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META-ANALYSIS

Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials

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Aims Current evidence on dyslipidaemia management has expanded to novel treatments and very low achieved levels of low-density lipoprotein cholesterol (LDL-C). We sought to compare the clinical impact of more-intensive vs. less-intensive LDL-C lowering by means of statins and currently recommended non-statin medications in secondary prevention.

Methods and results We searched Medline, EMBASE, and Cochrane databases for randomized controlled trials of statins, ezetimibe, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, or bile acid sequestrants with >500 patients followed for ≥1 year. We employed random-effects models using risk ratios (RRs) with 95% confidence intervals (CIs) to compare outcomes. We included 19 trials (15 of statins, 3 of PCSK9 inhibitors, and 1 of ezetimibe) with 152 507 patients randomly assigned to more-intensive ($n = 76\,678$) or less-intensive treatment ($n = 75\,829$). More-intensive treatment was associated with 19% relative risk reduction for the primary outcome, major vascular events (MVEs; RR 0.81, 95% CI 0.77–0.86). Risk reduction was greater across higher baseline levels and greater achieved reductions of LDL-C. The clinical benefit was significant across varying types of more-intensive treatment and was consistent for statins (RR 0.81, 95% CI 0.76–0.86) and non-statin agents (PCSK9 inhibitors and ezetimibe; RR 0.85, 95% CI 0.77–0.94) as active (more-intensive) intervention (P-interaction = 0.38). Each 1.0 mmol/L reduction in LDL-C was associated with 19% relative decrease in MVE. Death, cardiovascular death, myocardial infarction, stroke, and coronary revascularization also favoured more-intensive treatment.

Conclusion Reduction of MVE is proportional to the magnitude of LDL-C lowering across a broad spectrum of on-treatment levels in secondary prevention. Statin intensification and add-on treatment with PCSK9 inhibitors or ezetimibe are associated with significant reduction of cardiovascular morbidity in this very high-risk population.

Keywords Lipid lowering • LDL-cholesterol • Statin • Prevention • Outcomes

Introduction

Lowering of low-density lipoprotein cholesterol (LDL-C) halts the progression of atherosclerosis[1,2] and improves clinical outcomes in patients with atherosclerotic cardiovascular disease (ASCVD).[3] Although statins are established as first-line treatment for LDL-C lowering, many patients cannot achieve sufficient LDL-C reduction or tolerate effective doses of statins. Non-statin agents currently recommended as second-line options in patients with clinical ASCVD include cholesterol absorption inhibitors

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(ezetimibe), bile acid sequestrants, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors.[4–6]

Previous meta-analyses of randomized controlled trials (RCTs) established the safety and efficacy of statins in primary and secondary prevention,[3] showed a direct relation between the magnitude of LDL-C lowering and clinical risk reduction,[3] and collectively assessed the cardiovascular effects of variable lipid-lowering interventions including non-medical treatments (diet and surgical interventions) as well as medications that are currently not recommended or are contraindicated in combination with statins (niacin and fibrates).[7] Recently, preliminary evidence of clinical benefit with PCSK9 inhibitors[8] was confirmed in large, dedicated outcomes trials.[9] Against this background of novel available evidence, we sought to provide a contemporary quantitative synthesis of the efficacy of more-intensive vs. less-intensive LDL-C lowering and address the following key questions: (i) assess the relative clinical benefit of statins and currently recommended non-statin LDL-C-lowering medications in secondary prevention and (ii) evaluate the magnitude of cardiovascular risk reduction across a wide spectrum of achieved LDL-C reductions, extending to very low on-treatment levels uniquely achievable by means of PCSK9 inhibitors. We focused on patients with established ASCVD, i.e. those at highest cardiovascular risk and likely to derive maximal benefit from intensive LDL-C lowering.

Methods

Search methods and resources

Methods are described in detail in the Supplementary material online. The protocol was registered with PROSPERO (CRD42017059343). Following the Cochrane Handbook recommendations,[10] we searched the following databases [Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)] and websites (www.clinicaltrials.gov and www.cardiosource.com) to identify relevant trials of the competing interventions of interest. We applied a modified broad search strategy by including relevant keywords ('statin', 'ezetimibe', 'PCSK9 inhibitor', 'colestipol', 'cholestyramine', 'low-density lipoprotein cholesterol', 'LDL-C', and 'random') without restrictions on language or year of publication. We scrutinized the reference lists from all eligible studies to identify additional citations that would fit our inclusion criteria (see Supplementary material online, *Table S1*).

