Cost-effectiveness of lowering LDL cholesterol with statins and ezetimibe in chronic kidney disease

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Abstract

Statin-based treatments reduce cardiovascular risk in non-dialysis chronic kidney disease (CKD) but it is unclear which regimen is the most cost-effective. We used the SHARP CKD-CVD policy model to evaluate the effects of statins/ezetimibe (eg, ezetimibe 10mg, atorvastatin 20 or 40mg alone or plus ezetimibe) on quality-adjusted life years (QALYs) and healthcare costs in the US and UK settings. Treatment effects on cardiovascular risks per 1mmol/L LDL cholesterol reduction at each CKD stage, as reported by the Cholesterol Treatment Trialists’ Collaboration (CTT) meta-analysis, were used together with the LDL cholesterol reductions estimated for each statin/ezetimibe regimen considered.

In the US, the highest intensity low-cost statin considered safe in CKD (eg, atorvastatin 40mg at $0.103/day, January 2019) increased life expectancy by 0.23 to 0.31QALYs in non-dialysis patients in stages 3B to 5 CKD at net cost from $20,300/QALY to $78,200/QALY and was cost-effective. Adding ezetimibe ($0.203/day) increased life expectancy of these patients by further 0.05 to 0.07QALYs at net costs of $43,600 to $91,500/QALY. The cost-effectiveness findings and policy implications in the UK were similar.

In summary, in non-dialysis-dependent CKD the evidence suggests that low-cost statin/ezetimibe combination therapy is a cost-effective treatment, and that the most cost-effective regimen is one that maximises the dose of statin chosen without compromising safety.

Keywords: cost-effectiveness; statin; ezetimibe; chronic kidney disease; healthcare costs; quality-adjusted life years.
**Introduction**

With over 250 million people affected worldwide, chronic kidney disease (CKD) is a common disease\(^1,2\), and its prevalence is expected to increase further with rising levels of obesity and diabetes and an ageing population. In the US, around 7% of adults have CKD stage 3-5\(^3\). People with reduced kidney function have increased cardiovascular risk\(^4,5\), which is a key treatment target.

The Study of Heart and Renal Protection (SHARP) showed that lowering LDL cholesterol with a combination of simvastatin 20mg plus ezetimibe 10mg daily for about 5 years safely reduced the risk of major atherosclerotic events (MAE: nonfatal myocardial infarction or coronary death, non-haemorrhagic stroke, or arterial revascularisation procedure) in non-dialysis patients with moderate-to-advanced CKD\(^6\). Subsequently a large meta-analysis of individual participant data from 28 trials of statin therapy, or in the case of SHARP, statin plus ezetimibe, was coordinated by the Cholesterol Treatment Trialists’ (CTT) Collaboration\(^7\). This showed that the relative reduction in major vascular events (MVE: major atherosclerotic event, non-coronary cardiac death or haemorrhagic stroke) per 1mmol/L reduction in LDL cholesterol ranged from 22% among participants with estimated glomerular filtration rate (eGFR) of ≥60ml/min/1.73m\(^2\) to 15% among non-dialysis participants with eGFR<30ml/min/1.73m\(^2\), with a trend towards smaller risk reductions with lower eGFR and no evidence of clinical efficacy in dialysis patients. By design, SHARP did not assess the separate clinical effects of ezetimibe, but evidence of the effects on vascular outcomes of adding ezetimibe to simvastatin, albeit among patients with an acute coronary syndrome and without established CKD, has been provided by the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)\(^8\). In this trial, for each mmol/L reduction in LDL-cholesterol, the relative reduction in vascular events resulting from ezetimibe was consistent with that predicted by a meta-analysis of randomized trials of statin therapy alone\(^9\).
Based on all randomised trial evidence, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in CKD recommended use of a statin or statin/ezetimibe combination for adults ≥50 years old with an eGFR≤60ml/min/1.73m$^2$ who are not on renal replacement therapy (RRT: chronic dialysis or kidney transplantation), and a statin alone for other adults with non-dialysis-dependent CKD$^{10}$. The 2018 ACC/AHA Multisociety Guideline on cholesterol management recommends initiating statin or statin/ezetimibe combination in ≥40 years old CKD patients with an increased (>7.5%) 10-year risk of atherosclerotic cardiovascular disease$^{11-13}$. In the UK, the National Institute for Health and Care Excellence recommends atorvastatin 20mg daily for the primary prevention of cardiovascular disease in people with eGFR<60ml/min/1.73m$^2$, and suggests considering a higher dose, and/or combination with ezetimibe, in more advanced CKD (eg, eGFR<30ml/min/1.73m$^2$), for secondary cardiovascular disease prevention, or when the desired cholesterol reduction has not been achieved$^{14,15}$.

