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ORIGINAL PAPER

Ezetimibe in high-risk, previously treated statin patients: a systematic review and network meta-analysis of lipid efficacy

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Abstract

Purpose While statins are used as first-line treatments for high-risk patients with hypercholesterolemia, statin monotherapy is often insufficient to achieve target low-density lipoprotein cholesterol (LDL-C) levels. Second-line treatment options include up-titration of statin dose, switching to a more potent statin, or combination therapy, e.g., with ezetimibe. The aim of this study was to evaluate the efficacy of adding ezetimibe to simvastatin, atorvastatin, or rosuvastatin monotherapy versus doubling the dosage or switching to a higher-potency statin in a population of patients with hypocholesterolemia at high risk of cardiovascular disease (CVD) and who had been previously treated with a statin.

Methods A systematic literature search was performed and evidence bases were established for populations of atorvastatin-, simvastatin-, and rosuvastatin-experienced patients using eligible randomized controlled trials (RCTs). Based on the available data, we constructed networks of evidence and conducted a Bayesian network meta-analysis (NMA) within each statin population. The primary outcome of interest was percent change from baseline in LDL-C. Changes in total cholesterol were explored as a secondary outcome.

Findings Across all patient populations, 35 RCTs were identified and included in the evidence base. Among patients on simvastatin therapy, the addition of ezetimibe resulted in a mean difference (MD) in LDL-C of − 13.62% (95% CrI − 19.99, − 6.91; see table below) compared to doubling the starting dose of simvastatin. In the population of patients on atorvastatin therapy, the addition of ezetimibe resulted in an MD in LDL-C of − 14.71% (95% CrI − 16.46, − 12.95) compared to doubling the starting dose of atorvastatin. The addition of ezetimibe to rosuvastatin resulted in an MD in LDL-C of − 14.96% (95% CrI − 17.79, − 12.11), compared to doubling the starting rosuvastatin dose. Similar trends were observed for changes in total cholesterol.

Implications Given the available data, the addition of ezetimibe to ongoing simvastatin, atorvastatin, or rosuvastatin monotherapy offers greater reduction in LDL-C among patients at high risk of CVD compared to doubling the initial statin dose.

Keywords Network meta-analysis · Cholesterol · Statins · Ezetimibe

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Introduction

Patients with cardiovascular disease (CVD), the most common form being coronary heart disease (CHD), are at high risk of events such as myocardial infarction, angina, and stroke. Risk status may be defined according to the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) which consider patients with CHD or CHD risk equivalents as high risk [1, 2]. To reduce lipid levels, these high-risk patients are commonly managed with statins as a first-line treatment [1–5]. Many of these patients, however, do not reach low-density lipoprotein cholesterol (LDL-C) goals with statin monotherapy alone and may require titration to higher statin doses, switching to a more potent statin, or use of combination lipid-lowering therapy, such as ezetimibe and PCSK9 inhibitors [1, 3–11].

To date, no single head-to-head randomized controlled trial (RCT) has been conducted to evaluate additional treatment options in high-risk patients on existing statin therapy. When RCT evidence is available comparing subsets of treatments within the larger patient population framework, it is possible to propose a network of connected evidence. The results of these trials can then be synthesized by means of a network meta-analysis (NMA). Conceptually, the NMA pools the results of trials on a single intervention and uses multiple pairwise comparisons to estimate the relative treatment effects of all interventions included in the network of evidence. Thus, relative efficacy can be estimated between interventions for which no head-to-head RCT evidence currently exists.

Previous systematic reviews and meta-analyses have also analyzed the efficacy of ezetimibe as a supplementary treatment to statin monotherapy. A 2007 meta-analysis of five studies compared ezetimibe as an addition to a statin versus placebo in addition to a statin; results suggested that the addition of ezetimibe to ongoing statin therapy lowered LDL-C significantly more in patients who were not at LDL-C goal on previous treatment compared with those adhering only to statin monotherapy [12]. A 2011 systematic review and meta-analysis of 13 studies analyzed the LDL-C reduction of ezetimibe in combination with a statin versus doubling of statin dose; these results also suggested that ezetimibe as an add-on treatment was significantly more effective in lipid lowering than doubling of statin [13]. While a 2012 analysis looked at ezetimibe plus statin versus different statin monotherapies, including switching to another statin, it was a pooled analysis designed to assess the factors that might affect a patient's response to lipid-altering therapy, rather than a systematic review and meta-analysis [14]. While this analysis suggested that patient characteristics had a limited influence on the lowering of LDL-C, it also did not examine clinical outcomes.

The LDL-C-lowering efficacy of ezetimibe in combination with statin therapy has not yet been reviewed simultaneously alongside two different statin monotherapies (doubling statin dose or switching to higher-potency statin). The purpose of this study, therefore, was to evaluate, through an NMA, the efficacy of adding ezetimibe to existing simvastatin, atorvastatin, or rosuvastatin therapy compared to doubling the statin dose or switching to a higher-potency dose of another statin in patients with hypocholesterolemia and at high risk of CVD. The evidence was based on RCTs identified by means of a systematic literature review.

Methods

Literature search and eligibility criteria

MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials (CENTRAL) were systematically searched in May 2014 to identify RCTs evaluating changes in LDL-C and total cholesterol in patients with hypercholesterolemia and high or very high CVD risk, previously treated with atorvastatin, rosuvastatin, or simvastatin monotherapy. Studies evaluating combination ezetimibe and statin therapy, with either simvastatin, atorvastatin, or rosuvastatin, were considered eligible for inclusion. Placebo was included as a valid comparator. Only studies published in English after 1990 were considered. We excluded crossover or titration studies if outcomes were only reported at study end, but included these studies if outcomes were reported at the time of titration or crossover. Search strategies are presented in Appendix 1.

Data extraction and outcomes

Two researchers, independently and in duplicate, screened all abstracts to ascertain whether they met predefined inclusion criteria. Abstracts that either met inclusion criteria or for which decisions were unclear were evaluated at the full text level.

From the final set of included studies, details on study design, patient baseline characteristics (e.g., age, sex, weight, comorbidities), interventions, and percent change from baseline (CFB) in LDL-C and total cholesterol were extracted. Relative to patients' previous treatment, either pre-enrollment or as part of a trial run-in period, trial arms were classified as maintaining, increasing, switching, or adding new treatments. Potency relationships between statins were classified according to the clinical guidelines published by the National Institute for Clinical Excellence (NICE), presented in Appendix 2 [15]. The primary outcome of interest

was the percent CFB in LDL-C, with CFB in total cholesterol explored as a secondary outcome. Safety outcomes were not considered in the current analysis.

Statistical analyses

A Bayesian NMA was used to synthesize the results of the included studies, with the purpose of estimating the relative treatment effects for each intervention represented in the evidence base with respect to CFB in LDL-C and total cholesterol. This statistical approach combines both direct and indirect evidence to estimate the relative treatment effects between each intervention in the network, while weighting trials according to sample size [16]. Inconsistency between direct and indirect evidence in the network was evaluated using edge splitting, with three-sided loops evaluated according to the Bucher test [17]. To estimate these effects for the continuous outcomes of interest, a model with a normal likelihood and identity link was used.

To not influence the observed results by the prior distribution, non-informative priors were used (d_{AK} normal(0,10000) for (pooled) treatment effects with NMA models, and d_{XY} normal(0,10000) for (pooled) treatment effects with independent-means models; σ uniform$(0, u)$ for between-study heterogeneity with u set at five times the range of observed treatment effects across studies included in the NMA, and μ_{jb} normal(0,10000) for nuisance parameters of the models).

Both fixed and random effects models were fitted to the data using Bayesian Markov chain Monte Carlo methods and were evaluated according to the deviance information criteria (DIC), a measure of model fit [18]. A more complex model will generally be a better fit to the data and will result in a smaller residual deviance. Thus, the model with the lowest DIC is preferred.

All analyses were performed using R version 3.0.3 (http://www.r-project.org/) and OpenBUGS version 3.2.3 (OpenBUGS Project Management Group).

For each outcome, we presented mean differences and 95% credible intervals (CrI) from the posterior distribution of relative treatment effects for all interventions relative to each other in a cross table. The use of non-informative priors allowed the 95% CrI to be interpreted similarly to the 95% confidence interval of the frequentist framework. Modeled outcomes, which apply the relative treatment effect for each intervention to an anchor comparator, were also presented, where each bar represents the estimated CFB and whiskers represent the corresponding 95% CrI. As each CrI reflects both uncertainty in the estimation of the effect of the anchor comparator as well as the relative treatment effect, these figures should not be used for comparative purposes. For all analyses, the anchor comparator was doubling the existing statin therapy.

Results

Study identification and selection

The systematic search of the clinical literature databases returned 2,960 citations. After duplicate abstract screening, 691 citations were selected for full text review. The final review resulted in 37 publications [19–48] being selected, describing 35 RCTs. The flow of information through the screening process is shown in Fig. 1. An overview of the baseline patient characteristics of the included studies is presented in Appendix 3.

Evidence base and results of NMA, by population

Simvastatin-experienced patients

Thirteen RCTs [19–31] were identified evaluating outcomes in patients previously treated with simvastatin therapy. Most of the included trials specified treatment durations of 6 or 8 weeks, though two trials [20, 23] followed patients for 16 weeks. Trial inclusion criteria differed with respect to minimum required LDL-C levels as well as CHD risk requirements, with many trials specifying documented CHD and others specifying a presence of risk factors for developing CHD, such as diabetes or hypertension. Patients with liver disease, renal disease, or recent cardiovascular events were excluded in most trials. Patient baseline characteristics were consistent across trials with respect to mean age and BMI, though some variation was observed in the proportions of males, smokers, and patients with hypertension. Baseline LDL-C varied from 91 to 169 mg/dL and total cholesterol varied from 154 to 253 mg/dL.

All 13 RCTs ($N = 4535$) reported CFB outcomes for LDL-C (Fig. 2a). The results of the NMA are presented in Table 1 and modeled outcomes are presented in Fig. 3a. All interventions were more effective in lowering LDL-C relative to maintaining the baseline simvastatin dose. The addition of ezetimibe to simvastatin was significantly more efficacious than doubling the simvastatin dose (MD − 13.62%, CrI: − 19.99, − 6.91) or switching to a higher-potency dose of rosuvastatin (MD − 12.03%, CrI: − 19.37, − 4.73). There was no statistical difference between the addition of ezetimibe and a quadruple dose of the base simvastatin or switching to a higher-potency dose of atorvastatin.