Selection of studies

We considered eligible studies that included >500 patients (to exclude small studies with unreliable hazard ratios) and reported cardiovascular outcomes during at least 1 year of follow-up. Inclusion criteria were as follows: described as randomized, controlled trial; evaluated any comparison of the following strategies: statins, ezetimibe, bile acid sequestrants, PCSK9 inhibitors, or placebo (therapy vs. no therapy or more-intensive vs. less-intensive intervention or higher vs. lower dose of a medication); and included secondary-prevention patients (defined by a history of known ASCVD, i.e. coronary heart disease, peripheral artery disease, or cerebrovascular disease) or at least 60% secondary-prevention patients. 'More-intensive' vs. 'less-intensive' interventions included following possible comparisons: statin vs. control (no statin); more-intensive statin vs. less-intensive statin; non-statin agent vs. control; and more-intensive non-statin agent vs. less-intensive non-statin agent. Because the focus of this study was the effect of LDL lowering on clinical progression of ASCVD, we excluded studies of patients with significant competing risks (heart failure or chronic kidney disease), as the clinical benefit of lipid-lowering therapy is confounded by competing non-atherosclerotic risks.[3,11]

Data extraction and study outcomes

Two investigators (K.C.K. and G.C.M.S.) scrutinized titles and abstracts of all items independently and identified eligible trials. Consistent with previous reports,[3,7] we focused on cardiovascular events that are reduced by LDL-C-lowering therapies. Outcomes from each trial were selected to most closely approximate the composite endpoint of major vascular events (MVEs), which consisted of cardiovascular death, myocardial infarction or other acute coronary syndrome, coronary revascularization, and stroke when available. Secondary outcomes of interest included death, cardiovascular death, myocardial infarction, stroke, and coronary revascularization. Numbers of events in each arm were extracted to calculate risk ratios (RRs). We extracted data based on the intention-to-treat principle whenever available.

Risk of bias and quality assessment

Trial quality was assessed using Cochrane risk of bias assessment tool.[12] Two investigators (G.C.M.S. and R.P.) reviewed the studies and judged the risk of bias as low, unclear, or high risk.

Statistical analyses

We used DerSimonian and Laird random-effects meta-analysis to calculate summary RR.[13] Heterogeneity was estimated using restricted maximum likelihood and evaluated using I^2; values of 25%, 50%, and 75% represented mild, moderate, and high heterogeneity, respectively.[14] We stratified the meta-analysis of the primary outcome on a trial level by (i) type of intervention (statin vs. no statin, more-intensive statin vs. less-intensive statin, and non-statin vs. control), (ii) active intervention (statin or non-statin medication), (iii) mean baseline LDL-C levels (using the lower tertile across trials as cut-off), and (iv) mean absolute LDL-C reduction (using the median value across trials as cut-point). For the primary outcome, random-effects meta-regression analysis was performed with the reduction of LDL-C levels in each trial as moderator. To calculate absolute effect estimates, we applied pooled rate ratios and 95% confidence intervals (CIs) to what we deemed to be the most credible source for baseline risk estimates, i.e. the control rate of outcomes in the largest trial.[15]

In view of the time-dependent emergence of clinical benefit with statins[3,16] and to address the possibly confounding effect of shorter follow-up in trials with PCSK9 inhibitors, we performed the following sensitivity analyses: (i) we compared PCSK9 inhibitor trials vs. statin trials with follow-up ≤2.2 years (i.e. the median follow-up of the largest PCSK9 inhibitor trial[9]) and (ii) we compared PCSK9 trials vs. statin trials focusing only on outcomes up to 2.2 years. For the latter analysis, in statin trials with follow-up >2.2 years, we derived estimates from reconstructed time-to-event data of individual trials using Cox regression analysis. The Kaplan–Meier curves (whenever available) were digitized, and time-to-event data were reconstructed using a previously described algorithm.[17,18] Details are provided in the Supplementary material online.

We explored potential publication bias via its common proxy of small study effects by visual estimation of funnel plots and Egger's regression test.[19] All *P*-values were two tailed with statistical significance set at 0.05, and CIs were calculated at the 95% level for the overall estimates effect. Analyses were performed in STATA version 13.0.