Despite these recommendations, it remains unclear which statin/ezetimibe combination is the most cost-effective treatment in moderate-to-advanced CKD (ie, offers the greatest benefits and is affordable). A cost-effectiveness study of 5-year simvastatin plus ezetimibe treatment in SHARP concluded that high-intensity generic treatments, rather than more expensive proprietary treatments, are cost-effective$^{16}$. However, a more pertinent question for healthcare providers is the cost-effectiveness of long-term treatments. We use the SHARP CKD-CVD policy model$^{17}$ to project lifetime risks of cardiovascular disease and CKD progression and the net effects and cost-effectiveness of long-term statin/ezetimibe treatments in categories of patients with CKD.

**Results**

**CKD patients**

Results are presented only for non-dialysis patients, since there is no clear evidence that LDL cholesterol lowering therapy is effective in dialysis patients$^7$. The mean age of the 6,235 such
patients in the SHARP study was 63 years (SD 12); 62% were male; 23% had diabetes and 15% had prior history of (non-coronary) vascular disease. There were 2,020 participants with stage 3B, 2,767 with stage 4, and 1,448 with stage 5 not on dialysis. The participants’ median 5-year cardiovascular risk ranged from 10% among those in stage 3B to 20% among non-dialysis participants in stage 5, and from 6% to 31% across the three categories of baseline risk (Table 1). Within each stage of CKD, participants at higher risk at baseline were older and more likely to have previous vascular disease or diabetes (Table S1).

**Effects of statin/ezetimibe treatments**

Among the treatments considered, the least potent was ezetimibe 10mg daily, reducing LDL cholesterol by 18.5%, and the most potent was atorvastatin 40 plus ezetimibe 10mg daily, reducing LDL cholesterol by 60.1%; atorvastatin 40mg daily reduced LDL cholesterol by 48% (Table S2). The proportional reductions in risk of major vascular events with use of (i) ezetimibe 10mg, were 8% [99% CI 2%, 14%] in stage 3B, 8% [-1%, 17%] in stage 4, and 8% [-1%, 16%] in stage 5 not on dialysis; (ii) atorvastatin 40mg daily, were 20% [6%, 33%] in stage 3B, 20% [-3%, 38%] in stage 4, and 19% [-3%, 36%] in stage 5 not on dialysis; and (iii) atorvastatin 40mg plus ezetimibe 10mg, were 25% [7%, 40%] in stage 3B, 25% [-4%, 45%] in stage 4, and 23% [-3%, 43%] in stage 5 not on dialysis patients (Table S3).

**US cost-effectiveness of statin/ezetimibe treatments**

In all categories of CKD patients, at current statin/ezetimibe prices (January 2019), treatment with ezetimibe 10mg was both less effective and more expensive and, therefore, (in health economic jargon) was ‘dominated’ by atorvastatin 20mg; rosuvastatin 20mg was dominated by similarly effective and slightly cheaper atorvastatin 40mg; simvastatin 20mg plus ezetimibe 10mg was dominated by atorvastatin 40mg; and atorvastatin 20mg plus ezetimibe 10mg was dominated by atorvastatin 40mg (Table S2). Additionally, atorvastatin 20mg was projected to produce very
similar health benefits at a similar additional cost per QALY to atorvastatin 40mg (Table S4).

Therefore, we present results for atorvastatin 40mg and atorvastatin 40mg plus ezetimibe 10mg only. However, since atorvastatin 20mg could be considered as a less intensive treatment option, and ezetimibe 10mg could be used by patients who cannot tolerate or do not use a statin-based regimen, we also present results for these regimens.

Lifetime use of atorvastatin 40mg is projected to increase life expectancy by 0.26 years (0.23QALYs) at a net cost of $20,300/QALY in patients with stage 3B, 0.37 years (0.31QALYs) at a net cost of $44,200/QALY in patients with stage 4, and 0.31 years (0.26QALYs) at $78,200/QALY in patients with stage 5 not on dialysis. Similarly, it would increase life expectancy by 0.29 years (0.26QALYs) at $38,100/QALY in those at low cardiovascular risk (<10%), 0.32 years (0.27QALYs) at $41,000/QALY in those at medium cardiovascular risk (10-20%), and 0.36 years (0.29QALYs) at $55,000/QALY in those at high cardiovascular risk (≥20%) (Table 2).