Changes in total cholesterol were reported by 11 RCTs ($N = 3458$), as presented in Appendix 4. All interventions, with the exception of doubling simvastatin, significantly lowered total cholesterol relative to maintaining the baseline dose. The addition of ezetimibe lowered total cholesterol relative to doubling the base simvastatin dose (MD − 8.43%, CrI − 16.01, − 0.73) and switching to a higher-potency dose

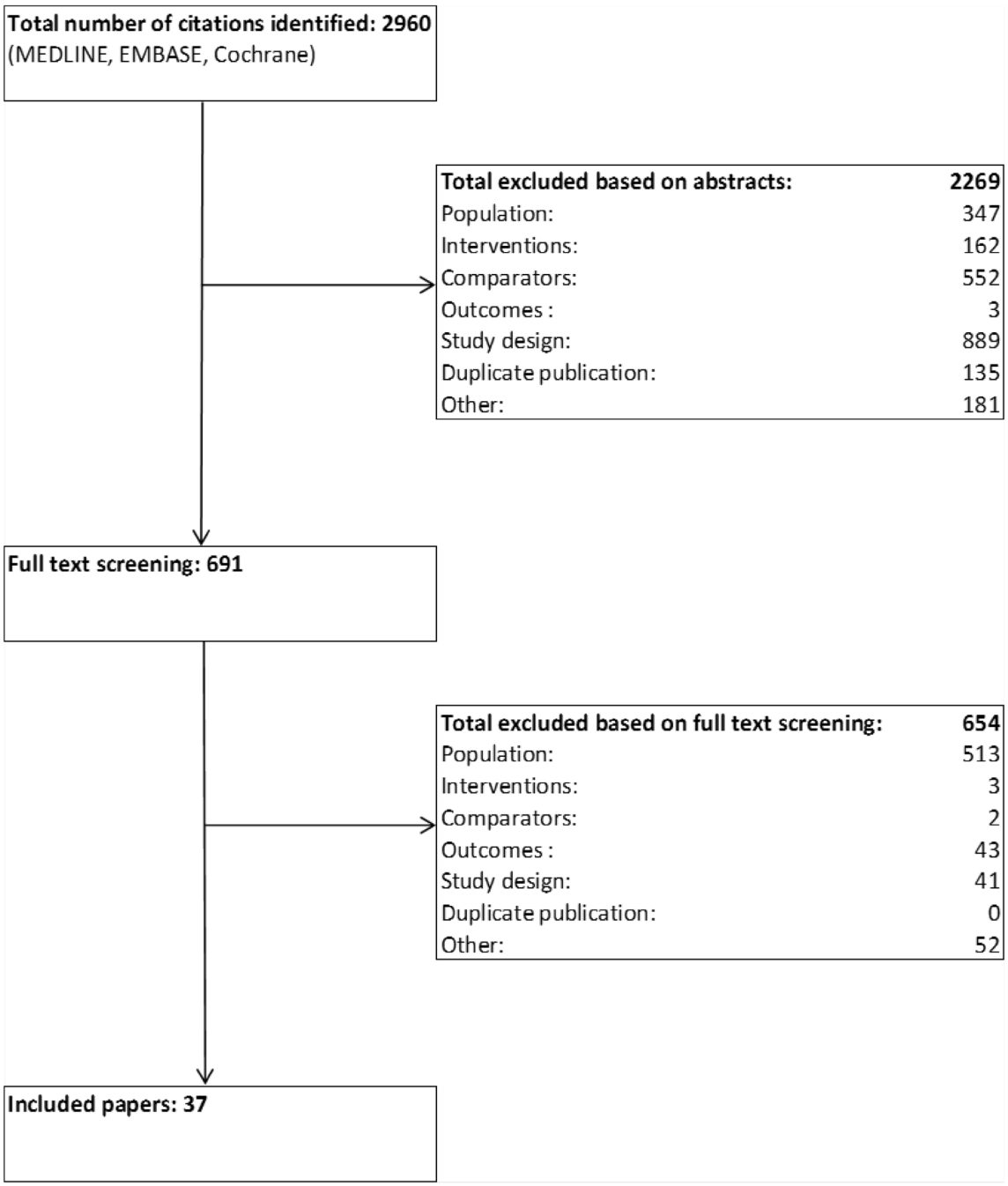

Fig. 1 Flow of information

of rosuvastatin (MD − 8.79%, CrI − 17.08, − 0.84). No statistically important difference was found between the addition of ezetimibe and a quadruple dose of simvastatin or switching to a higher-potency dose of atorvastatin.

Atorvastatin-experienced patients

We identified 16 RCTs reporting outcomes for patients previously treated with atorvastatin [20, 25, 27, 29, 32–45]. One trial, however, did not include any study arms that could be incorporated into the network of evidence [32]. There was some variation in the baseline dose of atorvastatin, though the majority of trials included patients previously treated

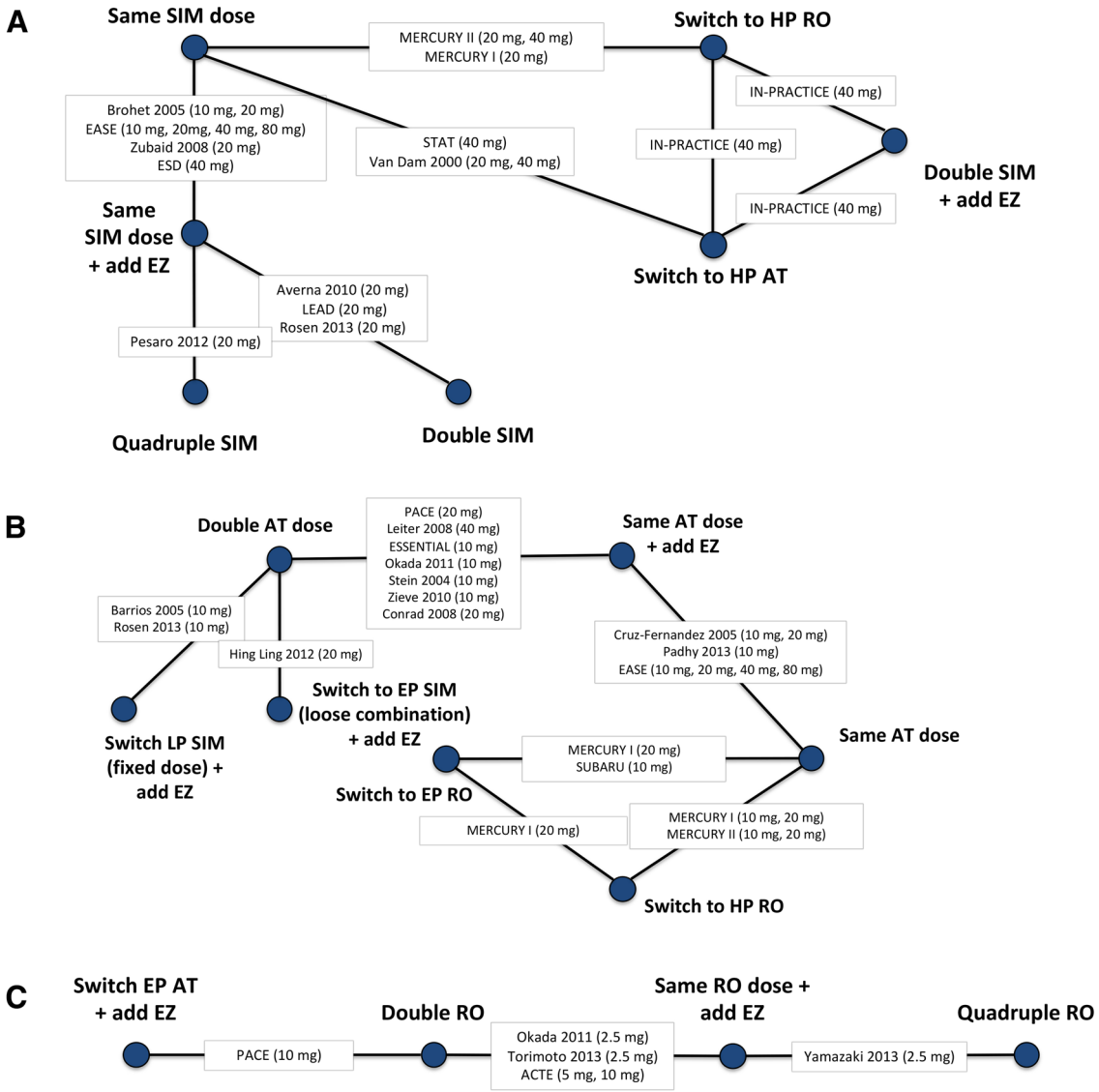

Fig. 2 Network diagrams of evidence for change from baseline in LDL-C. **a** Simvastatin experienced; **b** Atorvastatin experienced; **c** Rosuvastatin experienced. *HP* higher potency; *LP* lower potency; *EP* equal potency; *SIM* simvastatin; *RO* rosuvastatin; *AT* atorvastatin; *EZ* ezetimibe. Doses in brackets indicate the baseline or run-in statin dose

with 10 mg of atorvastatin. Most studies specified treatment durations between 6 and 12 weeks, though a single study only followed patients for 4 weeks [43]. There was inconsistency with respect to exclusion criteria for patients with liver disease, kidney disease, or diabetes. Baseline characteristics were comparable across study arms with respect to mean age and BMI, though there was variation with respect to the proportion of males, smokers, and mean LDL-C (82–187 mg/dL) and mean total cholesterol (160–264 mg/dL) at enrollment.

Sixteen RCTs ($N=7167$) reported mean CFB in LDL-C in atorvastatin-experienced patients (Fig. 2b). The results of the NMA are presented in Table 2, with modeled outcomes available in Fig. 3b. All interventions significantly lowered LDL-C relative to maintaining the baseline atorvastatin dose. The addition of ezetimibe to atorvastatin significantly lowered LDL-C relative to doubling the base atorvastatin dose (MD −14.71%, CrI −16.46, −12.95) or switching to an equal- or higher-potency dose of rosuvastatin (MD −15.78%, CrI −19.21, −12.45). No statistically meaningful differences were found between the fixed-dose and loose combination of simvastatin and ezetimibe. Adding ezetimibe to atorvastatin produced similar reductions in LDL-C as switching to lower-potency simvastatin and adding ezetimibe.