Results

This meta-analysis included 19 trials that fulfilled pre-specified criteria (see Supplementary material online, *Figure S1*): 15 trials of statins,[20–34]

1 trial of ezetimibe,[35] and 3 trials of PCSK9 inhibitors.[9,36,37] No eligible trial of bile acid sequestrants was identified. The characteristics of individual trials and patient populations are summarized in *Tables 1* and *2* and Supplementary material online, *Tables S2–S3*. All trials except one[27] were multicentre studies. Overall, 152 507 patients were randomly assigned to more-intensive ($n = 76\,678$) or less-intensive LDL-C lowering treatment ($n = 75\,829$). Mean follow-up duration was 3.95 years (median 4.3, range 1–6.7 years), yielding 602 587 patient-years. The definition of more-intensive vs. less-intensive included following three comparisons: (i) statin vs. no statin (placebo, no treatment, or usual care, nine trials[20,21,23–27,30,33]); (ii) more-statin vs. less-statin (six trials[22,28,29,31,32,34]); and (iii) non-statin agent (on top of statin) vs. placebo (on top of statin) (four trials[9,35–37]). *Table 2* summarizes pooled clinical characteristics for these three groups of trials, indicating higher baseline LDL-C in trials of statin vs. no statin as well as higher prevalence of diabetes, smoking, and hypertension, a greater proportion of acute coronary syndrome patients, and shorter follow-up in trials with non-statin agents.

Primary outcome

Figure 1 presents a random-effects meta-analysis of the primary outcome. There were 25 260 MVEs, 11 591 for more-intensive vs. 13 669 for less-intensive treatment. The summary estimate showed a 19%

Table 1 Study characteristics of included trials

Trial name	Publication year	Recruitment period (years)	No. of centres	Active intervention (more intensive)	Control (less intensive)	Follow-up (years)[a]	Patients randomized
4S	1994	1988–1989	94	Simvastatin 20–40 mg	Placebo	5.4	4444
CARE	1996	1989–1991	80	Pravastatin 40 mg	Placebo	5	4159
Post-CABG	1997	1989–1991	7	Lovastatin 40–80 mg	Lovastatin 2.5–5 mg	4.3	1351
LIPID	1998	1990–1992	87	Pravastatin 40 mg	Placebo	6.1	9014
GISSI-P	2000	1993–1996	172	Pravastatin 20 mg	No treatment	2	4271
LIPS	2002	1996–1998	57	Fluvastatin 80 mg	Placebo	3.9	1677
HPS	2002	1994–1997	69	Simvastatin 40 mg	Placebo	5	20 536
GREACE	2002	1998–2000	1	Atorvastatin 10–80 mg	Usual care[b]	3	1600
PROVE-IT	2004	2000–2001	349	Atorvastatin 80 mg	Pravastatin 40 mg	2	4162
A to Z	2004	1999–2003	322	Simvastatin 40–80 mg	Placebo titrated to Simvastatin 20mg	2	4497
ALLIANCE	2004	1995–2002	16	Atorvastatin 10–80 mg	Usual care[b]	4.5	2442
TNT	2005	1998–1999	256	Atorvastatin 80 mg	Atorvastatin 10 mg	4.9	10 001
IDEAL	2005	1999–2001	190	Atorvastatin 40–80 mg	Simvastatin 20–40mg	4.8	8888
SPARCL	2006	1998–2001	205	Atorvastatin 80 mg	Placebo	4.9	4731
SEARCH	2010	1998–2001	88	Simvastatin 80 mg	Simvastatin 20 mg	6.7	12 064
IMPROVE-IT	2015	2005–2010	1147	Ezetimibe 10 mg plus simvastatin 40 mg	Placebo plus simvastatin 40 mg	6	18 144
ODYSSEY LONG TERM	2015	2012–2015	320	Alirocumab 150 mg Q2W plus high-dose statin or statin therapy at the maximum tolerated dose	Placebo Q2W plus high-dose statin or statin therapy at the maximum tolerated dose	1.34	2341
SPIRE-2	2017	2013–2016	1568	Bococizumab 150 mg Q2W plus statin (atorvastatin ≥40 mg daily; rosuvastatin ≥20 mg or simvastatin ≥40 mg unless not tolerated)	Placebo Q2W plus statin (atorvastatin ≥40 mg daily; rosuvastatin ≥20 mg or simvastatin ≥40 mg unless not tolerated)	1	10 621
FOURIER	2017	2013–2015	1242	Evolocumab 140 mg Q2W or 420 mg QM plus statin (at least atorvastatin 20mg)	Placebo Q2W or QM plus statin (at least atorvastatin 20mg)	2.2	27 564

[a]Mean or median (as reported in respective trial).
[b]Usual care was defined in GREACE as lifestyle interventions (diet and exercise) or lipid-lowering medications left at the discretion of treating physicians. In ALLIANCE, patients allocated to usual care were maintained on the lipid-lowering programme already prescribed prior to enrolment, and adjustments in lipid therapy were made entirely at the discretion of regular physicians.