Within each cardiovascular risk group, the net cost per QALY was lowest for patients in stage 3B and highest for those in stage 5 not on dialysis, while within each CKD stage, net costs per QALY were similar at all levels of cardiovascular risk (Figure S1). In almost all subgroups, patients who were younger at treatment initiation were projected to benefit the most but at the highest net cost per QALY. For example, patients <60 years old were projected to gain between 0.28QALYs (if at low risk) and 0.51QALYs (if at high risk) at a net cost, respectively, of $42,000 to $76,400/QALY; while the respective estimates for the patients ≥70 years old were 0.13 (low risk) to 0.22 (high risk) QALYs at a net cost of $10,700 to $42,300/QALY (Table S5).

Adding ezetimibe 10mg was estimated to provide further benefits: there were an additional 0.06 years (0.05QALYs, net cost $43,600/QALY) in stage 3B, 0.08 years (0.07QALYs, net cost $58,400/QALY) in stage 4, and 0.07 years (0.06QALYs, net cost $91,500/QALY) in stage 5 not on dialysis, and an additional 0.06 years (0.06QALYs, net cost $65,100/QALY) in low risk, 0.07 years (0.06QALYs, net cost $56,700/QALY) in medium risk, and 0.08 years (0.07QALYs, net cost
$64,400/QALY) in high risk patients (Table 2). At the $100,000/QALY cost-effectiveness threshold, atorvastatin 40mg plus ezetimibe 10mg would be considered cost-effective with >95% probability in all patients except those in stage 5 not on dialysis (76%) (Figure 1).

Similar to treatment with atorvastatin 40mg alone, the net cost per QALY with the combination of atorvastatin 40mg and ezetimibe 10mg daily, compared to atorvastatin 40mg daily, was lowest for patients in stage 3B and highest for those in stage 5 not on dialysis, at each level of risk (Figure S1).

Ezetimibe 10mg daily, compared to no lipid-lowering treatment, was projected to result in 0.09 extra QALYs in stage 3B, 0.13 extra QALYs in stage 4, and 0.10 extra QALYs in stage 5 not on dialysis at a net cost of, respectively, $31,000, $50,600 and $84,200/QALY, and 0.11 extra QALYs in low risk, 0.11 extra QALYs in medium risk and 0.12 extra QALYs in high risk patients at net cost of $50,900, $48,300 and $58,800/QALY (Table S6).

**UK cost-effectiveness of statin/ezetimibe treatments**

In the UK setting, ezetimibe is now also available at low prices from generic treatment manufacturers (£0.074/day, January 2019). The treatment benefits, cost-effectiveness and policy implications for different statin/ezetimibe treatments (ie, atorvastatin 40mg daily, ezetimibe alone and in combination with a statin) were similar to those in the US (Table 2, Figure 1, Tables S5-S7, Figure S1).

**Sensitivity analyses**

The cost-effectiveness results were only minimally sensitive to further falls in the price of ezetimibe (Figure 2). If ezetimibe 10mg were priced at less than $0.323/day (£0.019/day in the UK), its net cost per QALY would be under $100,000 (£20,000) for all non-dialysis CKD patients.

When analyses were repeated with the annual treatment costs for RRT assumed similar to those for CKD stage 5 not on dialysis, the net cost per QALY with statin/ezetimibe treatments decreased
substantially. In the US setting, the net cost per QALY with atorvastatin 40mg daily decreased from $20,300 to $5,000 in stage 3B, from $44,200 to $6,900 in stage 4, and from $78,200 to $7,100 in CKD stage 5 not on dialysis; the net cost per QALY for atorvastatin 40mg plus ezetimibe 10mg daily decreased from $43,600 to $27,500 in stage 3B, from $58,400 to $20,600 in stage 4, and from $91,500 to $19,900 in stage 5 not on dialysis; the impact was similar in the UK setting (Table S8).

The net costs per QALY only minimally increased when potential adverse effects of statin/ezetimibe treatments and their costs were projected (Table S9). Reduced compliance with treatment was projected to result in lower health benefits but also lower incremental hospital costs, and did not materially affect the results (Table S10).

**Discussion**

Lowering LDL cholesterol with statin-based treatments safely reduces cardiovascular risk in patients with moderate-to-advanced CKD who are not receiving maintenance dialysis, but there is no evidence that such treatment is effective in dialysis patients. We report that under the standard cost-effectiveness assumptions, ie a threshold of $100,000/QALY (£20,000 to £30,000/QALY in the UK), low-cost statin treatments (eg atorvastatin 40mg daily) are cost-effective in non-dialysis CKD patients. Ezetimibe has recently come off patent in both countries and, at current prices ($0.203/day and £0.074/day, respectively), adding ezetimibe 10mg to atorvastatin 40mg daily is a cost-effective option in non-dialysis CKD patients and would thus be the treatment of choice. The results remain robust across a range of sensitivity analyses.

