary.

- Cerebrovascular accident was diagnosed when 1 of the following symptoms was present: recent onset of severe headache, loss of consciousness, or unequivocal objective findings of a localizing neurological deficit, duration 24 hours, and absence of other disease process causing neurological deficit, such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder in combination with an abnormal CT scan or MRI scan.

WOSCOPS - ‘cardiovascular mortality, nonfatal MI, coronary revascularization, or stroke’

- expanded outcome of trial
  - see below for further details

Coronary Heart Disease Events Definitions

AFCAPS - ‘fatal and nonfatal coronary events’

- Fatal myocardial infarction or sudden cardiac death: The definition requires that there be no noncardiac cause of death and 1 of the following: fatal myocardial infarction-death within 28 days from the onset of symptoms of a definite acute myocardial infarction; witnessed unexpected sudden cardiac death-within 1 hour of symptoms; death occurring 1 hour but >24 hours after collapse; and unwitnessed unexpected death, presumed sudden-must have confirming autopsy data or, if autopsy not performed, preceding history of CHD events or symptoms.

- Nonfatal myocardial infarction: Acute Q-Wave Myocardial Infarction - requires definitive electrocardiogram (ECG): Acute Non–Q-wave myocardial infarction—definitive ECG or, if equivocal, enzymes must be diagnostic. Non–Q-wave myocardial infarction includes myocardial infarctions reperfused by either mechanical or pharmacologic means providing there is supporting ECGs and enzyme data; Silent subclinical (remote) myocardial infarction—definitive ECG, or, if ECG is equivocal, focal wall motion abnormality consistent with myocardial infarction on rest echo or stress thallium (fixed defect) and on catheterization, a ≥50% stenosis in a major corresponding epicardial vessel. Participants who have had a cardiac catheterization as the first diagnostic test for presumed silent (or remote)
myocardial infarction are considered to have met criteria for an end point event if the catheterization findings indicate focal wall abnormalities consistent with myocardial infarction and ≥50% stenosis in a corresponding artery.

- Unstable angina:* New-onset exertional and/or accelerated or rest angina and requires at least 1 of the following: stress perfusion study- ≥1 mm ST-segment changes and reversible defect; 90% epicardial vessel stenosis or ≥50% stenosis in the left main artery; ≥1 mm ST-segment changes with pain on stress testing and/or resting ECG and evidence of ≥50% stenosis in a major epicardial vessel.

CARDS

‘Hospital-verified non-fatal acute myocardial infarction’

(a) Non-fatal definite acute myocardial infarction
   (i) Definite ECG or
   (ii) Typical symptoms AND highly abnormal enzymes, irrespective of ECG or
   (iii) Typical or atypical or inadequately described symptoms AND probable ECG AND highly abnormal enzymes or
   (iv) Troponin I or T above the 99th centile for the reference population of the local (testing) lab in the presence of typical or atypical ischaemic symptoms, irrespective of ECG.

(b) Non-fatal probable acute myocardial infarction
   (i) Typical symptoms AND probable ECG or abnormal enzymes or
   (ii) Atypical or inadequately described symptoms AND probable ECG AND abnormal enzymes.

‘Silent myocardial infarction’

This category includes definite myocardial infarctions diagnosed on the basis of serial readings of annual ECGs for which no corresponding hospital-verified myocardial infarction exists.

‘Coronary heart disease (CHD) deaths’

(a) Fatal definite acute myocardial infarction

This means death within 28 days from the onset of symptoms of a hospital-verified definite acute myocardial infarction, or in cases of death occurring outside the hospital, autopsy findings showing a recent myocardial infarction or a recent occluding coronary thrombus.

(b) Fatal probable acute myocardial infarction

This means death within 28 days from the onset of symptoms of a hospital-verified probable acute myocardial infarction in the absence of autopsy confirmation. This category also includes cases where an available autopsy report indicates a probable acute myocardial infarction.

(c) CHD death - new acute myocardial infarction not confirmed

This includes the following subcategories:
   (i) Witnessed instantaneous unexpected death occurring without any preceding symptoms.
   (ii) Cardiac death occurring within 1 h after the onset of typical chest pain, syncope, acute pulmonary oedema, or cardiogenic shock.
   (iii) Cardiac death occurring > 1 h but < 24 h after the onset of typical chest pain, syncope, acute pulmonary oedema, or cardiogenic shock.
   (iv) Cardiac death occurring >24 h but <72 h after the onset of typical chest pain, syncope, acute pulmonary oedema or cardiogenic shock.
(v) Non-witnessed unexpected death, if other causes of death can be excluded with reasonable certainty (excluded are those patients who were known to have signs or symptoms of other fatal disease when last observed).