Changes in total cholesterol were reported by 14 RCTs ($N=5775$), as presented in Appendix 4. All interventions, with the exception of switching to equal potency

Table 1 Mean differences in mean percent change from baseline in LDL-C among simvastatin-experienced patients from random-effects network meta-analysis

Double simvastatin	**13.62 (6.91, 19.99)**	**23.38 (10.34, 35.81)**	**–9.46 (–18.04, –1.24)**	12.62 (–2.96, 27.49)	6.81 (–3.07, 16.51)	1.60 (–8.30, 11.33)
–13.62 (–19.99, –6.91)	**Add ezetimibe**	9.74 (–1.39, 20.66)	**–23.07 (–28.27, –17.91)**	–1.01 (–14.79, 12.55)	–6.80 (–14.15, 0.68)	**–12.03 (–19.37, –4.73)**
–23.38 (–35.81, –10.34)	–9.74 (–20.66, 1.39)	**Double simvastatin + add ezetimibe**	**–32.82 (–42.54, –23.04)**	–10.78 (–28.38, 6.80)	**–16.56 (–25.83, –7.02)**	**–21.78 (–31.08, –12.47)**
9.46 (1.24, 18.04)	**23.07 (17.91, 28.27)**	**32.82 (23.04, 42.54)**	**Maintain simvastatin**	**22.09 (7.39, 36.51)**	**16.30 (11.06, 21.64)**	**11.06 (5.92, 16.15)**
–12.62 (–27.49, 2.96)	1.01 (–12.55, 14.79)	10.78 (–6.80, 28.38)	**–22.09 (–36.51, –7.39)**	**Quadruple simvastatin**	–5.79 (–21.13, 9.98)	–11.00 (–26.45, 4.63)
–6.81 (–16.51, 3.07)	6.80 (–0.68, 14.15)	**16.56 (7.02, 25.83)**	**–16.30 (–21.64, –11.06)**	5.79 (–9.98, 21.13)	**Switch to HP atorvastatin**	–5.25 (–11.72, 1.13)
–1.60 (–11.33, 8.30)	**12.03 (4.73, 19.37)**	**21.78 (12.47, 31.08)**	**–11.06 (–16.15, –5.92)**	11.00 (–4.63, 26.45)	5.25 (–1.13, 11.72)	**Switch to HP rosuvastatin**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC 59.7; deviance 30.86; SD 4.35

HP higher potency

rosuvastatin, lowered total cholesterol relative to maintaining the baseline atorvastatin dose. The addition of ezetimibe was statistically more efficacious in lowering total cholesterol than either doubling the atorvastatin dose (MD −9.41%, CrI: −10.89, −7.92) or switching to a higher-potency dose of rosuvastatin (MD −11.61%, CrI: −15.19, −7.88).

Rosuvastatin-experienced patients

Five trials investigated patients currently treated with rosuvastatin [34, 42, 46–48]. Four trials reported patient outcomes after 12 weeks, with a single trial [46] reporting outcomes after 6 weeks. Four trials specified minimum LDL-C levels of 100 mg/dL, with one study each specifying minimums of 70 mg/dL [48] and 80 mg/dL [47]. These trials were well matched in terms of mean age, BMI, and proportion of males, though there was more variability in the proportion of patients with diabetes. Baseline lipid levels were relatively consistent across trials, though baseline mean LDL-C was below 100 mg/dL in one trial [48].

All five RCTs ($N=1074$) were included in the network of evidence for LDL-C (Fig. 2c). The results of the fixed-effects NMA are presented in Table 3, with modeled outcomes in Fig. 3c. A fixed-effects model was applied as there were too few studies to inform the estimate of between-study heterogeneity. No study included a treatment arm where patients maintained their baseline rosuvastatin dose. All interventions significantly lowered LDL-C relative to doubling the base rosuvastatin dose. The addition of ezetimibe to rosuvastatin significantly lowered LDL-C relative to doubling the base rosuvastatin dose (MD −14.96%, CrI: −17.79, −12.11). The addition of ezetimibe was not statistically different from switching to a quadruple dose of base rosuvastatin.

Four RCTs ($N=999$) described changes in the mean percent CFB in total cholesterol, as presented in Appendix 4. The addition of ezetimibe to either the base dose of rosuvastatin or to a switch to an equipotent dose of atorvastatin with ezetimibe was found to significantly lower total cholesterol relative to doubling the base rosuvastatin dose. No statistically important difference was observed between the addition of ezetimibe and switching to a quadruple dose of rosuvastatin.

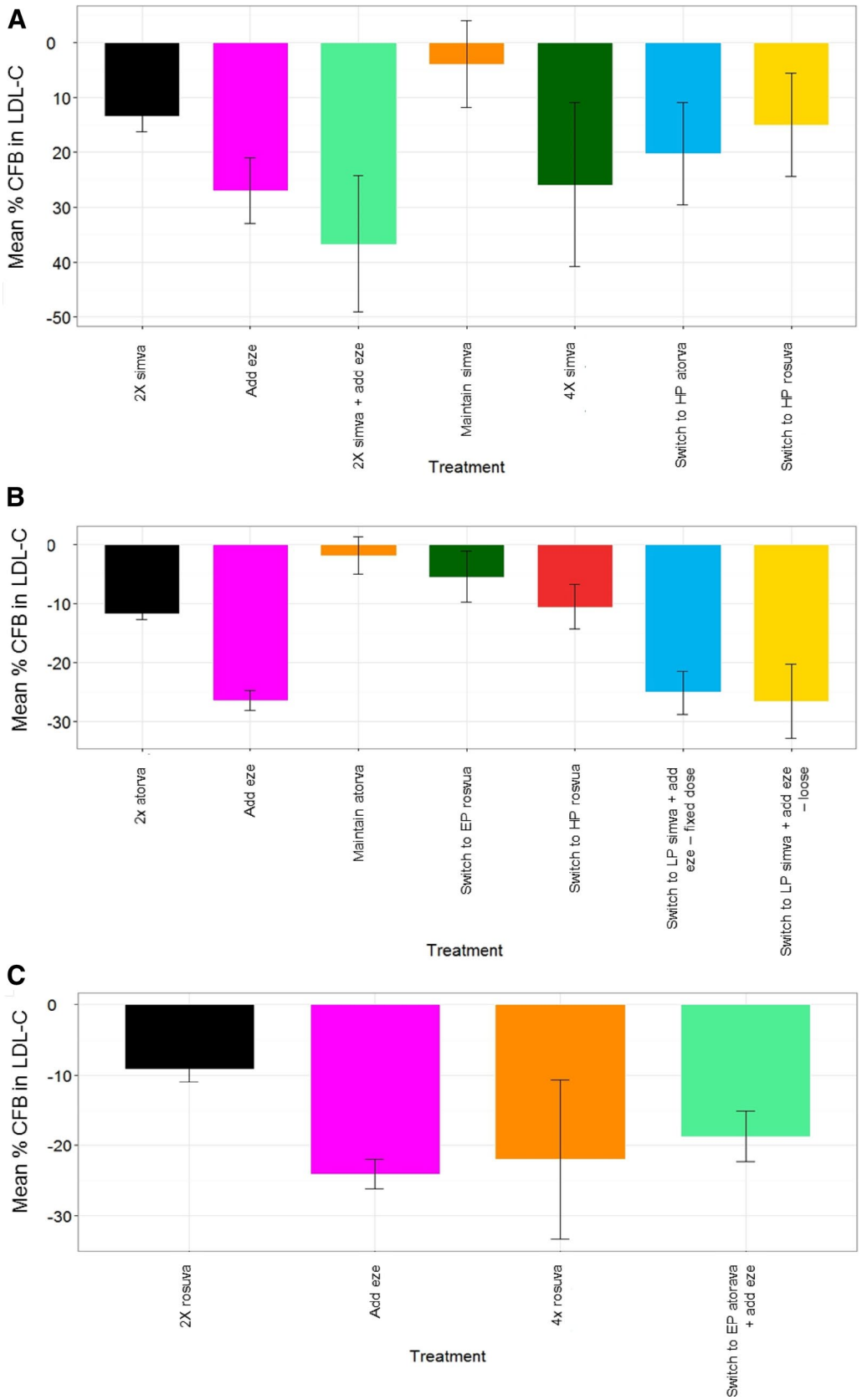

Fig. 3 Modeled outcomes for change from baseline in LDL-C. *HP* higher potency, *LP* lower potency, *EP* equal potency, *SIM* simvastatin, *RO* rosuvastatin, *AT* atorvastatin, *EZ* ezetimibe

Table 2 Mean differences in mean percent change from baseline in LDL-C among atorvastatin-experienced patients from random-effects network meta-analysis

Double atorvastatin	**14.71 (12.95, 16.46)**	**–9.78 (–13.15, –6.64)**	**–6.25 (–10.58, –1.99)**	–1.07 (–4.99, 2.68)	**13.25 (9.53, 17.19)**	**15.00 (8.35, 21.42)**
–14.71 (–16.46, –12.95)	**Add ezetimibe**	**–24.50 (–27.30, –21.86)**	**–20.95 (–24.93, –17.09)**	**–15.78 (–19.21, –12.45)**	–1.48 (–5.54, 2.88)	0.30 (–6.54, 6.89)
9.78 (6.64, 13.15)	**24.50 (21.86, 27.30)**	**Maintain atorvastatin**	**3.56 (0.75, 6.43)**	**8.72 (6.71, 10.81)**	**23.04 (18.20, 28.29)**	**24.85 (17.41, 31.91)**
6.25 (1.99, 10.58)	**20.95 (17.09, 24.93)**	**–3.56 (–6.43, –0.75)**	**switch to EP rosuvastatin**	**5.17 (2.04, 8.29)**	**19.50 (13.85, 25.40)**	**21.30 (13.22, 28.84)**
1.07 (–2.68, 4.99)	**15.78 (12.45, 19.21)**	**–8.72 (–10.81, –6.71)**	**–5.17 (–8.29, –2.04)**	**Switch to HP rosuvastatin**	**14.33 (9.09, 19.97)**	**16.14 (8.41, 23.44)**
–13.25 (–17.19, –9.53)	1.48 (–2.88, 5.54)	**–23.04 (–28.29, –18.20)**	**–19.50 (–25.40, –13.85)**	**–14.33 (–19.97, –9.09)**	**switch to LP simvastatin + add ezetimibe – FD**	1.75 (–6.25, 9.17)
–15.00 (–21.42, –8.35)	–0.30 (–6.89, 6.54)	**–24.85 (–31.91, –17.41)**	**–21.30 (–28.84, –13.22)**	**–16.14 (–23.44, –8.41)**	–1.75 (–9.17, 6.25)	**switch to LP simvastatin + add ezetimibe – loose**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC 67.96; deviance 39.12; SD 1.26