Despite the higher net cost per QALY, the finding that low-cost generic statins/ezetimibe are cost-effective for primary prevention of cardiovascular disease in CKD is consistent with results for the general population at an increased cardiovascular risk. Unlike general population estimates, in non-dialysis-dependent CKD, the net cost per QALY was generally higher among patients at more advanced CKD stage and/or higher predicted cardiovascular risk, especially for very low-cost
treatments (eg atorvastatin 40mg, or ezetimibe 10mg at a lower price). This is driven by reduced life expectancy, higher end stage kidney disease risks and RRT costs, which are incurred during the gained life expectancy and are substantial in more advanced CKD. Statin-based treatments would also be more cost-effective in patients receiving a kidney transplant, with lower RRT costs in the years following the transplantation.

The present study builds upon a study by Erickson et al\textsuperscript{21}, and our findings support its conclusion that cheaper generic statins are likely cost-effective in CKD. However, our study takes a substantially more detailed look into the long-term effects of individual treatments across categories of CKD patients. We used the rich individual data from the SHARP study, which enabled us to present results generalizable to CKD patients at similar cardiovascular risk and/or CKD stage. We also used results from the CTT individual participant meta-analysis of 28 large trials, which provide best available estimates for cardiovascular risk reductions with statin-based treatments at different levels of renal function.\textsuperscript{7} Linking these with the potency of individual statin/ezetimibe regimens enabled evaluation of the cost-effectiveness of different regimens reliably.

In the present study, treatment with rosuvastatin 20mg was similarly effective but slightly more expensive than atorvastatin 40mg (atorvastatin 40mg available at $0.103/day in the US and £0.034/day in the UK compared to $0.119/day and £0.077/day, respectively, for rosuvastatin 20mg); small further fluctuations in prices would make rosuvastatin a cost-effective option. The use of less potent treatments, eg atorvastatin 20mg or ezetimibe 10mg alone, achieves smaller cardiovascular benefits. In general, statin/ezetimibe treatments that achieve larger reductions in LDL cholesterol are expected to achieve greater health benefits and, if available at low cost, be cost-effective. In the present analyses we did not consider more potent statin treatments such as atorvastatin 80mg and rosuvastatin 40mg as they are not routinely used in CKD patients due to safety concerns. However, if future evidence indicates safety of these regimens in CKD, our analysis suggests that, if available at low cost, they will be cost-effective.
Several limitations of the present analyses should be acknowledged. Firstly, SHARP included only CKD patients without a prior history of myocardial infarction or coronary revascularisation, whereas in routine practice coronary heart disease is highly prevalent in people with moderate-to-advanced CKD and therefore patients outside SHARP at similar CKD stages are likely to be at higher cardiovascular risk. However, the cost-effectiveness estimates corresponding to categories of risk are likely to be generalisable to such patients. Secondly, since SHARP did not directly assess the effects of ezetimibe monotherapy in patients with CKD, we incorporated an assumption that its effects on clinical outcomes are equivalent, per mmol/L reduction in LDL cholesterol, to those of statins. This assumption was derived from the results of the CTT meta-analysis of the effects of statin-based regimens at different levels of eGFR and by the IMPROVE-IT trial, conducted among people with an acute coronary syndrome treated with statin, which demonstrated further cardiovascular risk reductions with ezetimibe similar to those with statin only regimens achieving similar LDL cholesterol reductions. Thirdly, the impact of treatments on non-healthcare costs, such as productivity or long-term care costs, were not included in the present analysis, which was conducted exclusively from a health services perspective. Finally, safety of statin-based regimens has been a subject of debate despite the acknowledgement that any adverse effects are rare and benefits strongly outweigh any harm. We did not include adverse effects in our primary analysis due to paucity of data for different treatments. However, sensitivity analyses incorporating estimated rates of potential adverse effects on muscle (eg myopathy, rhabdomyolysis) and diabetes yielded similar results.

In conclusion, statin-based treatments effectively reduce cardiovascular risk in non-dialysis patients with CKD and, at current prices and cost-effectiveness thresholds, the available evidence suggests that low-cost statin/ezetimibe combination therapy is cost-effective. The most cost-effective regimen is one that maximises the dose of statin chosen without compromising safety.
Methods

The SHARP CKD-CVD policy model

The SHARP CKD-CVD policy model, a Markov state-transition model developed using the SHARP study\textsuperscript{6,18} data and validated in three external CKD cohorts\textsuperscript{17}, was used to project cardiovascular events, CKD progression, healthcare costs and health-related quality of life (QoL). A full description of the model has been published elsewhere\textsuperscript{17}. Briefly, it is based on parametric risk equations (three survival equations for cardiovascular outcomes, a multinomial regression and a logistic regression for CKD progression, and two linear regressions predicting hospital costs and QoL). Each equation includes a range of clinically and/or statistically important covariates including patient’s socio-demographic status, co-morbidities and risk factors, eg age, most recent CKD stage and detailed cardiovascular disease history.

