Meta-analysis of Statins in Chronic Kidney Disease: Who Benefits?

Messow CM[1], Isles C[2].
[1]Robertson Centre for Biostatistics, University of Glasgow; [2]Medical Unit, Dumfries and Galloway Royal Infirmary, Dumfries DG1 4AP

Claudia-Martina Messow	Consultant Statistician
Chris Isles	Emeritus Professor

Correspondence:
Prof Chris Isles
Medical Unit
Dumfries Infirmary
Dumfries DG1 4AP
chris.isles@nhs.net
07590 317255

Abstract

Background - attempts to reduce the burden of vascular disease in advanced chronic kidney disease (CKD) by control of lipids have not been as successful as predicted.

Aim - to determine the extent to which the effectiveness of statins varies by kidney class.

Design - meta-analysis

Methods – we selected randomised trials of statin versus placebo that gave outcomes for CKD3 (eGFR 30-59ml/min), CKD4 (eGFR 15-29ml/min), CKD5 (eGFR <15ml/min)/5D(dialysis) and transplant patients separately. Data sources were the Cholesterol Triallists' Treatment Collaboration and previously published meta-analyses. Main outcome measures were major cardiovascular events (MACE), cardiovascular death and all cause mortality.

Results – 13 studies provided 19386 participants with CKD3, 2565 with CKD4, 7051 with CKD5/5D and 2102 with a functioning renal transplant. Statins reduced MACE (pooled HR 0.72, 95% CI 0.67 to 0.78) and all-cause mortality (0.82, 0.73 to 0.91) in CKD3; probably reduced MACE (0.78, 0.62 to 0.99) in CKD4; and probably reduced cardiovascular death (0.62, 0.40 to 0.96) in renal transplants. There were no cardiovascular or all cause mortality data in CKD4; there was no convincing evidence of benefit for any outcome in CKD5/5D; and no significant reduction in MACE or all cause mortality in patients with a functioning transplant.

Conclusions - statins are indicated in CKD3, probably indicated in CKD4, not indicated in CKD5/5D and probably indicated in patients with a functioning transplant. Too few patients with CKD4 and renal transplants have been included in lipid lowering trials for confident conclusions to be drawn.

Word count 244

Strengths and Limitations of this Study

- Strength - we analysed patients with CKD3, CKD4, CKD5/5D and renal transplant separately and
- Strength – we were able to include 19,386 patients with CKD3.
- Strength - we included all relevant studies published by 11/5/16.
- Limitation – our meta-analysis includes RCTs of patients with CKD together with post hoc CKD substudies of general population surveys.
- Limitation - definitions of MACE and cardiovascular death often differed between trials.

What is already known on this subject

- People with chronic kidney disease (CKD) carry a high risk of vascular disease and are much more likely to die from vascular causes than those who do not have CKD.
- Attempts to reduce the burden of vascular disease in advanced CKD by control of lipids have not been as successful as predicted.

What this study adds

- Statins are indicated in CKD3, probably indicated in CKD4, not indicated in CKD5/5D and probably indicated in patients with a functioning transplant.
- Too few patients with CKD4 and transplants have been included in lipid lowering trials for confident conclusions to be drawn.

Key Words

Major cardiovascular events. Cardiovascular mortality. All cause mortality. Statins. Chronic kidney disease. Meta-analysis.

Introduction

People with chronic kidney disease (CKD) carry a high risk of vascular disease and are much more likely to die from vascular causes than those who do not have CKD[1.] The risk of vascular death increases with the severity of CKD and may be between 8 and 10 times greater than that of the general population by the time a patient starts dialysis[2]. It is disappointing therefore that attempts to reduce the burden of vascular disease in advanced CKD by control of lipids have not been as successful as predicted[3-6], contradicting the widely held view that patients at higher risk of disease generally benefit more from treatment.

Eight meta-analyses of lipid lowering in renal disease have been published. The most recent and largest of these, the Cholesterol Triallists Treatment Collaboration, chose not to present data for patients with CKD4 or with renal transplants separately[7]. Palmer et al considered all patients from those microalbuminuria to CKD5 as one group then compared outcomes with patients on dialysis and patients with transplant[8]. Both Upadhyay[9] and Su[910] pooled outcomes for all patients from microalbuminuria to transplant. Hou et al combined CKD2 and CKD3 before comparing outcomes with a combined group of CKD4 and CKD5/5D[11]. Green and colleagues limited their analysis to dialysis patients only[12] while Major et al limited theirs to patients with CKD3 and no prior coronary heart disease (CHD)[13]. The meta-analysis by Yan and colleagues was primarily a comparison of more versus less statin[14]. With one exception[8] the authors of the meta-analyses comparing statins with placebo felt their findings supported the widespread use of statins in patients with CKD. Yan et al concluded that the benefits of high intensity statin therapy were unclear[14].

We chose not to replicate these studies for two reasons: first, we did not wish to include patients with microalbuminuria and CKD2 as this would have meant assessing all trials of statins in older adults which was not our primary objective; and second, we felt that pooling patients with different severity of CKD would assume that all patients with CKD behave similarly irrespective of stage. We do not believe that this is the case. Indeed it would appear that statins are more effective in CKD3 than in patients on dialysis[15]. We suspect

this is a consequence of a change in the nature of the vascular disease in kidney patients from primarily atherosclerotic to predominantly calcific pathology with myocardial fibrosis an important contributory factor[1]. If true this might be a reason why statins lose their benefit as renal failure progresses.