EP equal potency, *HP* higher potency, *LP* lower potency, *FD* fixed dose

Table 3 Mean differences in mean percent change from baseline in LDL-C among rosuvastatin-experienced patients from fixed-effects network meta-analysis

Double rosuvastatin	**14.96 (12.11, 17.79)**	**12.91 (1.36, 24.47)**	**9.61 (6.16, 12.99)**
–14.96 (–17.79, –12.11)	**Add ezetimibe**	–2.03 (–13.33, 9.18)	**–5.36 (–9.82, –0.87)**
–12.91 (–24.47, –1.36)	2.03 (–9.18, 13.33)	**Quadruple rosuvastatin**	–3.31 (–15.39, 8.77)
–9.61 (–12.99, –6.16)	**5.36 (0.87, 9.82)**	3.31 (–8.77, 15.39)	**switch to EP atorvastatin + add ezetimibe**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC 23.83; deviance 14.82

EP equal potency

Discussion

The purpose of this study was to evaluate the relative efficacy of adding ezetimibe to current statin treatment, in terms of lowering LDL-C and total cholesterol, compared to doubling the statin dose or switching to a higher-potency dose of another statin in patients previously treated with simvastatin, atorvastatin, or rosuvastatin. This objective was addressed through an NMA, which simultaneously estimated the relative treatment effect for all interventions in a network of evidence. Treatment regimens were classified according to their relationship (switch, augmentation, equipotency) to prior statin using the NICE statin conversion table; it should be noted that the FDA uses a different conversion table. In all patient populations, the addition of ezetimibe resulted in a statistically larger reduction in LDL-C than doubling the prior statin dose. Among patients on simvastatin or atorvastatin, adding ezetimibe was more efficacious than switching

to higher-potency rosuvastatin. In these populations, the addition of ezetimibe was similarly efficacious as quadrupling the statin dose; however, this regimen is not seen as an appropriate option for many patients. Similar results were found with respect to lowering of total cholesterol levels. It should be noted that in the simvastatin and atorvastatin populations, the percent reduction in LDL-C for doubling the prior statin was slightly larger than that predicted by the "rule of 6" [49]; for patients on simvastatin and atorvastatin, the reduction was 9.5% and 9.8%, respectively, although the CrI included 6% in the simvastatin population, so this result is still statistically consistent with the "rule of 6". The Cholesterol Treatment Trialists (CTT) group has described the relationship between lowering LDL-C and reducing major vascular events for statin therapy. In 2010 an updated meta-analysis, which included individual patient data from 170,000 patients in 26 RCTs, described a relationship between lowered LDL-C and a protective effect against vascular events [50]. Twenty-one trials compared statins to controls, with an additional 5 trials comparing higher-intensity to lower-intensity statin treatments. In the overall meta-analysis, a reduction in relative risk of 22% (95% CI 20, 24) was estimated for every 1.0 mmol/L reduction in LDL-C. The results also suggested that these reductions in vascular risk can be achieved safely even in patients who already have low LDL-C concentrations. In a pooled analysis of over 11,000 patients in 17 RCTs, similar results were found; adding ezetimibe resulted in a statistically meaningful reduction in LDL-C, with more than twice the percent change in LDL as doubling the dose of ongoing statin [51].

The recently published IMPROVE-IT trial [52] compared the combination of simvastatin and ezetimibe to simvastatin monotherapy in a population of 18,144 patients who had been recently hospitalized for acute coronary syndrome. Patients on combination therapy achieved a 0.43 mmol/L greater reduction in LDL-C than those on simvastatin monotherapy, signifying a 24% additional reduction in LDL-C in the combination group. The trial found an absolute risk difference of 2.0% (in favor of simvastatin plus ezetimibe) of a composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, unstable angina, or coronary revascularization); HR 0.936 (95% CI 0.89—0.99, $p = 0.016$). Utilizing similar methods as utilized in the CTT meta-analysis (with imputation for missing LDL-C values) to estimate the clinical benefit to a per mmol/L basis of LDL-C reduction with ezetimibe in IMPROVE-IT resulted in a hazard ratio (HR) of 0.80 [95% CI (0.68; 0.94)], which is consistent with the HR 0.78 (95% CI [0.76; 0.80], $p < 0.0001$) observed with statins in the meta-analysis performed by the CTT in 2010. These results further strengthen the evidence of the relationship between absolute reduction in LDL-C levels through up-regulating LDL receptors and lowering of cardiovascular risk beyond therapy with statins alone. The recent ACC consensus statement [53] further supports consideration of the addition of ezetimibe to statin therapy, given its benefits in reduction of cardiovascular outcomes and demonstrated safety profile.

The evidence supporting the efficacy of ezetimibe in combination with a statin to further lower LDL-C is important given the number of patients that do not reach the recommended LDL-C values. The Dyslipidemia International Study (DYSIS) II was an observational, cross-sectional study conducted in 21 countries in Asia/Pacific, Europe, and Middle East/Africa in 2012–2014 that evaluated lipid-lowering treatment and LDL-C goal attainment in two distinct cohorts: patients who survive an ACS event and in patients with a documented history of stable CHD. In the global ACS cohort, 24.8% of patients achieved an LDL-C < 70 mg/dl at admission for their ACS event and 34.4% attained the same goal at 4 month follow-up; at follow-up 87% received statin monotherapy with a mean atorvastatin equivalent dose of 32 mg/day. In the global CHD cohort, 30.6% of patients achieved an LDL-C < 70 mg/dl; 82% received statin monotherapy with a mean atorvastatin equivalent dose of 25 mg/day. These data indicate that either the statin can be intensified (same dose or switch) or, if a larger decrease in LDL-C is required, ezetimibe can be used in combination with a statin to ensure that more high-risk patients reach the recommended LDL-C values to prevent CV events.

The results of the current study were based on clinical evidence identified through an exhaustive, systematic review of the literature. While the timing of the search precluded the addition of IMPROVE-IT, the results of the current analysis are in line with the IMPROVE-IT study and serve to reinforce the findings of that study. The estimation of relative treatment effects through an NMA is an established methodology and is accepted by numerous health technology assessment agencies worldwide. Extensive validation of NMA models was also performed to investigate the possible sources of heterogeneity and inconsistency in the network of evidence. Despite this, there are some limitations to this analysis. Safety outcomes were not considered, as the purpose of the current study was restricted to determining the relative efficacy. Relatively few studies were identified in rosuvastatin-experienced patients, so these results must be interpreted with some caution. Some inconsistencies were observed between patient baseline characteristics across study arms in the atorvastatin- and simvastatin-experienced trials, such as in the proportion of males, smokers, and patients with hypertension. Some differences were also observed in baseline lipid levels of some study arms. Trials in rosuvastatin-experienced patients were more consistent, though there was some variation in the proportion of patients with diabetes. It is unclear whether these differences impacted outcome estimates. Future studies may investigate

the impact of these differences through a meta-regression NMA approach.

Conclusion

Through a systematic search of the literature, we identified trials in high-risk patients previously treated with simvastatin, atorvastatin, and rosuvastatin, and evaluated CFB in LDL-C and total cholesterol for alternative treatment options. Regardless of the base statin, the addition of ezetimibe resulted in a statistically larger reduction in LDL-C compared to doubling the prior statin dose or switching to higher-potency rosuvastatin. Given the proven LDL-C lowering and CV benefit provided by ezetimibe, it remains an important option to enable more patients to reach the recommended LDL-C values and prevent CV events.

Appendix 1: Search strategies.

A comprehensive systematic search of the literature was conducted of Medline, EMBASE, and Cochrane Central Register of Controlled Trials databases with a pre-specified search strategy.

The combined search strategy for Medline and EMBASE using OVID is presented as follows:

1. randomized controlled trial.pt.;
2. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.;
3. (retraction of publication or retracted publication).pt.;
4. 1 or 2 or 3;
5. (animals not humans).sh.;
6. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.;
7. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.;
8. 5 or 6 or 7;
9. 4 not 8;
10. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.;
11. RETRACTED ARTICLE/;
12. 10 or 11;
13. (animal$ not human$).sh,hw.;
14. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/;
15. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/;
16. 13 or 14 or 15;
17. 12 not 16;
18. 9 or 17;
19. (cholesterol OR lipid OR hypercholesterolaemia OR hypercholesterolemia OR hyperlipidaemia OR hyperlipidemia OR dyslipidaemia OR dyslipidemia).ti.ab
20. (statin or simvastatin or atorvastatin or rosuvastatin or ezetimibe).ti,ab.;
21. 18 and 19 and 20;
22. limit 21 to human;
23. remove duplicates from 22;
24. limit 23 to yr="1990-Current".

.pt. denotes a publication type term;
.ab. denotes a word in the abstract;
.sh. denotes a medical subject heading (MeSH) term;
.ti. denotes a word in the title.

The following search strategy was be used for the Cochrane Central Register of Controlled Trials (clinical trials):

"hyperlipidemia" OR "hypercholesterolemia" OR "hypercholesterolaemia" OR "dyslipidemia" OR "dyslipidaemia" in all fields.

Appendix 2: Statin potency relationships according to the National Institute for Clinical Excellence (NICE)

Atorvastatin	Rosuvastatin	Simvastatin
–	–	10 mg
–	–	20 mg
10 mg	5 mg	40 mg
20 mg	10 mg	80 mg
40 mg	20 mg	–
80 mg	40 mg	–

This table was reproduced from the National Clinical Guideline Centre [15].

Appendix 3: Baseline characteristics

See Tables 4 and 5.