The model simulates annual risks of dying from vascular and non-vascular causes; experiencing an MAE, a haemorrhagic stroke; and progressing through CKD stages 3B (30≤eGFR<45mL/min/1.73 m\(^2\)), 4 (15≤eGFR<30mL/min/1.73 m\(^2\)) and 5 (eGFR<15mL/min/1.73 m\(^2\)), or having dialysis or kidney transplant (Figure S2).

CKD patients

Results are presented only for the 6,235 SHARP non-dialysis patients (since previous analyses have shown that lowering LDL cholesterol is not clinically effective in dialysis patients\textsuperscript{7}); all such patients had moderate-to-advanced CKD (Table 1, Table S1). At baseline, the study participants were categorised according to their CKD stage: (i) CKD stage 3B; (ii) CKD stage 4; or (iii) CKD stage 5 not on dialysis, and their 5-year risk of major vascular event\textsuperscript{16}: (i) low (< 10%); (ii) medium (≥10%, <20%) and (iii) high (≥20%) risk. eGFR was calculated using the CKD-EPI equation\textsuperscript{24}. The rates of non-vascular mortality were obtained from relevant population data (see Table S11 for US rates and Schlackow et al\textsuperscript{17} for UK rates).
Effects of statin/ezetimibe treatments

We considered a range of statin/ezetimibe regimens that are believed to be safe in CKD, including ezetimibe 10mg, atorvastatin 20mg, atorvastatin 40mg, rosuvastatin 20mg, simvastatin 20mg plus ezetimibe 10mg, atorvastatin 20mg plus ezetimibe 10mg, and atorvastatin 40mg plus ezetimibe 10mg daily. Treatment effects were projected on the risks of vascular death and major vascular events but not CKD progression or non-vascular mortality. For each statin/ezetimibe regimen, the effects on vascular endpoints were expressed as relative risk reductions and evaluated separately for each CKD stage in two steps. First, the absolute reductions in LDL cholesterol were calculated using the expected proportional reductions in LDL cholesterol (Table S2) and the mean LDL cholesterol among the SHARP participants in the respective CKD stage (Table 1, Table S3). Second, these absolute reductions were combined with the rate ratios for vascular events per 1mmol/L reduction in LDL cholesterol reported in the individual participant data meta-analysis by the CTT Collaboration (Table S3).

Costs and quality of life

Annual hospital costs of managing a patient with CKD cardiovascular complications were based on published data (see Table S12 for the US costs; and Kent et al\textsuperscript{26} for the UK costs) and inflated to 2015 using the Consumer Price Index (US) or Hospital & Community Health Services Index (UK). The costs of statin and ezetimibe treatments (January 2019) were obtained from the National Average Drug Acquisition Cost (NADAC) reports (US) and NHS Electronic Drug Tariff (UK) (Table S2).

Patients’ health-related QoL was derived from responses to the EuroQoL 5-dimensions 3-level (EQ-5D-3L) questionnaire distributed at the final SHARP follow-up visit and using the US or UK EQ-5D-3L utility tariffs (see Table S13 for US estimates; Schlackow et al\textsuperscript{17} for UK estimates), and stratified by CKD stage, cardiovascular morbidity and other characteristics.
Cost-effectiveness analyses

The cost-effectiveness analyses were performed from the perspectives of the US and UK healthcare systems. Health outcomes and costs were projected with lifelong treatment with each statin/ezetimibe regimen as well as no treatment, until patients reached 95 years or died. Costs and QALYs were discounted at an annual rate of 3% (US\textsuperscript{34}) or 3.5% (UK\textsuperscript{35}). For each treatment, the incremental cost-effectiveness ratios (ICERs) were calculated as the incremental cost per QALY gained with the treatment against the next less effective (and not dominated) treatment\textsuperscript{36}. Results are presented for categories of participants by CKD stage and, separately, by cardiovascular risk at baseline. Uncertainty in the cost-effectiveness was assessed using the non-parametric bootstrap\textsuperscript{37}, with the analysis replicated on 1,000 sets of risk, cost, and QoL parameter estimates derived from re-fitting the original SHARP CKD-CVD risk equations\textsuperscript{17} on bootstrapped SHARP data or, for US hospital costs, using sampled values from the parametric distribution of costs (Table S12)\textsuperscript{38}. Uncertainty in the treatment effects was incorporated using values sampled from the respective lognormal distribution corresponding to the relative risk (99% CI) reported by the CTT collaboration\textsuperscript{7}. Cost-effectiveness acceptability curves were derived to summarise the probability of each treatment being cost-effective at different levels of willingness-to-pay thresholds\textsuperscript{36}.