Against this background the aim of our meta-analysis was to quantify the benefits of statin therapy at different stages of CKD and to determine the point at which statins become less effective by examining, where possible, patients with CKD3 (eGFR 30-59ml/min), CKD4 (eGFR 15-29ml/min), CKD5 (eGFR <15ml/min)/5D (patients on dialysis) and those with renal transplant separately.

Methods

We selected studies by checking the reference lists of previous systematic reviews in order to avoid duplicating the work of others. Sources of studies about the effect of statins in patients with CKD were the Cholesterol Treatment Triallists Collaboration[7], the meta-analyses by Palmer[8], Upadhyay[9], Su[10], Hou[11], Green[12], Major[13] and Yan[14], and the Cochrane Review by Taylor et al[16].

From these reports we included randomised trials of statin versus placebo that gave outcomes for CKD3, CKD4, CKD5, dialysis (CKD5D) or transplant patients separately in their main results papers, in CKD substudies or in pooled analyses. Four trials were conducted exclusively in subjects with CKD[3-6], eight were CKD substudies of primary or secondary prevention trials[17-24] and one was a pooled analysis of WOSCOPS, CARE and LIPID[25]. We excluded studies with fewer than 300 patients, trials of more versus less statin but no placebo group[26-28], trials of less than one year's duration[29] and an open label extension to ALERT that increased average follow up from 5.1 to 6.7 years for patients randomized to fluvastatin[30] .

We independently extracted data for the following three outcomes: major cardiovascular events (MACE), cardiovascular death and all cause mortality (ACM); and for the following five categories of CKD: CKD3, CKD4, CKD5, dialysis (CKD5D) and renal transplant. The definitions of MACE and

cardiovascular death varied, as shown in Appendix 1.

We obtained hazard ratios and confidence intervals from each paper and derived variances of the log hazard ratios from the reported confidence intervals. For the LIPS substudy[23], log hazard ratio and variance were derived from the numbers at risk and numbers of events per year given in the paper, using the method suggested by Parmar et al[31]. We weighted results by the inverse of the variance of the log hazard ratio and derived pooled effects within each CKD group by fitting a meta regression model predicting log hazard ratio from CKD class. We used mixed effect models to account for heterogeneity of the studies. To quantify residual heterogeneity, I^2 and τ^2 were calculated for each regression model. In addition, we performed a sensitivity analysis incorporating an indicator for study type, namely study in CKD patients only vs. CKD substudy, into the model. All statistical analysis was carried out using R version 3.2.4[32] with packages MAd[33] and metafor[34]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were patients involved in the design and implementation of the study. There are no plans to involve patients in disseminating the results.

Results

Table 1 shows the characteristics of the 13 studies in our meta-analysis. 17263 participants in eight primary or secondary prevention trials and one pooled analysis had CKD3. One trial had a mixed population of both dialysis and non-dialysis patients including 2111 with CKD3, 2565 with CKD4, 1221 with CKD5 and 3023 with CKD5D. Two trials were conducted exclusively in patients on dialysis contributing 4028 to a total of 8272 CKD5/5D patients for the meta-analysis. One trial with 2102 participants was undertaken in patients with a functioning renal transplant. Study duration varied from 1.9 to 5.5 years.

Table 1 about here

Baseline estimated GFR was as reported in the original papers. All included trials were placebo controlled. Six different statins were assessed: pravastatin in 3 trials, atorvastatin, rosuvastatin, simvastatin and fluvastatin in 2 trials each, lovastatin in one trial. One trial tested a combination of simvastatin and ezetimibe. The statin dose, absolute and percentage LDL reduction and achieved LDL in each trial are as shown. There is a suggestion here that absolute LDL reduction was less in the trials of patients with more advanced renal failure. All 13 studies reported MACE, 4 reported cardiovascular mortality while 9 reported all cause mortality. The total number of events available for meta-analysis were 5406, 1183 and 3518 for MACE, cardiovascular death and all cause mortality respectively.

The number of events with hazard ratios and confidence intervals for each end point are given by trial in Table 2 and by CKD class in Figure 1. For MACE, we found a significant protective treatment effect for CKD3 (HR 0.72, 95%CI 0.67-0.78, p<0.001) and CKD4 (HR 0.78, 95%CI 0.61-0.99, p=0.041), but not for CKD5/5D (HR 0.92, 95%CI 0.84-1.02, p=0.099) or transplant patients (HR 0.83, 95%CI 0.64-1.08, p=0.161). The treatment effect in CKD3 was significantly stronger than for CKD5/5D (p<0.001), other pairwise comparisons were not significant. Residual heterogeneity of the model was low (I^2=8.06%, p=0.235). In the sensitivity analysis for MACE, study type was not significant (p=0.723).

For all-cause mortality, we found again that the treatment effect was strongest in CKD3 (HR 0.82, 95%CI 0.73 to 0.91, p=0.001) with no significant benefit in CKD5/5D (HR 0.95, 95%CI 0.87 to 1.04, p=0.262) or transplant patients (HR 1.02, 95%CI 0.81 to 1.29, p=0.870). The treatment effect was stronger in CKD3 than in CKD5/5D (p=0.040), otherwise pairwise comparisons were not significant. There were no all cause mortality data for CKD4. Residual heterogeneity of the model was low (I^2=0.00%, p=0.291).