Table 4 Baseline patient characteristics of included studies, arranged by prior statin

Trial; prior treatment	Intervention	Absolute dose	*N*	Men (%)	Age	White (%)	Smokers (%)	Hypertension (%)	Diabetes (%)	BMI
Simvastatin trials										
Averna, 2010; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	56	30 (54)	61 (8)	56 (100)		30 (54)	0 (0)	27 (3)
	2x base simvastatin	40 mg simvastatin	56	32 (57)	62 (8)	56 (100)		28 (50)	0 (0)	26 (3)
MERCURY II; simvastatin 20 mg	Maintain simvastatin	20 mg simvastatin	190	106 (56)	62 (10)	151 (80)			86 (45)	31 (6)
	Switch to HP rosuvastatin	10 mg rosuvastatin	183	102 (56)	62 (10)	146 (80)			83 (45)	31 (6)
MERCURY II; simvastatin 40 mg	Maintain simvastatin	40 mg simvastatin	191	107 (56)	62 (10)	152 (80)			86 (45)	31 (6)
	Switch to HP rosuvastatin	20 mg rosuvastatin	189	105 (56)	62 (10)	150 (80)			85 (45)	31 (6)
LEAD; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	37	21 (57)	65 (7)	37 (100)		30 (81)	37 (100)	29 (4)
	2x Base simvastatin	40 mg simvastatin	50	38 (76)	64 (6)	50 (100)		32 (64)	50 (100)	28 (4)
Brohet, 2005; simvastatin 10 mg or 20 mg	Maintain simvastatin + add ezetimibe	10 or 20 mg simvastatin + 10 mg ezetimibe	208	145 (70)	64 (11)					27 (4)
	Maintain simvastatin + add placebo	10 or 20 mg simvastatin	210	158 (75)	63 (10)					27 (4)
IN-PRACTICE; simvastatin 20 mg	2x Base simvastatin + add ezetimibe	40 mg simvastatin + 10 mg ezetimibe	261	160 (61)	65 (9)	254 (97)	44 (17)		42 (16)	
	Switch to HP atorvastatin	40 mg atorvastatin	263	185 (70)	64 (8)	261 (99)	55 (21)		27 (10)	
STAT; simvastatin 40 mg	Maintain simvastatin	40 mg simvastatin	92	71 (77)	58 (10)		72 (78)	65 (71)		27 (4)
	Switch to HP atorvastatin	40 mg atorvastatin	91	75 (82)	58 (9)		79 (87)	63 (69)		28 (4)
EASE; simvastatin 10 mg or 20 mg or 40 mg or 80 mg	Maintain simvastatin + add ezetimibe	10, 20, 40, or 80 mg simvastatin + 10 mg ezetimibe	562	298 (53)	62 (11)	481 (82)			223 (38)	
	Maintain simvastatin	10, 20, 40, or 80 mg simvastatin	279	141 (51)	62 (12)	236 (81)			115 (39)	
Pesaro, 2012; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	40	27 (68)	65 (9)[a]		5 (13)	36 (90)	16 (40)	29 (4)
	4x Base simvastatin	80 mg simvastatin	38	21 (55)	62 (10)[a]		8 (23)	26 (68)	20 (53)	28 (3)
Rosen, 2013; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	162	81 (50)	64 (9)				158 (100)	
	2x Base simvastatin	40 mg simvastatin	81	40 (49)	65 (8)				78 (100)	
ESD; simvastatin 40 mg	Maintain simvastatin + add ezetimibe	40 mg simvastatin + 10 mg ezetimibe	54	34 (63)	66		24 (45)		54 (100)	29 (4)
	Maintain simvastatin + add placebo	40 mg simvastatin	54	30 (56)	65		30 (56)		54 (100)	29 (4)
MERCURY I; simvastatin 20 mg	Switch to HP rosuvastatin	10 mg rosuvastatin	277	156 (56)	62 (11)	275 (99)	197 (71)			28 (5)
	Maintain simvastatin	20 mg simvastatin	250	141 (56)	62 (11)	248 (99)	178 (71)			28 (5)
Van Dam, 2000; simvastatin 20 mg	Maintain simvastatin	20 mg simvastatin	129	90 (70)	56 (12)		35 (28)	36 (29)		27 (4)
	Switch to HP atorvastatin	10 mg rosuvastatin	124	87 (70)	55 (12)		31 (26)	40 (33)		27 (4)
Van Dam, 2000; simvastatin 40 mg	Maintain simvastatin	40 mg simvastatin	64	32 (50)	56 (10)		13 (20)	15 (23)		27 (4)
	Switch to HP atorvastatin	40 mg atorvastatin	61	40 (66)	54 (12)		10 (16)	18 (30)		27 (3)

Table 4 (continued)

Trial; prior treatment	Intervention	Absolute dose	*N*	Men (%)	Age	White (%)	Smokers (%)	Hypertension (%)	Diabetes (%)	BMI
Zubaid, 2008; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	60	52 (87)	55 (8)	60 (100)	8 (12)	29 (41)	21 (29)	26 (4)
	Maintain simvastatin	20 mg simvastatin	60	54 (90)	52 (8)	60 (100)	3 (5)	30 (42)	26 (35)	27 (4)
Atorvastatin trials										
MERCURY II; atorvastatin 10 mg	Maintain atorvastatin	10 mg atorvastatin	185	103 (56)	62 (10)	147 (80)			84 (45)	31 (6)
	Switch to HP rosuvastatin	10 mg rosuvastatin	191	107 (56)	62 (10)	152 (80)			86 (45)	31 (6)
MERCURY II; atorvastatin 20 mg	Maintain atorvastatin	20 mg atorvastatin	186	104 (56)	62 (10)	148 (80)			84 (45)	31 (6)
	Switch to HP rosuvastatin	10 mg rosuvastatin	186	104 (56)	62 (10)	148 (80)			84 (45)	31 (6)
Barrios, 2005; atorvastatin 10 mg	Switch to LP simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	221	141 (64)	64 (10)	205 (93)		141 (64)	59 (27)	29 (4)
	2x Base atorvastatin	20 mg atorvastatin	214	128 (60)	63 (10)	197 (92)		116 (54)	53 (25)	28 (4)
PACE; atorvastatin 20 mg	Maintain atorvastatin + add ezetimibe	20 mg atorvastatin + 10 mg ezetimibe	124	69 (56)	60 (11)	120 (97)			55 (44)	29 (5)
	2x Base atorvastatin	40 mg atorvastatin	126	63 (50)	58 (11)	122 (97)			57 (45)	30 (4)
Conard, 2008 (Protocol 079); atorvastatin 20 mg	Maintain atorvastatin + add ezetimibe	20 mg atorvastatin + 10 mg ezetimibe	98	58 (59)	56 (10)	58 (59)	32 (33)	89 (91)	0 (0)	
	2x Base atorvastatin	40 mg atorvastatin	98	49 (50)	58 (10)	60 (61)	28 (29)	87 (89)	0 (0)	
Cruz-Fernandez, 2005 (Protocols 803 + 804); atorvastatin 10 mg or 20 mg	Maintain atorvastatin + add ezetimibe	10 or 20 mg atorvastatin + 10 mg ezetimibe	220	153 (70)	63 (9)	219 (99)		127 (58)	38 (17)	28 (3)
	Maintain atorvastatin	10 or 20 mg atorvastatin	230	157 (68)	63 (10)	227 (99)		124 (54)	41 (18)	27 (4)
Hing Ling, 2012; atorvastatin 20 mg	Switch to LP simvastatin + add ezetimibe	40 mg simvastatin + 10 mg ezetimibe	120	63 (53)	59 (10)	89 (74)			42 (35)	
	2x Base atorvastatin	40 mg atorvastatin	130	65 (50)	60 (8)	90 (69)			45 (35)	
SUBARU; atorvastatin 10 mg	Maintain atorvastatin	10 mg atorvastatin	207	78 (38)	64 (10)	0 (0)	61 (29)	155 (75)	134 (65)	
	Switch to EP rosuvastatin	5 mg rosuvastatin	208	95 (46)	67 (10)	0 (0)	53 (25)	148 (71)	132 (63)	
Leiter, 2008; atorvastatin 40 mg	Maintain atorvastatin + add ezetimibe	40 mg atorvastatin + 10 mg ezetimibe	288	173 (60)	61 (10)	237 (82)		266 (92)	155 (54)	
	2x Base atorvastatin	80 mg atorvastatin	291	178 (61)	62 (9)	232 (80)		273 (94)	153 (53)	
ESSENTIAL; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	10 mg atorvastatin + 10 mg ezetimibe	115	83 (72)	69 (9)		20 (17)	90 (78)	42 (37)	24 (4)
	2x Base atorvastatin	20 mg atorvastatin	128	96 (75)	70 (10)		22 (17)	104 (81)	52 (41)	25 (4)
Okada, 2011; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	10 mg atorvastatin + 10 mg ezetimibe	43	28 (65)	66 (8)		14 (33)	33 (77)	17 (40)	25 (3)
	2x Base atorvastatin	20 mg atorvastatin	35	29 (83)	65 (9)		11 (31)	27 (77)	19 (54)	25 (4)
Padhy, 2013; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	10 mg atorvastatin + 10 mg ezetimibe	15	10 (67)	54 (2)		3 (20)	12 (80)	3 (20)	
	Maintain atorvastatin	10 mg atorvastatin	15	13 (87)	54 (3)		3 (20)	11 (73)	1 (7)	
EASE; atorvastatin 10 mg or 20 mg or 40 mg or 80 mg	Maintain atorvastatin + add ezetimibe	10, 20, 40, or 80 mg atorvastatin + 10 mg ezetimibe	769	408 (53)	62 (11)	663 (82)			292 (38)	
	Maintain atorvastatin	10, 20, 40, or 80 mg atorvastatin	386	195 (51)	62 (12)	326 (81)			151 (39)	

Table 4 (continued)