A schematic of our approach is presented in Figure S3.

Sensitivity analyses

Sensitivity analyses were performed to assess robustness of the results. The price of ezetimibe was varied from the current prices of $0.203/day (US) and £0.074/day (UK) to the price of atorvastatin 40mg of $0.103/day (US) and £0.034/day (UK). The price at which ezetimibe becomes cost-effective for the commonly used thresholds of $100,000 (US) and £20,000 (UK) per QALY was calculated. Secondly, to estimate the likely effect of dialysis costs on cost-effectiveness results, the analyses were repeated with RRT costs replaced with those for CKD stage 5 not on dialysis.
Thirdly, an analysis incorporating potential rare adverse effects of atorvastatin 40mg alone or in combination with ezetimibe 10mg daily was performed. Specifically, we assumed that during each year among patients taking atorvastatin 40mg daily (with or without ezetimibe), 0.011% will experience myopathy at a cost of $33 (£19; derived as the cost of 3 creatine kinase tests) and 0.001 QoL decrement (ie, 0.017 decrement over 30 days), and 0.0042% will experience rhabdomyolysis at a cost of $13,600 (£8,000), of whom 10% will die with the rest experiencing a 3% QoL decrement (ie, 50% decrement over 7.5 days of hospitalisation followed by 20% decrement over 30 days of recovering) in the year of the rhabdomyolysis; and 0.2% will develop diabetes. Finally, the effect of non-adherence to treatment was explored in scenarios where, respectively, 40%, 60%, and 80% of the patients were taking the medication.

All analyses were performed with R 3.4.1; the graphs were produced with the ggplot2 plotting system.

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The procedure for access requests to the SHARP (Trial registration: NCT00125593) data is available at [http://www.ndph.ox.ac.uk/about/data-access-policy](http://www.ndph.ox.ac.uk/about/data-access-policy). The SHARP CKD-CVD model interface and userguide are available at [http://dismod.ndph.ox.ac.uk/kidneymodel/app/](http://dismod.ndph.ox.ac.uk/kidneymodel/app/).
### Supplementary Material

**Table S1** Characteristics of SHARP non-dialysis participants by CKD stage and cardiovascular disease risk at baseline

**Table S2** Reductions in LDL cholesterol with statin-based treatments and daily drug treatment cost

**Table S3** Average LDL cholesterol, relative risk with statin-based treatment per 1 mmol/L reduction in LDL cholesterol and relative risk with specific statin-based treatments, by CKD stage

**Table S4** Health outcomes, US hospital care costs and US additional cost per quality-adjusted life year with lifetime use of ATORVASTATIN and EZETIMIBE treatments in moderate-to-advanced non-dialysis CKD

**Figure S1** Additional QALYs, hospital care costs and cost-effectiveness of lifetime use of ATORVASTATIN and EZETIMIBE treatments in categories of moderate-to-advanced non-dialysis CKD patients, by CKD stage and cardiovascular risk at baseline. Legend: CKD, chronic kidney disease; QALY, quality-adjusted life-year. *338 (17%) of participants with CKD stage 3A (eGFR 60-45 mL/min/1.73 m2).

**Table S5** Cost-effectiveness of lifetime use of ATORVASTATIN and EZETIMIBE treatments in categories of moderate-to-advanced non-dialysis CKD patients, by AGE at treatment initiation

**Table S6** Added (quality-adjusted) life years, extra hospital care costs and additional cost per quality-adjusted life year with lifetime use of EZETIMIBE 10mg daily compared to no LDL-C lowering treatment in moderate-to-advanced non-dialysis CKD

**Table S7** Health outcomes, UK hospital care costs and UK additional cost per quality-adjusted life year with lifetime use of ATORVASTATIN and EZETIMIBE treatments in moderate-to-advanced non-dialysis CKD

**Table S8** Sensitivity analysis of cost-effectiveness of lifetime use of ATORVASTATIN and EZETIMIBE treatments in moderate-to-advanced non-dialysis CKD patients with future RENAL REPLACEMENT THERAPY COSTS EXCLUDED

**Table S9** Sensitivity analysis of cost-effectiveness of lifetime use of ATORVASTATIN and EZETIMIBE treatments in moderate-to-advanced non-dialysis CKD patients, incorporating potential ADVERSE EFFECTS on myopathy, rhabdomyolysis and diabetes