For cardiovascular mortality, we noted a significant treatment effect in transplant patients (HR 0.62, 95%CI 0.40 to 0.96, p=0.031) but no significant benefit for CKD3 (HR 0.75, 95%CI 0.52 to 1.09, p=0.130) or CKD5/5D (HR 0.92, 95%CI 0.75 to 1.12, p=0.409). Pairwise comparisons were not significant. There were no cardiovascular mortality data for CKD4. There was residual heterogeneity (I^2 52.64%), but homogeneity was not rejected (p=0.146).

Table 2 and Figure 1 about here

There were 9674 subjects with CKD3 in five primary prevention trials and 9712 subjects with CKD3 in five trials that included a significant proportion of subjects with prior CHD (Table 1). Splitting CKD3 into those with and without prior CHD and repeating the analyses for MACE and ACM (none of the primary prevention trials reported cardiovascular mortality), we found that the benefits of statins were not simply confined to CKD3 participants with CHD. Hazard ratios for MACE were 0.75 (95% CI 0.70 to 0.81, p<0.001) for those with and 0.60 (95%CI 0.50 to 0.72, p<0.001) for those without prior CHD. The treatment effect in CKD3 without prior CHD was significantly stronger than for CKD3 with prior CHD (p=0.023). Residual heterogeneity of the model was low (I^2=0.00%, p=0.533).

Corresponding hazard ratios for all cause mortality in CKD3 were 0.86 (95%CI 0.76 to 0.97, p=0.013) for those with and 0.62 (95%CI 0.46 to 0.822, p=0.001) for those without prior CHD. Again, there was a significant difference in the treatment effects between CKD3 with and without prior CHD, favouring those without CHD (p=0.036). Residual heterogeneity of the model was low (I^2=0.03%, p=0.712). There was no difference in treatment effects for MACE when we split CKD 5/5D into trials that included or did not include patients with prior CHD (analysis not possible for ACM or cardiovascular mortality), though we recognise this could also be due to low numbers of events in subgroups.

Discussion

The authors of SHARP, the largest of the lipid lowering trials in patients with CKD, interpreted the results of that trial as supporting the widespread use of statins in both dialysis and non-dialysis patients[6]. That view has since been challenged by the consistent failure of lipid lowering studies to benefit dialysis patients, leading KDIGO in 2014 to recommend treatment with statin or statin/ezetimibe combination in adults aged >= 50 years with eGFR <60ml/min but not treated with renal replacement therapy or renal transplant[15].

There is an assumption here that all predialysis patients will benefit and it is possibly for this reason that none of the recent guidelines distinguish between CKD3, CKD4 and CKD5. The Joint British Societies 3 Guideline suggests that lipid lowering therapy with statins be considered in all adults with stages 3-5 CKD[35], while NICE advise atorvastatin 20 mg daily for the primary or secondary prevention of CVD for all people with CKD (which they define as eGFR <60ml/min and/or urine ACR >3mg/mmol)[36]. Five of the eight CKD meta-analyses came to essentially the same conclusion, namely that statins be considered for cardiovascular disease prevention in most patients with CKD[9-13]. The CTTC observed a trend towards smaller reduction in major vascular events as eGFR declined but did not advise against treating patients with advanced renal failure, concluding instead that statin based regimens should be chosen to maximise the absolute reduction in LDL cholesterol to achieve the largest treatment benefit[7].

Pooling patients with CKD3, 4 and 5 seems illogical to us for two reasons: first, CKD3 occurs in up to one third of UK adults over 75 years of age and is around 20x more common than CKD4 and 5[37]; and second, pooling takes no account of the change in pathophysiology of the vascular disease from atherosclerotic to calcific arteriopathy and myocardial fibrosis as renal failure progresses[1]. The other meta-analyses[7-14] did not address this question directly and it was for this reason that we undertook our own.

The main findings of our meta-analysis were as follows. We found a convincing benefit of statins for MACE and all cause mortality in CKD3 especially in patients without prior CHD but also in those with prior CHD. Reduction of cardiovascular mortality in CKD3 is not significant, but the estimated HR is of similar magnitude. In CKD4, statins reduce MACE significantly but for ACM and cardiovascular mortality there are no data. In CKD5/5D, estimated treatment effects are small and not significant for any of the endpoints. In transplant patients the results do not suggest a treatment effect on ACM or MACE. For cardiovascular mortality, there appears to be a protective effect which just achieves statistical significance. We are aware that an open label extension to ALERT has suggested a likely benefit for MACE but since both groups received statins in the extension period we did not feel that those results could be incorporated in the meta-analysis[30] .

There are several possible explanations why statins become less effective at reducing vascular events as renal function declines. First, the changes in pathophysiology described above may lead to death from heart failure and arrhythmia rather than myocardial infarction[1]. We would not expect lipid-lowering therapy to benefit either of these conditions. Second, dialysis patients have additional uremia-related risk factors that include anaemia, hyperphosphatemia, oxidative stress, inflammation, and accumulation of the endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine, which results in reduced nitric oxide synthesis and may significantly contribute to CVD[1]. Again, none of these factors are likely to be improved by lipid lowering therapy. Third, it is possible that failure to demonstrate benefit with statins in patients with more severe kidney disease reflects lower baseline LDL cholesterol and smaller absolute reductions in LDL cholesterol as eGFR declines[7]. However, the CTTC adjusted for these possibilities by reporting event rates per mmol of LDL reduction and showed that the relative reduction in major vascular events observed with statin-based treatment does indeed become smaller as renal failure progresses[7]