Trial; prior treatment	Intervention	Absolute dose	*N*	Men (%)	Age	White (%)	Smokers (%)	Hypertension (%)	Diabetes (%)	BMI
Rosen, 2013; atorvastatin 10 mg	Switch to LP simvastatin + add ezetimibe	20 mg simvastatin + 10 mg ezetimibe	160	80 (50)	64 (9)				160 (100)	
	2x Base atorvastatin	20 mg atorvastatin	81	40 (49)	65 (8)				81 (100)	
MERCURY I; atorvastatin 10	Switch to HP rosuvastatin	10 mg rosuvastatin	276	166 (60)	62 (10)	274 (99)	196 (71)		75 (27)	29 (13)
	Maintain atorvastatin	10 mg atorvastatin	240	144 (60)	62 (10)	239 (99)	171 (71)		65 (27)	29 (13)
MERCURY I; atorvastatin 20	Switch to EP rosuvastatin	5 mg rosuvastatin	293	173 (59)	62 (10)	289 (99)	208 (71)		80 (27)	28 (4)
	Switch to HP rosuvastatin	10 mg rosuvastatin	305	180 (59)	62 (10)	301 (99)	217 (71)		83 (27)	28 (4)
	Maintain atorvastatin	20 mg atorvastatin	299	177 (59)	62 (10)	295 (99)	213 (71)		81 (27)	28 (4)
Stein, 2004; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	10 mg atorvastatin + 10 mg ezetimibe	305	159 (52)	53 (18–82)[b]	279 (91)	76 (25)	108 (35)	19 (6)	
	2x base atorvastatin	20 mg atorvastatin	316	171 (54)	52 (18–80)[b]	289 (91)	85 (27)	124 (39)	23 (7)	
Zieve, 2010; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	10 mg atorvastatin + 10 mg ezetimibe	526	249 (47)	71 (5)	503 (96)			110 (21)	
	2x Base atorvastatin	20 mg atorvastatin	527	241 (46)	71 (5)	505 (96)			113 (21)	
Rosuvastatin trials										
ACTE; rosuvastatin 5 mg	Maintain rosuvastatin + add ezetimibe	5 mg rosuvastatin + 10 mg ezetimibe	99	64 (65)	61 (9)	66 (67)			25 (25)	30 (5)
	2x Base rosuvastatin	10 mg rosuvastatin	98	58 (59)	61 (10)	67 (68)			21 (21)	28 (5)
ACTE; rosuvastatin 10 mg	Maintain rosuvastatin + add ezetimibe	10 mg rosuvastatin + 10 mg ezetimibe	122	66 (54)	62 (9)	106 (87)			31 (25)	29 (5)
	2x Base rosuvastatin	20 mg rosuvastatin	121	84 (69)	61 (9)	99 (82)			25 (21)	30 (5)
PACE; rosuvastatin 10 mg	Switch to EP atorvastatin + add ezetimibe	20 mg atorvastatin + 10 mg ezetimibe	234	111 (47)	59 (10)	222 (95)			116 (50)	30 (5)
	2x Base rosuvastatin	20 mg rosuvastatin	206	107 (52)	58 (10)	196 (95)			92 (45)	29 (5)
Okada, 2011; rosuvastatin 2.5 mg	Maintain rosuvastatin + add ezetimibe	2.5 mg rosuvastatin + 10 mg ezetimibe	49	37 (76)	66 (11)		25 (51)	41 (84)	27 (55)	24 (3)
	2x Base rosuvastatin	5 mg rosuvastatin	38	26 (68)	68 (7)		15 (39)	27 (71)	18 (47)	25 (3)
Torimoto, 2013; rosuvastatin 2.5 mg	2x Base rosuvastatin	5 mg rosuvastatin	36	16 (44)	63 (13)	0 (0)		23 (64)	36 (100)	27 (5)
	maintain rosuvastatin + add ezetimibe	2.5 mg rosuvastatin + 10 mg ezetimibe	39	24 (62)	66 (12)	0 (0)		28 (72)	39 (100)	25 (4)
Yamazaki, 2013; rosuvastatin 2.5 mg	4x Base rosuvastatin	10 mg rosuvastatin	24	15 (63)	72 (8)	0 (0)	15 (63)	19 (79)	10 (42)	26 (3)
	maintain rosuvastatin + add ezetimibe	2.5 mg rosuvastatin + 10 mg ezetimibe	22	14 (64)	70 (10)	0 (0)	11 (50)	17 (77)	8 (36)	24 (3)

ESD Ezetimibe and Simvastatin in Dyslipidemia of Diabetes, *PACE* primary hypercholesterolemia and high cardiovascular risk patients who are not adequately controlled with atorvastatin 10 mg: a comparison of the efficacy and safety of switching to coadministration ezetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin

BMI is expressed as mean (SD); age is measured in years, expressed as mean (SD) or median (Q1, Q3), unless otherwise noted

[a]Expressed as median (SD)

[b]Expressed as mean (min, max)

Table 5 Laboratory measures at baseline, arranged by prior statin

Trial; prior treatment	Intervention	*N*	Total cholesterol	LDL	HDL	Non-HDL	ApoB	Triglycerides	CRP
Simvastatin trials									
Averna, 2010; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	56	201 (23)	126 (16)	51 (11)			120 (48)	
	2x Base simvastatin	56	202 (19)	128 (17)	49 (9)			124 (42)	
MERCURY II; simvastatin 20 mg	Maintain simvastatin	190	253 (31)	169 (26)	47 (10)	206 (30)	163 (26)	183 (66)	
	Switch to HP rosuvastatin	183	253 (31)	169 (26)	47 (10)	206 (30)	163 (26)	183 (66)	
MERCURY II; simvastatin 40 mg	Maintain simvastatin	191	252 (32)	169 (28)	47 (11)	206 (33)	162 (26)	185 (68)	
	Switch to HP rosuvastatin	189	252 (32)	169 (28)	47 (11)	206 (33)	162 (26)	185 (68)	
LEAD; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	37	201 (23)[a]	128 (19)[a]	46 (12)[a]			142 (62)[c]	
	2x Base simvastatin	50	197 (23)[a]	124 (19)[a]	43 (12)[a]			142 (62)[c]	
Brohet, 2005; simvastatin 10 mg or 20 mg	Maintain simvastatin + add ezetimibe	208	204 (22)[a]	122 (16)[a]	51 (12)[a]	153 (22)[a]	129 (19)[b]	137 (77)[c, f]	
	Maintain simvastatin + add placebo	210	204 (21)[a]	123 (14)[a]	51 (12)[a]	152 (19)[a]	129 (17)[b]	136 (62)[c, f]	
IN-PRACTICE; simvastatin 40 mg	2x Base simvastatin + add ezetimibe	261	182 (19)	101 (16)	54 (12)			142 (62–337)	
	Switch to HP atorvastatin	263	182 (23)	101 (16)	54 (12)			133 (62–354)	
STAT; simvastatin 40 mg	Maintain simvastatin	92	217 (36)[a]	138 (31)[a]	45 (13)[a]			167 (85)[c]	0.2 (0.1, 0.4)
	Switch to HP atorvastatin	91	221 (37)[a]	144 (32)[a]	45 (12)[a]			167 (74)[c]	0.2 (0.1, 0.4)
EASE; simvastatin 10 mg or 20 mg or 40 mg or 80 mg	Maintain simvastatin + add ezetimibe	586		129	48	162	129	151	0.2[d]
	Maintain simvastatin	293		129	49	163	130	151	0.2[d]
Pesaro, 2012; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	40	175 (157, 195)	99 (89, 117)	42 (37, 48)		90 (80, 100)[b]	139 (108, 168)	0.2 (0.1, 0.4)
	4x Base simvastatin	38	171 (155, 212)	101 (85, 130)	45 (38, 50)		90 (70, 100)[b]	117 (85, 150)	0.2 (0.1, 0.6)
Rosen, 2013; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	162	180 (31)	99 (22)	50 (14)	129 (28)	102 (20)	139 (67)	0.2 (0.3)
	2x Base simvastatin	81	177 (27)	97 (21)	51 (12)	126 (26)	101 (19)	131 (61)	0.2 (0.3)
ESD; simvastatin 40 mg	Maintain simvastatin + add ezetimibe	54	162 (36)	99 (31)	48 (11)		83 (22)	123 (95)	
	Maintain simvastatin + add placebo	54	154 (30)	91 (28)	50 (12)		81 (23)	106 (65)	

Table 5 (continued)

Trial; prior treatment	Intervention	*N*	Total cholesterol	LDL	HDL	Non-HDL	ApoB	Triglycerides	CRP
MERCURY I; simvastatin 20 mg	Switch to HP rosuvastatin	277	247 (34)	166 (29)	48 (12)			164 (63)	
	Maintain simvastatin	250	248 (34)	165 (29)	49 (12)			171 (68)	
Van Dam, 2000; simvastatin 20 mg	Maintain simvastatin	108	217 (31)[a]	139 (26)[a]	49 (11)[a]			150 (71)[c]	
	Switch to HP atorvastatin	107	215 (31)[a]	138 (27)[a]	49 (10)[a]			144 (66)[c]	
Van Dam, 2000; simvastatin 40 mg	Maintain simvastatin	54	225 (31)[a]	145 (27)[a]	54 (12)[a]			129 (60)[c]	
	Switch to HP atorvastatin	55	220 (34)[a]	143 (27)[a]	51 (14)[a]			136 (66)[c]	
Zubaid, 2008; simvastatin 20 mg	Maintain simvastatin + add ezetimibe	60	197 (3)[e]	127 (2)[e]	40 (1)[e]			145 (8)[e]	
	Maintain simvastatin	60	202 (4)[e]	131 (3)[e]	43 (4)[e]			156 (8)[e]	
Atorvastatin trials									
MERCURY II; atorvastatin 10 mg	Maintain atorvastatin	185	253 (33)	169 (28)	47 (11)	206 (33)	161 (27)	184 (66)	
	Switch to HP rosuvastatin	191	253 (33)	169 (28)	47 (11)	206 (33)	161 (27)	184 (66)	
MERCURY II; atorvastatin 20 mg	Maintain atorvastatin	186	251 (32)	168 (26)	47 (10)	204 (33)	160 (26)	181 (68)	
	Switch to HP rosuvastatin	186	251 (32)	168 (26)	47 (10)	204 (33)	160 (26)	181 (68)	
Barrios, 2005; atorvastatin 10 mg	Switch to LP simvastatin + add ezetimibe	221	207 (23)	124 (18)	54 (12)	153 (21)	114 (16)	132 (61)	
	2x Base atorvastatin	214	211 (23)	126 (19)	56 (14)	154 (23)	113 (16)	122 (65)	
PACE; atorvastatin 20 mg	Maintain atorvastatin + add ezetimibe	124	202 (23)	119 (16)	51 (12)	151 (22)	102 (19)	144 (79)	0.2 (0.3)[d]
	2x Base atorvastatin	126	203 (25)	121 (21)	52 (13)	151 (24)	103 (18)	141 (65)	0.2 (0.3)[d]
Conard, 2008 (Protocol 079); atorvastatin 20 mg	Maintain atorvastatin + add ezetimibe	98	203 (25)	120 (20)	51 (12)	152 (24)	123 (23)	155 (72)	0.2 (0.3)
	2x Base atorvastatin	98	201 (22)	118 (17)	52 (12)	149 (22)	120 (21)	148 (77)	0.1 (0.2)
Cruz-Fernandez, 2005 (Protocols 803 + 804); atorvastatin 10 mg or 20 mg	Maintain atorvastatin + add ezetimibe	220	206 (23)	124 (17)	52 (12)	154 (21)	129 (17)	137 (69)	
	Maintain atorvastatin	230	204 (23)	122 (16)	52 (12)	152 (21)	127 (18)	134 (69)	
Hing Ling, 2012; atorvastatin 20 mg	Switch to LP simvastatin + add ezetimibe	120	203 (21)	122 (17)	52 (13)	151 (20)	120 (16)	135 (67)	0.2 (0.3)
	2x Base atorvastatin	130	199 (23)	119 (16)	51 (13)	147 (20)	117 (16)	132 (67)	0.2 (0.3)