‘Coronary artery bypass graft surgery (CABG)’
Other coronary artery revascularization procedures
This includes angioplasty, atherectomy, laser ablation or stenting or any newly introduced invasive method for the management of coronary artery disease.

‘Unstable angina’
Chest pain event or symptoms consistent with angina of sufficient severity to cause the patient to have a hospital-verified episode within 28 days of symptom onset, accompanied by:
(i) New resting ECG changes, defined as any new Minnesota code change consistent with ischaemia or
(ii) A troponin rise not sufficient to meet the definition of an MI, i.e. above the 50th centile but below the 99th centile of the reference population, in association with ischaemic symptoms.

‘Resuscitated cardiac arrest’
Ischaemic cardiac arrest with successful resuscitation which involved DC shock, in which a non-fatal definite or probable

JUPITER - ‘myocardial infarction’
MEGA - fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention.
• primary outcome of study - composite of major CHD events

PREVEND-IT - hospitalisation for ‘Nonfatal myocardial infarction and/or myocardial ischemia’ or ‘Heart failure’
• See above for precise definitions

WOSCOPS - ‘coronary mortality, nonfatal MI, and coronary revascularization’
• primary outcome of trial
  ° All deaths will be recorded, and details sought from death certificates, autopsy reports, hospital case records, general practitioner’s records and interview of family and/or witness. The principal endpoints of the trial have been specified as follows:
    (1) CHD death plus non-fatal myocardial infarction.
    (2) CHD death (whether preceded by a non-fatal myocardial infarction or not).
    (3) Non-fatal myocardial infarction.
• In the categories of CHD death and myocardial infarction, there will be sub-categories of “definite” and “suspect”. These conditions will be defined as follows:
  (1) Definite atherosclerotic CHD death-ither or both of the following categories:
    (A) Death certificate with consistent underlying or immediate cause plus one or more of the following:
    Preterminal hospitalization with definite or
suspect myocardial infarction (see below). Previous definite angina or suspect or definite myocardial infarction when no cause other than atherosclerotic CHD could be ascribed as the cause of death. Autopsy evidence of acute coronary arterial thrombosis and/or acute myocardial infarction.

(B) Sudden and unexpected death (requires all 3 characteristics):
- Deaths occurring within 1 hr after the onset of severe symptoms or having last been seen without them.
- No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
- An “unexpected” death occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hr before death.

(2) Criteria for definite non-fatal myocardial infarction any one or more of the following categories using the stated definitions:

(i) Diagnostic ECG at the time of the event.
(ii) Ischaemic cardiac pain and diagnostic enzymes.
(iii) Ischaemic cardiac pain with both equivocal enzymes and equivocal ECG.
(iv) An ECG at the annual visit or at an unscheduled visit is diagnostic for myocardial infarction while the previous one was not.

(3) Suspect atherosclerotic CHD death-one or both of the following categories:

(i) Death certificate with consistent underlying or immediate cause but neither adequate preterminal documentation of the event nor previous atherosclerotic CHD diagnosis.
(ii) Rapid and unexpected death (requires all 3 characteristics):
   (a) Death occurring between one and 24 hr after the onset of severe symptoms or having last been seen without them.
   (b) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
   (c) An “unexpected death” occurs only in a person who is not confined to his home, hospital or other institution because of illness within 24 hr before death.

(4) Suspect myocardial infarction-any one or more of the following categories using the stated definitions:

(i) Ischaemic cardiac pain, except when infarction is excluded by ECG or enzymes.
(ii) Diagnostic enzymes.
(iii) Equivocal ECG and equivocal enzymes.
(iv) Equivocal ECG alone, provided that it is not based on ST or T-wave changes only.