Our meta-analysis did not directly address the question whether benefit in CKD3 reflected statin responsive atherosclerotic disease and that failure to benefit in CKD5/5D was a consequence of calcific arteriopathy/myocardial fibrosis, though this may be inferred from a comparison of outcomes in WOSCOPS[38] and SHARP[6]. WOSCOPS was a primary prevention trial of middle aged men with essentially normal renal function whereas SHARP was a trial of men and women, 27% of whom had CKD3 and 73% CKD4+CKD5/5D. Average follow up in both trials was 4.9 years. All cause mortality in SHARP participants randomized to placebo was 6x that of the WOSCOPS placebo group, yet the proportion of participants who died a CHD death in the placebo groups of SHARP and WOSCOPS was identical (Figure 2). CHD deaths were responsible for only 7.9% of SHARP deaths but for 46.3% of WOSCOPS deaths. If statins were only able to reduce the incidence of CHD deaths in both trials then it is perhaps unsurprising that statins appeared less effective in SHARP than in WOSCOPS.

Figure 2 about here

We acknowledge limitations. In our comparison of statin trials it was not always possible to compare like with like as definitions of MACE and cardiovascular death differed. Some of these differences were minor and some not (Appendix 1). AURORA included fatal stroke in their cardiovascular deaths[5] whereas 4D did not[4]. Cardiovascular deaths in ALERT were cardiac deaths only[3]. In each of these examples the choice of endpoint may have inadvertently influenced the result of the trial in question: respectively more fatal strokes and non-cardiac vascular deaths occurred in 4D and ALERT patients who were randomised to statin therapy. There is, moreover, no agreed method for determining the precise cause of vascular death in patients with advanced CKD, an issue that has recently been addressed, though not completely resolved, by the CTTC meta-analysis[7]. We also recognise that we did not attempt to analyse outcomes other than MACE, vascular death and all cause mortality. Others have done so and have found no increase in risk of adverse events[16] with the possible exception of type 2 diabetes[39].

We accept that our analysis sheds no light on the question whether statins started in CKD3 should be stopped if and when a patient reaches stage 5/5D. The trials were of patients starting statins in different stages of CKD and didn't include patients already on statins. We further acknowledge that we relied on local expertise, previously published meta-analyses and systematic reviews rather than duplicate the work of others by conducting a formal literature search. As a direct consequence of this approach, however, we were able to incorporate data from PROSPER that were not included in several other meta-analyses[8-11,13], allowing us to analyse results from no fewer than 19386 subjects with CKD3. We are confident that this strategy has yielded all relevant studies up to and including those published by 11th May 2016 and that risk of bias in included trials was low[7].

Based on our meta-analysis and on our interpretation of the literature we believe that statins are indicated in CKD3, probably indicated in CKD4, not indicated in CKD5/5D and probably indicated in patients with a functioning transplant. We do not feel the available evidence currently supports the more widespread use of statins in CKD that has been recommended by some authorities[9,11,13,35,36] simply because the trials and meta-analyses on which

their recommendations are based have not yet included large enough numbers of patients with CKD4 and functioning renal transplants for confident conclusions to be drawn.

Word count 2852 (excl abstract)

References

1. Qunibi WY. Dyslipidaemia in dialysis patients. Seminars in dialysis 2015; 28: 345-53

2. De Jager DJ, Grootendorst DC, Jager KJ, Van Dijk PC, Tomas LM, Ansell D et al. Cardiovascular and non cardiovascular mortality among patients starting dialysis. JAMA 2009; 302:1782-9.

3. Holdaas H, Fellstrom B, Jardine AG et al on behalf of the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of Fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003; 361: 2024-2031.

4. Wanner C, Krane V, Marz W, Olschewski M, Mann JFE, Ruf G for the German Diabetes and Dialysis Study Investigators. Atorvastatin in Patients with Type 2 Diabetes Mellitus undergoing Hemodialysis. N Engl J Med 2005; 353: 238-248.

5. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J et al for the AURORA Study Group. Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. N Engl J Med 2009; 360: 1393-1407.

6. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C et al on behalf of the SHARP investigators. The Effects of Lowering LDL Cholesterol with Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease (Study of Heart and Renal Protection): a Randomised Placebo-Controlled Trial. Lancet 2011; 377: 2181-2192.

7. Cholesterol Triallists Treatment Collaboration. 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. Lancet 2016; 4: 829-839 (published online 28th July 2016)

8. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GFM. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 263-275.

9. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM: Lipid-lowering therapy in persons with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med 2012; 157: 251– 262.

10. Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, Zhang H. Effects of statins on kidney disease outcomes: a systematic review and meta-analysis. Am J Kidney Dis 2016; 67: 881-92

11. Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ et al. Outcome of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Europe Heart J 2013; 34: 1807-1817.

12. Green D, Ritchie JP, Kalra PA. Meta-analysis of lipid lowering therapy in maintenance dialysis patients. Nephron Clinical Practice 2013; 124: 209-17

13. Major RW, Cheung CK, Gray LJ, Brunskill NJ. Statins and Cardiovascular Prevention in CKD: a meta-analysis. CJASN 2015; 10: 732-9.

14. Yan Y-L, Qiu B, Wang J, Deng S-B, Wu L, Jing X-D et al. High intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 2015; 5: e006886

15. Tonelli M, Wanner C for the Kidney Disease Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid Management in a Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving a Global Outcomes 2013 Clinical Practice Guideline. Ann Intern Med 2014; 160: 182-189.

16. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub5.

17. Kendrick J, Shlipak MG, Targher G, Cook T, Lindenfeld J, Chonchol M: Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: A post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. Am J Kidney Dis 55: 42–49, 2010.

18. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Charlton-Menys V, DeMicco DA, Fuller JH; CARDS Investigators: Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: An analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis 54: 810–819, 2009.

19. Ridker PM, MacFadyen J, Cressman M, Glynn RJ: Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: A secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol 2010; 55: 1266–1273.

20. Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y; MEGA Study Group: Pravastatin and cardiovascular risk in moderate chronic kidney disease. Atherosclerosis 2009; 206: 512–517.

21. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis. 2007; 49: 373-8.

22. Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled trial. Lancet 2002; 360: 7-22.

23. Lemos PA, Serruys PW, de Feyter P, Mercado N, Goedhart D, Saia F et al. Long term Fluvastatin reduces the hazardous effect of renal impairment on four year atherosclerotic outcomes (a LIPS substudy). Am J Cardiology 2005; 95: 445-51.

24. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30.

25. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J et al. Effect of Pravastatin on Cardiovascular Events in People with Chronic Kidney Disease. Circulation 2004;110:1557-1563.

26. Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP on behalf of the ALLIANCE Investigators. Focused Atorvastatin Therapy

in Managed-Care Patients With Coronary Heart Disease and CKD. Am J. Kidney Dis 2009; 53: 741-50.

27. Study of the effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Study Group. Intensive lowering of LDL cholesterol with 80mg versus 20mg simvastatin daily in 12064 survivors of myocardial infarction: a double blind randomized trial. Lancet 2010; 376: 1658-69.

28. Shepherd J, Kastelein JJP, Bittner V, Deedwania P, Breazna V, Dobson S et al for the TNT Investigators. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: The TNT (Treating to `new Targets) Study. J Am Coll Cardiol 2008; 51:1448–54.

29. Landray M, Baigent C, Leaper C, Adu D, Altman P, Armitage A et al. The second UK Heart and Renal Protection (UK-HARP-II) study: a randomised controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with chronic kidney disease. Am J Kidney Disease 2006;47: 385-95.

30. Holdaas H, Fellstrom B, Cole E, Nyberg G, Olsson AG, Pedersen TR et al on behalf of the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Long term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplantation 2005; 5: 2929-2936

31. Parmar MK, Torri V, Stewart L. Extracting Summary Statistics to Perform Meta-Analyses of the Published Literature for Survival Endpoints. Statistics in Medicine 1998; 17: 2815-2834.

32. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2016. URL https://www.R-project.org/.

33. Del Re AC, Hoyt WT. MAd: Meta-analysis with mean differences. R package version 0.8-2, 2014. URL: http://cran.r-project.org/web/packages/MAd

34. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software, 2010; 36: 1-48. URL: http://www.jstatsoft.org/v36/i03/

35. JBS3: Joint British Societies' consensus recommendations for the prevention of cardiovascular disease Heart 2014;100: supp 2:1-67.

36. NICE CG181. Lipid Modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease, July 2014.

37. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney International 2007; full reference required.

38. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW for the West of Scotland Coronary Prevention Study Group. Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolaemia. N Engl J Med 1995; 333:1301-1307.

39. Sattar N, Preiss D, Murray H, Welsh P, Buckley B, de Crean AJM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735-42.

Authorship

CI had the idea for this study and wrote the first draft. MM was responsible for the statistical analyses. Both authors contributed to the final version of the paper and both are guarantors for the study.

Competing interests

We have read and understood BMJ policy on declaration of interests and declare the following interests:

C-MM: No conflict of interests.
CI: Steering committee of WOSCOPS

Funding

Study was supported by a grant from Dumfries and Galloway Health Board

Ethical approval

Because this was a meta-analysis of previously published and anonymised trial data we did not seek ethical approval, in keeping with our health boards policies.

Appendix 1 - Vascular end points

MACE

4S - coronary deaths, definite or probable hospital verified nonfatal acute MI, resuscitated cardiac arrest, and definite silent MI verified by using electrocardiogram.
AFCAPS/TEXCAPS - unstable angina, fatal or nonfatal MI, and sudden cardiac death.
CARDS – acute CHD death, nonfatal MI including silent MI, hospitalized unstable angina, resuscitated cardiac arrest, coronary revascularization or stroke.
HPS - nonfatal MI, death from coronary disease, strokes of any type, and coronary or non-coronary revascularization.
JUPITER - nonfatal MI, nonfatal stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death.
MEGA - fatal and nonfatal MI, angina pectoris, cardiac/sudden death, and coronary revascularization.
LIPS - cardiac death (all deaths except those unequivocally related to a noncardiac cause), nonfatal MI and all reinterventions (surgical or percutaneous) not caused by coronary restenosis occurring after a first successful PCI.
PPP - death from cardiovascular causes, non fatal MI, coronary revascularization or stroke
PROSPER - definite or suspected death from coronary heart disease, non-fatal MI, and fatal or non-fatal stroke.
SHARP - first non fatal MI or coronary death, non haemorrhagic stroke or any revascularisation procedure
4D - death from cardiovascular causes, non fatal MI or non fatal stroke.
AURORA - death from cardiovascular causes, non fatal MI or non fatal stroke.
ALERT - cardiac deaths, non fatal MI or coronary intervention procedures

Cardiovascular deaths

PROSPER – cardiac and other vascular deaths including fatal stroke
AURORA - cardiac and other vascular deaths including fatal stroke
4D - cardiac and other vascular deaths excluding fatal stroke
ALERT - cardiac deaths only.