**Table S10** Sensitivity analysis of cost-effectiveness of lifetime use of ATORVASTATIN and EZETIMIBE treatments in moderate-to-advanced non-dialysis CKD patients under different scenarios of COMPLIANCE with treatment

**Figure S2** Schematic of the SHARP CKD-CVD lifetime health outcomes model

**Table S11** Annual rates of non-vascular death in moderate-to-advanced CKD patients (US)

**Table S12** US annual hospital care costs

**Table S13** Health-related quality of life in moderate-to-severe CKD: a linear regression model derived from SHARP participant data using US EQ-5D value set
1. **Figure S3** Schematic of the information sources of the SHARP CKD-CVD lifetime health outcomes model

2. Supplementary information is available at Kidney International's website
References


### Table 1 Characteristics of non-dialysis SHARP participants by CKD stage and cardiovascular disease risk at baseline

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<td>Age, years</td>
<td>62 (11)</td>
<td>64 (12)</td>
<td>62 (12)</td>
<td>53 (8) 65 (9) 71 (9)</td>
</tr>
<tr>
<td>Male</td>
<td>1,461 (72%)</td>
<td>1,653 (60%)</td>
<td>760 (52%)</td>
<td>1,080 (50%) 1,337 (65%) 1,457 (71%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>271 (13%)</td>
<td>336 (12%)</td>
<td>162 (11%)</td>
<td>219 (10%) 273 (13%) 277 (14%)</td>
</tr>
<tr>
<td>Previous vascular disease</td>
<td>283 (14%)</td>
<td>430 (16%)</td>
<td>217 (15%)</td>
<td>43 (2%) 146 (7%) 741 (36%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>469 (23%)</td>
<td>662 (24%)</td>
<td>293 (20%)</td>
<td>106 (5%) 345 (17%) 973 (48%)</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>1,701 (84%)</td>
<td>2,389 (86%)</td>
<td>1,261 (87%)</td>
<td>1,841 (86%) 1,751 (85%) 1,767 (87%)</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>28 (5)</td>
<td>28 (6)</td>
<td>27 (5)</td>
<td>27 (5) 28 (5) 27 (6)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 (13)</td>
<td>79 (13)</td>
<td>80 (12)</td>
<td>82 (12) 80 (12) 77 (13)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>139 (20)</td>
<td>139 (21)</td>
<td>141 (21)</td>
<td>132 (17) 139 (20) 147 (22)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.9 (0.8)</td>
<td>2.9 (0.8)</td>
<td>2.7 (0.9)</td>
<td>2.9 (0.8) 2.9 (0.9) 2.8 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 (0.3)</td>
<td>1.1 (0.3)</td>
<td>1.1 (0.3)</td>
<td>1.2 (0.3) 1.1 (0.3) 1.1 (0.3)</td>
</tr>
<tr>
<td>Estimated 5-year risk of cardiovascular disease, median (IQR)</td>
<td>10% (6%, 18%)</td>
<td>14% (9%, 24%)</td>
<td>20% (11%, 32%)</td>
<td>6% (5%, 8%) 14% (12%, 17%) 31% (24%, 42%)</td>
</tr>
</tbody>
</table>
### CKD stage at baseline

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>n</th>
<th>SD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD stage 3</td>
<td>967 (45%)</td>
<td>649 (32%)</td>
<td>404 (20%)</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>882 (41%)</td>
<td>968 (47%)</td>
<td>917 (45%)</td>
</tr>
<tr>
<td>CKD stage 5, not on dialysis</td>
<td>302 (14%)</td>
<td>428 (21%)</td>
<td>718 (35%)</td>
</tr>
</tbody>
</table>

SHARP, Study of Heart and Renal Protection; CKD, chronic kidney disease; IQR, interquartile range.

Results are shown as mean (SD) or N (%), as appropriate, unless otherwise specified. Ten participants on kidney transplant at baseline were excluded. *338 (17%) of participants with CKD stage 3A (eGFR 60-45 mL/min/1.73 m2).
Table 2 Health benefits and cost-effectiveness of STATIN-BASED treatments in moderate-to-advanced non-dialysis CKD patients

<table>
<thead>
<tr>
<th>Category of CKD patient</th>
<th>Atorvastatin 40mg daily(^1) compared to no LDL-C lowering treatment</th>
<th>Ezetimibe 10mg plus atorvastatin 40mg daily compared to atorvastatin 40mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Life-years gained</td>
<td>QALYs gained</td>
</tr>
<tr>
<td>A. US healthcare setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By CKD stage at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage 3B(^*)</td>
<td>0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>0.37</td>
<td>0.31</td>
</tr>
<tr>
<td>CKD stage 5, not on dialysis</td>
<td>0.31</td>
<td>0.26</td>
</tr>
<tr>
<td>By 5-year risk of cardiovascular disease at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>0.29</td>
<td>0.26</td>
</tr>
<tr>
<td>Medium (10-20%)</td>
<td>0.32</td>
<td>0.27</td>
</tr>
<tr>
<td>High (≥20%)</td>
<td>0.36</td>
<td>0.29</td>
</tr>
</tbody>
</table>