Other endpoints

As well as the main endpoints, statistics will also be reported on the frequency of:

1. All cause mortality.
2. Coronary artery bypass surgery/angioplasty: subjects will be deemed to have reached the secondary endpoint on the day on which the procedure is undertaken.
3. Coronary arteriography.
4. Angina: positive response to chest pain questionnaire when previously negative.
5. Intermittent claudication: positive response to claudication questionnaire when previously negative.
6. Cerebrovascular disease: a single episode of motor paralysis, sensory or speech dysfunction, diplopia or visual disturbance lasting more than 1 hr, or repetitive episodes of a similar nature lasting for 5 min or more.
## Risk of Bias Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-published Methods</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Performance Bias</th>
<th>Detection Bias</th>
<th>Attrition Bias</th>
<th>Reporting Bias</th>
<th>Proteinuria Measurement</th>
<th>eGFR Measurement</th>
<th>Other Bias</th>
<th>Overall Bias Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS (16)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>CARDS (17)</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
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<td>JUPITER (18)</td>
<td>Yes</td>
<td>Low</td>
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<td>Unclear</td>
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<tr>
<td>MEGA (19)</td>
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<td>Low</td>
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<tr>
<td>PREVEND-IT (20)</td>
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<td>Low</td>
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<td>Low</td>
<td>Medium</td>
<td>No downgrading</td>
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<td>Low</td>
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<tr>
<td>WOSCOPS (21)</td>
<td>Yes</td>
<td>Low</td>
<td>Low</td>
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<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Medium</td>
<td>Downgrade by 2</td>
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## Summary of Adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Information in Relation to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS (16)</td>
<td>No significant increase in creatinine kinase levels or any cases of rhabdomyolysis in participants with CKD in the lovastatin group. Abnormal liver function tests were 'rare' and 'the incidence was similar in both treatment groups'.</td>
</tr>
<tr>
<td>CARDS (17)</td>
<td>None published for CKD sub-analysis.</td>
</tr>
<tr>
<td>JUPITER (18)</td>
<td>Similar rates of 'serious adverse events', 9.16 per 100 person-years (PYs) for rosuvastatin group and 9.40 per 100 PYs for placebo (p=0.73). 1 case of rhabdomyolysis in rosuvastatin group versus none in the placebo group. For full details see table 4, reference 15</td>
</tr>
<tr>
<td>MEGA (19)</td>
<td>Rates of 'serious adverse events or subjective complaints of side effects' similar (diet group 11.3%; diet plus pravastatin group 10.5%; P = 0.088). Rates of abnormal laboratory finding were similar. ALT &gt;100 IU/L 2.7% and 2.5% (P = 0.73); creatine kinase &gt; 500 IU/L was 2.6% and 2.6% (P = 0.96). No significant difference was found in total cancer incidence.</td>
</tr>
<tr>
<td>PREVEND-IT (20)</td>
<td>'Intolerability' of medication 5.1% in the placebo group versus 3.0% in pravastatin group. No specific other statin related side effects reported.</td>
</tr>
<tr>
<td>WOSCOPS (21)</td>
<td>None published for CKD sub-analysis.</td>
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</table>
## Basis for Calculations of Reduction in Events

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Excess Mls</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 3-5 England prevalence or excess events calculated (26)</td>
<td>1810000</td>
<td>12100</td>
<td>6500</td>
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<tr>
<td>Proportion of CKD 3-5 who are CKD 3 (26)</td>
<td>0.92537</td>
<td>0.92537</td>
<td>0.92537</td>
</tr>
<tr>
<td>Proportion eligible for primary prevent (1, Hallan et al, Stadler et al)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Proportion not on statin already (40)</td>
<td>0.5337</td>
<td>0.5337</td>
<td>0.5337</td>
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<tr>
<td>Rate per PY of total mortality in CKD population ((2) and current study control group rate)</td>
<td>0.011</td>
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<td>N/A</td>
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<tr>
<td>For number over 5 years</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>This study’s RR reduction (CKD3)</td>
<td>0.38</td>
<td>0.45</td>
<td>0.57</td>
</tr>
<tr>
<td>Reduction in total mortality over 5 years</td>
<td>14,946</td>
<td>10,756</td>
<td>7,319</td>
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<tr>
<td>Upper CI RR</td>
<td>0.18</td>
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<td>0.25</td>
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<td>Upper CI Events</td>
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<td>3210</td>
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<td>Lower CI Events</td>
<td>20846</td>
<td>13864</td>
<td>9630</td>
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</table>

All numerical references are as numbered in the main text of the manuscript.

**Additional References for Supplementary Material:**