Table 1 Baseline Characteristics of Included Studies

Study	CKD stage	Definition of CKD	Number of patients	Prior CHD	Active treatment	Baseline LDL (mmol/l)	LDL reduction (%)	LDL reduction (mmol/l)	LDL achieved (mmol/l)	Duration (years)	MACE	CV mortality	All cause mortality
AFCAPS	CKD 3	eGFR <60ml/min (may include some patients with CKD4)	304	No	Lovastatin 20mg	3.9	27	1.05	2.85	5.2	Yes	No	No
CARDS	CKD 3	eGFR 30-60 ml/min (1 patient had CKD4)	970	No	Atorvastatin 10mg	3.1	41	1.27	1.83	3.9	Yes	No	Yes
JUPITER	CKD 3	eGFR 30-60ml/min (14 patients had eGFR <30 ml/min)	3267	No	Rosuvastatin 10mg	2.8	52	1.46	1.34	1.9	Yes	No	Yes
MEGA	CKD 3	eGFR 30-60ml/min	2978	No	Pravastatin 40mg	4.0	19	0.76	3.24	5.3	Yes	No	Yes
SHARP	CKD 3	eGFR 30-59ml/min	2155	No	Simvastatin 20mg and ezetimibe 10mg	2.9[1]	34	0.99	1.91	4.0	Yes	No	No
4S	CKD 3	eGFR 30-59ml/min	505	100%	Simvastatin 40mg	4.9[2]	28	1.37	3.53	5.5	Yes	No	Yes
HPS	CKD 3	Serum creatinine 11-200umol/l in women and 130-200umol/l in men	1329	65%	Simvastatin 40mg	3.4[3]	29	0.99	2.41	4.8	Yes	No	No
LIPS	CKD 3	Creatinine clearance <55.9ml/min with baseline serum creatinine <159umol/l	310	100%	Fluvastatin 40mg	3.4	24	0.82	2.58	3.8	Yes	No	No
PROSPER	CKD 3	eGFR 30-60ml/min	3077	44%	Pravastatin 40mg	3.8	34	1.29	2.51	3.2	Yes	Yes	Yes
PPP	CKD 3	eGFR 30-60ml/min	4491	74%	Pravastatin 40mg	3.9	32	1.25	2.65	5.0	Yes	No	Yes
SHARP	CKD 4	eGFR 15-29ml/min	2565	No	Simvastatin 20mg and ezetimibe 10mg	2.9	36	1.04	1.86	4.0	Yes	No	No
SHARP	CKD 5	eGFR <15ml/min but not on dialysis	1221	No	Simvastatin 20mg and ezetimibe 10mg	2.9	25	0.73	2.17	4.0	Yes	No	No
SHARP	CKD 5D	Dialysis	3023	No	Simvastatin 20mg and ezetimibe 10mg	2.6	23	0.60	2.00	4.0	Yes	No	No
4D	CKD 5D	Dialysis	1255	29%	Atorvastatin 20mg	3.1	42	1.3	1.8	4.0	Yes	Yes	Yes
AURORA	CKD 5D	Dialysis	2773	40%	Rosuvastatin 10mg	2.6	43	1.12	1.48	3.2	Yes	Yes	Yes
ALERT	TX	Transplant	2102	10%	Fluvastatin 40mg	4.1	32	1.31	2.79	5.1.	Yes	Yes	Yes

[1]SHARP main results paper implies that baseline LDL was 2.9mmol/l for all non-dialysis patients. [2]Data for all 4S patients with eGFR <75ml/min as LDL levels for those with eGFR 30-59ml/min not given separately. [3]Data for all HPS trial participants as LDL levels in renal subgroup not given separately.