B. UK healthcare setting

| By CKD stage at baseline|                    |               |                            |                   |               |                            |
| CKD stage 3B\(^*\)     | 0.28              | 0.25          | £3,800                     | 0.07              | 0.06          | £12,500                   |
| CKD stage 4             | 0.42              | 0.33          | £10,500                    | 0.09              | 0.07          | £16,000                   |
| CKD stage 5, not on dialysis | 0.37 | 0.29          | £18,900                    | 0.09              | 0.07          | £23,900                   |
| By 5-year risk of cardiovascular disease at baseline|                    |               |                            |                   |               |                            |
| Low (<10%)              | 0.33              | 0.29          | £7,900                     | 0.08              | 0.07          | £17,800                   |
| Medium (10-20%)         | 0.36              | 0.29          | £9,400                     | 0.08              | 0.07          | £15,200                   |
| High (≥20%)             | 0.40              | 0.29          | £14,200                    | 0.09              | 0.07          | £17,800                   |

CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year. The CKD and cardiovascular risk categories are derived directly from the 6,235 moderate-to-advanced non-dialysis-dependent CKD patients in the Study of Heart and Renal Protection (SHARP). \(^*\)338 (17%) of participants with CKD stage 3A (eGFR 60-45 mL/min/1.73 m\(^2\)).

\(^1\)Atorvastatin 20mg daily was projected to produce only slightly smaller health benefits at similar additional cost per QALY to atorvastatin 40mg daily (see Tables S4 and S7 for detailed results) and could be considered as an alternative less intensive treatment option. \(^2\)Costs and outcomes discounted at 3% per mL/min/1.73 m\(^2\).
Figure 1 Probability of a STATIN-BASED treatment to be cost-effective in moderate-to-advanced non-dialysis CKD patients

CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year. Results shown for treatments on the cost-effectiveness frontier (ie, the most cost-effective treatment for a given value of willingness to pay) within the range of willingness-to-pay values per QALY shown. Typical cost-effectiveness thresholds are represented with dashed horizontal lines. Atorvastatin 20mg daily was largely dominated by atorvastatin 40mg daily and omitted from the graph.
Figure 2 Cost-effectiveness of adding EZETIMIBE 10mg to ATORVASTATIN 40mg daily for moderate-to-advanced non-dialysis CKD patients, at different ezetimibe cost

A. US healthcare setting

Baseline CKD stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Additional cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>3B*</td>
<td>$150,000</td>
</tr>
<tr>
<td>4</td>
<td>$100,000</td>
</tr>
<tr>
<td>5, not on dialysis</td>
<td>$50,000</td>
</tr>
</tbody>
</table>

Baseline 5-year risk of cardiovascular disease

- low (<10%)
- medium (10-20%)
- high (>20%)

Daily cost of ezetimibe 10mg

- $0.203 current cost
- $0.153 current cost
- $0.103 current cost

B. UK healthcare setting

Baseline CKD stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Additional cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>3B*</td>
<td>£50,000</td>
</tr>
<tr>
<td>4</td>
<td>£40,000</td>
</tr>
<tr>
<td>5, not on dialysis</td>
<td>£30,000</td>
</tr>
</tbody>
</table>

Baseline 5-year risk of cardiovascular disease

- low (<10%)
- medium (10-20%)
- high (>20%)

Daily cost of ezetimibe 10mg

- £0.074 current cost
- £0.054 current cost
- £0.034 current cost

CKD, chronic kidney disease. QALY, quality-adjusted life-year.

The CKD and cardiovascular risk categories are derived directly from the 6,235 moderate-to-advanced non-dialysis-dependent CKD patients in the Study of Heart and Renal Protection (SHARP). Typical cost-effectiveness thresholds are represented with dashed horizontal lines. *338 (17%) of participants with CKD stage 3A (eGFR 60-45 mL/min/1.73 m²).

At the $100,000/QALY threshold (panel A) in the US, ezetimibe 10mg daily becomes cost-effective in all categories of patient when its price reaches $0.323/day. At the £20,000/QALY threshold in the UK (panel B), ezetimibe 10mg daily becomes cost-effective in all categories of patient when its price reaches £0.019/day.