Table 5 (continued)

Trial; prior treatment	Intervention	*N*	Total cholesterol	LDL	HDL	Non-HDL	ApoB	Triglycerides	CRP
SUBARU; atorvastatin 10 mg	Maintain atorvastatin	207	192 (35)	109 (31)	60 (15)			131 (72)	0.2 (0.6)[d]
	Switch to EP rosuvastatin	207	186 (29)	103 (25)	61 (18)			129 (67)	0.1 (0.1)[d]
Leiter, 2008; atorvastatin 40 mg	Maintain atorvastatin + add ezetimibe	288	165 (22)	89 (16)	48 (11)	117 (21)	101 (19)	131 (72)	0.2
	2x Base atorvastatin	291	165 (23)	90 (16)	47 (10)	118 (22)	102 (19)	136 (72)	0.2
ESSENTIAL; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	115	169 (22)	94 (17)	52 (12)			111 (36)	0.1 (0.2)
	2x Base atorvastatin	128	167 (21)	95 (18)	51 (12)			106 (34)	0.1 (0.1)
Okada, 2011; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	43	199 (23)	121 (17)	53 (9)			133 (89, 157)	
	2x Base atorvastatin	35	191 (20)	114 (15)	51 (9)			126 (88, 188)	
Padhy, 2013; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	15	225 (12)[e]	145 (11)[e]	44 (2)[e]			193 (18)[e]	0.5 (0.2, 0.8)
	Maintain atorvastatin	15	192 (22)[e]	122 (5)[e]	44 (2)[e]			150 (15)[e]	0.1 (0.1, 0.5)
EASE; atorvastatin 10 mg or 20 mg or 40 mg or 80 mg	Maintain atorvastatin + add ezetimibe	808		129	48		129	151	0.2
	Maintain atorvastatin	404		129	49		130	151	0.2
Rosen, 2013; atorvastatin 10 mg	Switch to LP simvastatin + add ezetimibe	160	180 (31)	99 (22)	50 (14)	129 (28)	102 (20)	139 (67)	0.2 (0.3)
	2x Base atorvastatin	81	177 (27)	97 (21)	51 (12)	126 (26)	101 (19)	131 (61)	0.2 (0.3)
MERCURY I; atorvastatin 10	Switch to HP rosuvastatin	276	244 (33)	162 (27)	49 (13)			162 (61)	
	Maintain atorvastatin	240	242 (31)	163 (29)	49 (12)			160 (68)	
MERCURY I; atorvastatin 20	Switch to EP rosuvastatin	293	249 (34)	169 (31)	50 (11)			163 (65)	
	Switch to HP rosuvastatin	305	251 (37)	167 (33)	48 (11)			167 (59)	
	Maintain atorvastatin	299	248 (38)	167 (30)	50 (12)			159 (62)	
Stein, 2004; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	305	262 (3)[e]	186 (3)[e]	50 (1)[e]	212 (3)[e]		117 (4)[e]	
	2x Base atorvastatin	316	264 (3)[e]	187 (3)[e]	50 (1)[e]	214 (3)[e]		119 (4)[e]	
Zieve, 2010; atorvastatin 10 mg	Maintain atorvastatin + add ezetimibe	526	183 (32)	103 (28)	55 (14)	128 (31)	103 (23)	113 (54)	0.2
	2x Base atorvastatin	527	183 (26)	101 (21)	55 (13)	127 (25)	102 (21)	116 (62)	0.2

Table 5 (continued)

Trial; prior treatment	Intervention	*N*	Total cholesterol	LDL	HDL	Non-HDL	ApoB	Triglycerides	CRP
Rosuvastatin trials									
ACTE; rosuvastatin 5 mg	Maintain rosuvastatin + add ezetimibe	99	188 (29)	107 (23)	52 (15)	135 (27)	112 (22)	133 (80)	0.2 (0.3)[d]
	2x Base rosuvastatin	98	182 (29)	102 (23)	48 (12)	134 (29)	109 (23)	143 (87)	0.2 (0.3)[d]
ACTE; rosuvastatin 10 mg	Maintain rosuvastatin + add ezetimibe	122	183 (32)	101 (27)	54 (17)	129 (32)	107 (24)	131 (69)	0.2 (0.3)[d]
	2x Base rosuvastatin	121	178 (31)	98 (25)	52 (13)	126 (33)	103 (24)	116 (73)	0.2 (0.2)[d]
PACE; rosuvastatin 10 mg	Switch to EP atorvastatin + add ezetimibe	234	204 (24)	119 (16)	53 (15)	151 (21)	102 (18)	150 (61)	0.2 (0.3)[d]
	2x Base rosuvastatin	206	203 (23)	120 (17)	54 (13)	150 (21)	103 (18)	137 (73)	0.2 (0.3)[d]
Okada, 2011; rosuvastatin 2.5 mg	Maintain rosuvastatin + add ezetimibe	49	201 (24)	120 (13)	51 (14)			123 (96, 172)	
	2x Base rosuvastatin	38	198 (25)	120 (18)	50 (10)			134 (104, 171)	
Torimoto, 2013; rosuvastatin 2.5 mg	2x Base rosuvastatin	36		112 (22)	56 (11)			147 (79)	
	Maintain rosuvastatin + add ezetimibe	39		111 (26)	57 (16)			147 (71)	
Yamazaki, 2013; rosuvastatin 2.5 mg	4x Base rosuvastatin	24	168 (17)	89 (13)	46 (12)			165 (79)	0.2 (0.2)[d]
	Maintain rosuvastatin + add ezetimibe	22	164 (23)	84 (15)	50 (12)			149 (104)	0.3 (0.3)[d]

All estimates are in mg/dL and expressed as mean (SD) or median (Q1, Q3) unless otherwise noted

ESD Ezetimibe and Simvastatin in Dyslipidemia of Diabetes, *PACE* primary hypercholesterolemia and high cardiovascular risk patients who are not adequately controlled with atorvastatin 10 mg: a comparison of the efficacy and safety of switching to coadministration ezetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *Non-HDL* non-high-density lipoprotein cholesterol, *CRP* C-reactive protein, *ApoB* apolipoprotein B

[a]Estimates of total, LDL, HDL, and non-HDL cholesterol were converted from mmol/L to mg/dL by multiplying by 38.67

[b]Estimate converted from g/L to mg/Dl

[c]Estimates of triglycerides concentration were converted from mmol/L to mg/dL by multiplying by 88.57

[d]Estimate converted from mg/L to mg/dL

[e]Estimate expressed as mean (SEM)

[f]Expressed as mean (min, max)

Appendix 4: Evidence base and results of NMA for total cholesterol

Presented here are the evidence bases and respective NMA results for the change from baseline in total cholesterol outcome, arranged by patient treatment experience.

See Figs. 4, 5 and Tables 6, 7 and 8.

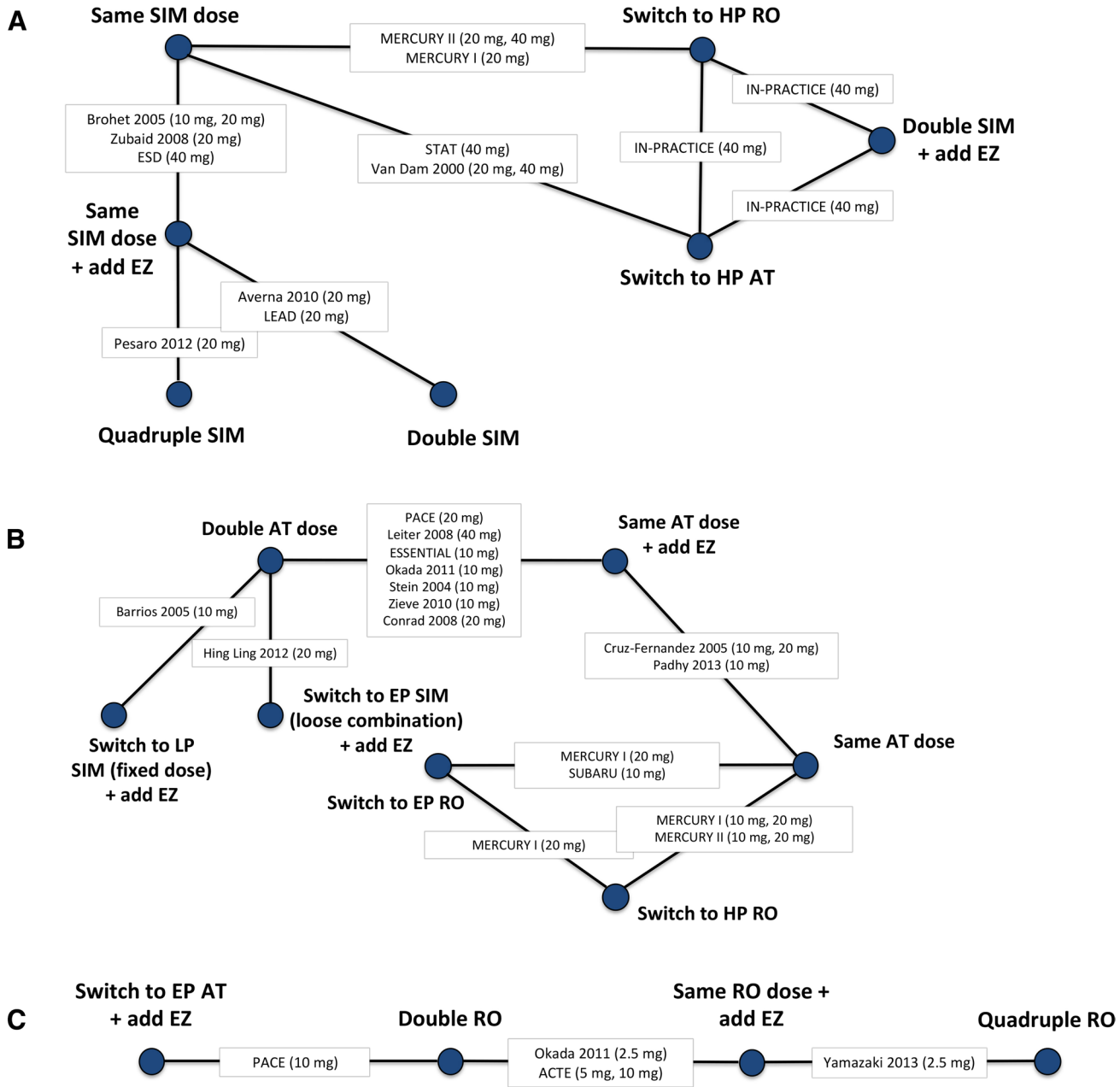

Fig. 4 Network diagrams of evidence for change from baseline in total cholesterol. **a** Simvastatin experienced, **b** atorvastatin experienced, **c** rosuvastatin experienced. *HP* higher potency, *LP* lower potency, *EP* equal potency, *SIM* simvastatin, *RO* rosuvastatin, *AT* atorvastatin, *EZ* ezetimibe. Doses in brackets indicate the baseline or run-in statin dose