Table 2 Cardiovascular outcomes and all cause mortality by CKD class

Study	CKD stage	Statin events (%)	Placebo events (%)	Estimated Hazard Ratio (95% CI)
Major Atherosclerotic Cardiac Event (MACE)				
AFCAPS	CKD 3	8/145 (5.5)	21/159 (13.2)	0.39 (0.16, 0.93)
CARDS	CKD 3	25/482 (5.2)	42/488 (8.6)	0.57 (0.35, 0.94)
JUPITER	CKD 3	40/1638 (2.4)	71/1629 (4.4)	0.56 (0.38, 0.82)
MEGA	CKD 3	33/1471 (2.2)	71/1507 (4.7)	0.45 (0.30, 0.69)
SHARP	CKD 3	87/1100 (7.9)	110/1055 (10.4)	0.75 (0.57, 1.00)
4S	CKD 3	53/245 (21.6)	77/260 (29.6)	0.73 (0.54, 0.99)
HPS	CKD 3	182/646 (28.1)	268/683 (39.2)	0.72 (0.62, 0.84)
LIPS	CKD 3	23/150 (15.3)	47/160 (29.4)	0.51 (0.31, 0.82)
PROSPER	CKD 3	220/1548 (14.2)	287/1529 (18.6)	0.74 (0.62, 0.88)
PPP	CKD 3	573/2217 (25.8)	730/2274 (32.1)	0.79 (0.71, 0.88)
SHARP	CKD 4	127/1246 (10.2)	168/1319 (12.7)	0.78 (0.62, 0.98)
SHARP	CKD 5	67/614 (10.9)	81/607 (13.3)	0.82 (0.59, 1.13)
SHARP	CKD 5D	230/1533 (15.0)	246/1490 (16.5)	0.90 (0.75, 1.08)
4D	CKD 5D	226/619 (36.5)	243/636 (38.2)	0.92 (0.77, 1.10)
AURORA	CKD 5D	396/1389 (28.5)	408/1384 (29.5)	0.96 (0.84, 1.11)
ALERT	TX	112/1050 (10.7)	134/1052 (12.7)	0.83 (0.64, 1.06)
Cardiovascular mortality				
PROSPER	CKD 3	76/1548 (4.9)	99/1529 (6.5)	0.75 (0.58, 1.01)
4D	CKD 5D	121/619 (19.5)	149/636 (23.4)	0.81 (0.64, 1.03)
AURORA	CKD 5D	324/1389 (23.3)	324/1384 (23.4)	1.00 (0.85, 1.16)
ALERT	TX	36/1050 (3.4)	54/1052 (5.1)	0.62 (0.40, 0.96)
All cause mortality				
CARDS	CKD 3	27/482 (5.6)	30/488 (6.2)	0.86 (0.51, 1.45)
JUPITER	CKD 3	34/1638 (2.1)	61/1629 (3.7)	0.56 (0.37, 0.85)
MEGA	CKD 3	16/1471 (1.1)	34/1507 (2.3)	0.49 (0.27, 0.89)
4S	CKD 3	37/245 (15.1)	40/260 (15.4)	0.99 (0.64, 1.55)
PPP	CKD 3	322/2217 (14.5)	383/2274 (16.8)	0.86 (0.74, 1.00)
PROSPER	CKD 3	156/1548 (10.1)	184/1529 (12.0)	0.83 (0.67, 1.03)
4D	CKD 5D	297/619 (43.1)	320/636 (50.3)	0.93 (0.79, 1.08)
AURORA	CKD 5D	636/1389 (45.7)	660/1384 (47.7)	0.96 (0.86, 1.07)
ALERT	TX	143/1050 (13.6)	138/1052 (13.1)	1.02 (0.81, 1.30)

Figure 1. Cardiovascular Outcomes and All Cause Mortality by CKD Class

	Statin Events (%)	Placebo Events (%)	Risk Ratio (95% CI)	p Value
Major Cardiovascular Events				
CKD3	1244/9642 (12.9)	1724/9744 (17.7)	0.72 (0.67, 0.78)	<0.001
CKD4	127/1246 (10.2)	168/1319 (12.7)	0.78 (0.62, 0.99)	0.041
CKD5/5D	919/4155 (22.1)	978/4117 (23.8)	0.92 (0.84, 1.02)	0.099
TX	112/1050 (10.7)	134/1052 (12.7)	0.83 (0.64, 1.08)	0.161
Cardiac or Cardiovascular Mortality				
CKD3	76/1548 (4.9)	99/1529 (6.5)	0.75 (0.52, 1.09)	0.130
CKD4	No data			
CKD5/5D	445/2008 (22.2)	473/2020 (23.4)	0.92 (0.75,1.13)	0.409
TX	36/1050 (3.4)	54/1052 (5.1)	0.62 (0.38, 1.01)	0.054
All Cause Mortality				
CKD3	592/7601 (7.8)	732/7687 (9.5)	0.82 (0.73, 0.91)	<0.001
CKD4	No data			
CKD5/5D	933/2008 (46.5)	980/2020 (48.5)	0.95 (0.87, 1.04)	0.262
TX	143/1050 (13.6)	138/1052 (13.1)	1.02 (0.81, 1.29)	0.870

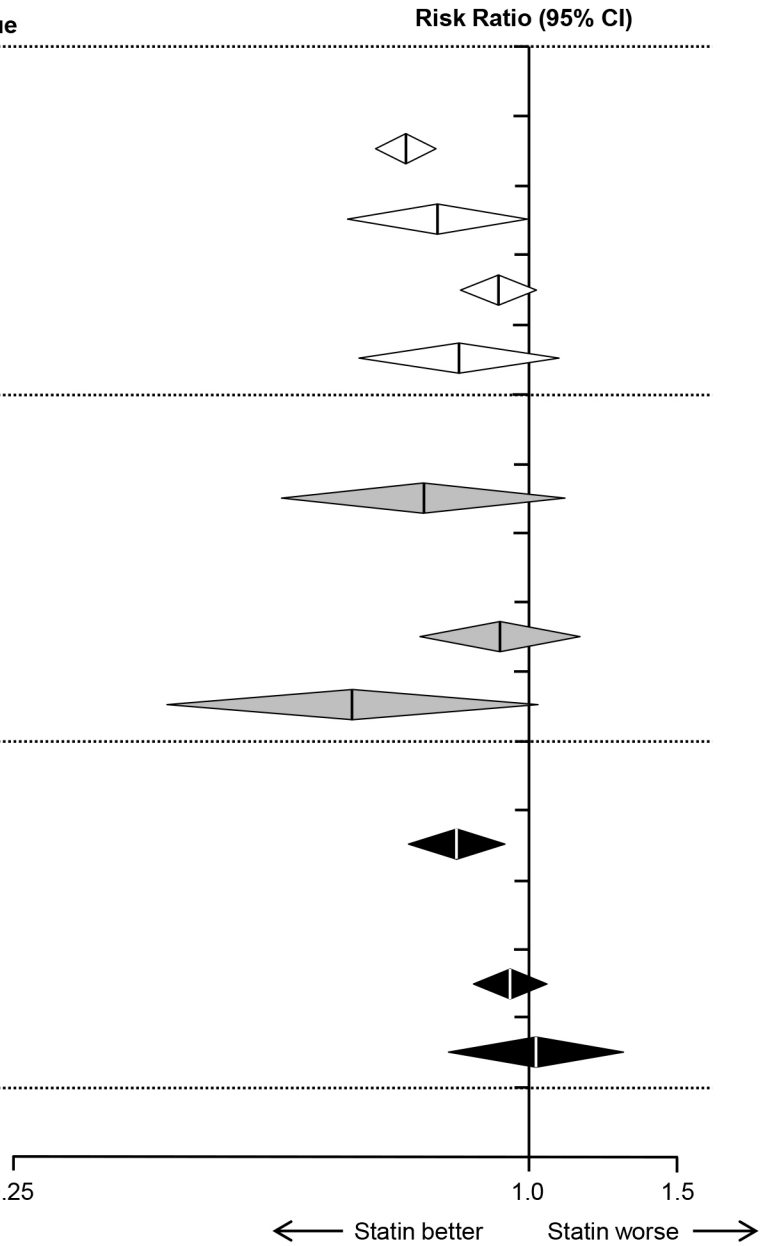
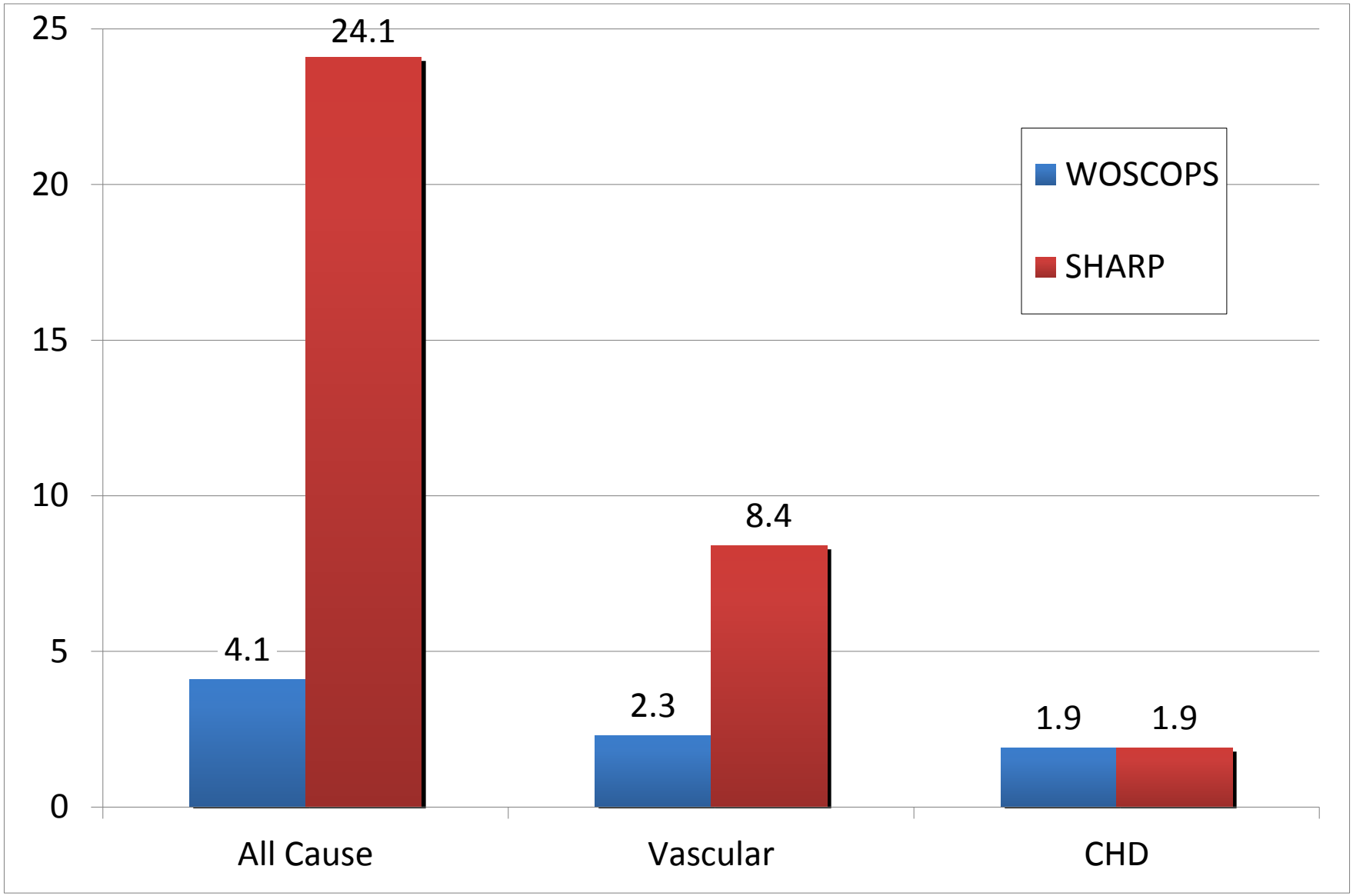


Figure 2


25
20
15
10
5
0
24.1
4.1
8.4
2.3
1.9
1.9
WOSCOPS
SHARP
All Cause
Vascular
CHD