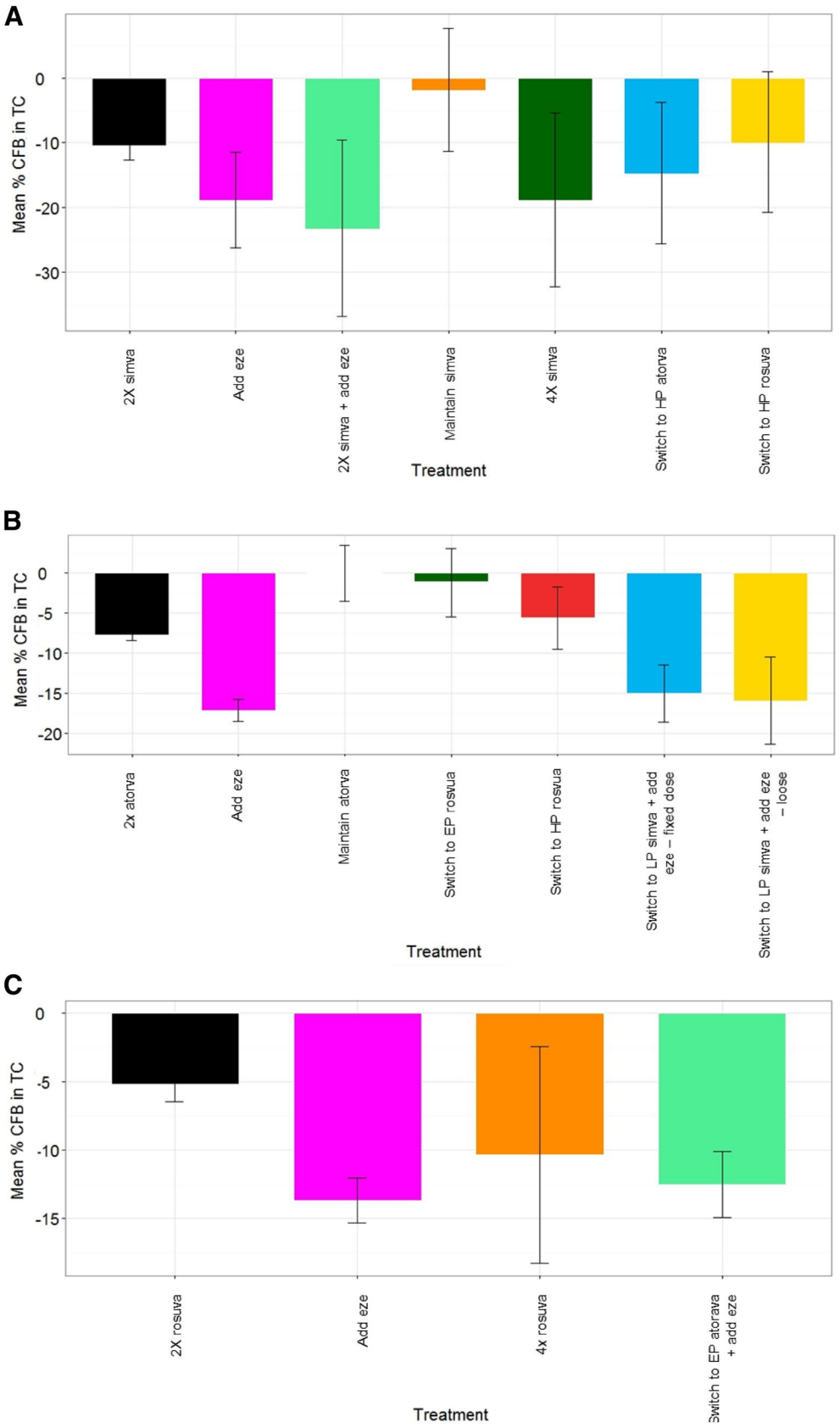

Fig. 5 Modeled outcomes for change from baseline in total cholesterol. *HP* higher potency, *LP* lower potency, *EP* equal potency, *SIM* simvastatin, *RO* rosuvastatin, *AT* atorvastatin, *EZ* ezetimibe

Table 6 Mean differences in mean percent change from baseline in total cholesterol among simvastatin-experienced patients from random-effects network meta-analysis

Double simvastatin	**8.43 (0.73, 16.01)**	12.86 (–1.11, 26.47)	–8.46 (–18.38, 1.06)	8.46 (–5.31, 21.88)	4.34 (–6.98, 15.25)	–0.37 (–11.68, 10.44)
–8.43 (–16.01, –0.73)	**Add ezetimibe**	4.42 (–7.28, 16.06)	**–16.89 (–23.16, –10.89)**	0.01 (–11.39, 11.24)	–4.07 (–12.48, 3.97)	**–8.79 (–17.08, –0.84)**
–12.86 (–26.47, 1.11)	–4.42 (–16.06, 7.28)	**Double simvastatin + add ezetimibe**	**–21.30 (–31.23, –11.54)**	–4.43 (–20.62, 11.90)	–8.52 (–18.10, 1.05)	**–13.23 (–22.77, –3.79)**
8.46 (–1.06, 18.38)	**16.89 (10.89, 23.16)**	**21.30 (11.54, 31.23)**	**Maintain simvastatin**	**16.88 (4.00, 29.80)**	**12.81 (7.35, 18.24)**	**8.10 (2.77, 13.33)**
–8.46 (–21.88, 5.31)	–0.01 (–11.24, 11.39)	4.43 (–11.90, 20.62)	**–16.88 (–29.80, –4.00)**	**Quadruple simvastatin**	–4.08 (–18.10, 9.85)	–8.80 (–22.85, 5.10)
–4.34 (–15.25, 6.98)	4.07 (–3.97, 12.48)	8.52 (–1.05, 18.10)	**–12.81 (–18.24, –7.35)**	4.08 (–9.85, 18.10)	**Switch to HP atorvastatin**	–4.73 (–11.37, 1.89)
0.37 (–10.44, 11.68)	**8.79 (0.84, 17.08)**	**13.23 (3.79, 22.77)**	**–8.10 (–13.33, –2.77)**	8.80 (–5.10, 22.85)	4.73 (–1.89, 11.37)	**Switch to HP rosuvastatin**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC 52.92; deviance 26.85; SD 4.69

HP higher potency

Table 7 Mean differences in mean percent change from baseline in total cholesterol among atorvastatin-experienced patients from random-effects network meta-analysis

Double atorvastatin	**9.41 (7.92, 10.89)**	**–7.90 (–11.29, –4.26)**	**–6.72 (–10.84, –2.31)**	–2.23 (–6.02, 1.82)	**7.26 (3.66, 10.92)**	**8.32 (2.66, 13.72)**
–9.41 (–10.89, –7.92)	**Add ezetimibe**	**–17.29 (–20.42, –13.99)**	**–16.11 (–19.99, –11.99)**	**–11.61 (–15.19, –7.88)**	–2.15 (–6.07, 1.78)	–1.08 (–6.98, 4.51)
7.90 (4.26, 11.29)	**17.29 (13.99, 20.42)**	**Maintain atorvastatin**	1.20 (–1.21, 3.58)	**5.69 (3.93, 7.41)**	**15.20 (9.98, 20.08)**	**16.16 (9.45, 22.66)**
6.72 (2.31, 10.84)	**16.11 (11.99, 19.99)**	–1.20 (–3.58, 1.21)	**switch to EP rosuvastatin**	**4.50 (1.84, 7.13)**	**14.00 (8.27, 19.37)**	**14.98 (7.96, 21.93)**
2.23 (–1.82, 6.02)	**11.61 (7.88, 15.19)**	**–5.69 (–7.41, –3.93)**	**–4.50 (–7.13, –1.84)**	**Switch to HP rosuvastatin**	**9.51 (4.01, 14.66)**	**10.50 (3.54, 17.23)**
–7.26 (–10.92, –3.66)	2.15 (–1.78, 6.07)	**–15.20 (–20.08, –9.98)**	**–14.00 (–19.37, –8.27)**	**–9.51 (–14.66, –4.01)**	**switch to LP simvastatin + add ezetimibe – FD**	1.01 (–5.63, 7.58)
–8.32 (–13.72, –2.66)	1.08 (–4.51, 6.98)	**–16.16 (–22.66, –9.45)**	**–14.98 (–21.93, –7.96)**	**–10.50 (–17.23, –3.54)**	–1.01 (–7.58, 5.63)	**switch to LP simvastatin + add ezetimibe – loose**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC 60.46; deviance 33.16; SD 1.23

HP higher potency, *EP* equal potency, *LP* lower potency, *FD* fixed dose

Table 8 Mean differences in mean percent change from baseline in total cholesterol among rosuvastatin-experienced patients from fixed-effects network meta-analysis

Double rosuvastatin	**8.49 (6.33, 10.65)**	5.12 (–2.91, 13.20)	**7.31 (4.97, 9.68)**
–8.49 (–10.65, –6.33)	**Add ezetimibe**	–3.37 (–11.09, 4.43)	–1.16 (–4.35, 2.02)
–5.12 (–13.20, 2.91)	3.37 (–4.43, 11.09)	**Quadruple rosuvastatin**	2.20 (–6.20, 10.52)
–7.31 (–9.68, –4.97)	1.16 (–2.02, 4.35)	–2.20 (–10.52, 6.20)	**switch to EP atorvastatin + add ezetimibe**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment

All bolded values are statistically meaningful at the 0.05 significance level

DIC 17.47, deviance 9.47

EP equal potency

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