Table 2 Pooled clinical characteristics across trials

	Statin vs. no statin (n = 52 874)	More statin vs. less statin (n = 40 963)	Non-statin agent vs. placebo (n = 58 670)
Age (years)[a]	60.6	61.9	62.7
Diabetes mellitus	9980/52 874 (18.9%)	5630/39 612 (14.2%)	20 809/58 670 (35.5%)
Female gender	11 551/52 874 (21.8%)	7772/40 963 (19%)	15 834/58 670 (27%)
Smoking	8128/51 274 (15.8%)	8181/40 963 (20%)	17 122/58/665 (29.2%)
Hypertension	20 958/50 432 (41.6%)	17 744/39 612 (44.8%)	41 776/56 320 (74.1%)
Acute coronary syndrome[b]	0 (0%)	8659/40 963 (21.1%)	h18 144/58, 670 (30.9%)
Baseline LDL-C (mmol/L)	3.72	2.76	2.63
Reduction in LDL-C (mmol/L)[c]	1.04	0.54	1.15
Follow-up (years)[a]	4.83	4.77	3.12

[a]Weighed means derived from mean or median values, as reported in respective individual trials.
[b]In the 'more statin vs. less statin' group, two trials enrolled patients with acute coronary syndrome (ACS): PROVE-IT included patients with ACS in the preceding 10 days prior to enrolment and A to Z included ACS patients stabilized for at least 12 h within 5 days after symptom onset. In the 'non-statin vs. placebo' group, one trial (IMPROVE-IT) included patients with ACS in the preceding 10 days prior to enrolment.
[c]Difference in achieved LDL-C between treatment arms.

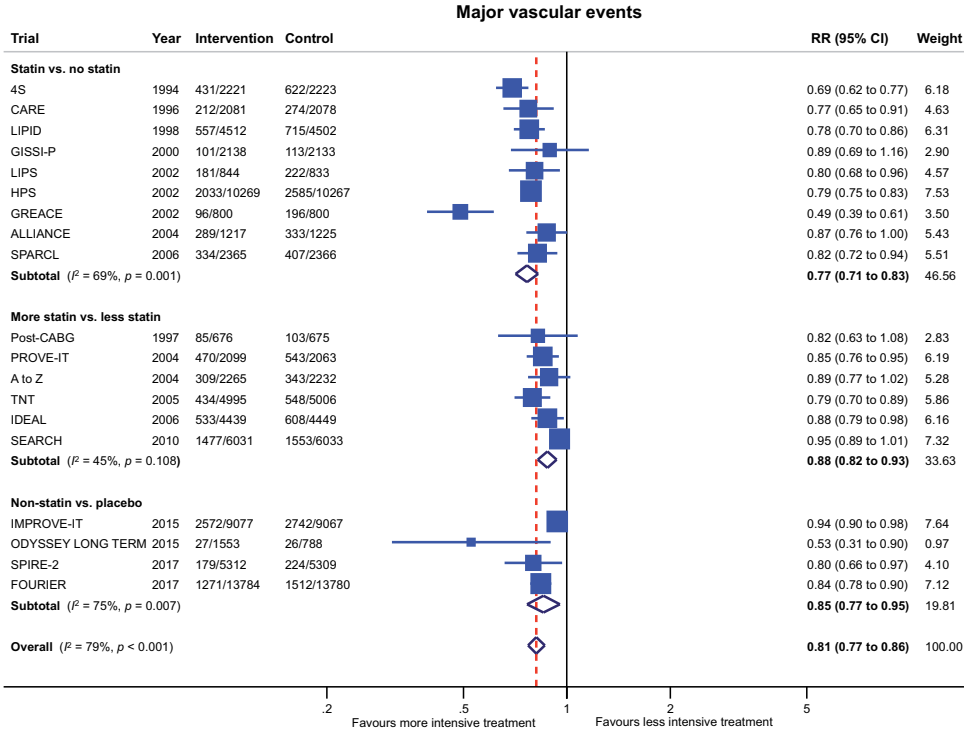

Figure 1 Random-effects meta-analysis of more-intensive vs. less-intensive LDL-C-lowering treatment for the primary outcome of major vascular events. Trials are stratified by the type of intervention. Risk ratio (RR) estimates according to intention-to-treat principle for all trials. Boxes and horizontal lines represent the respective RR and 95% confidence interval (CI) for each trial. The vertical solid line on the forest plot represents the point estimate of RR = 1. The red dashed line represents the point estimate of overall RR. Box sizes are proportional to weight of respective trial result. Diamonds represent the 95% CI for pooled estimates of the effect and are centred on pooled RR. Heterogeneity estimate of I^2 accompanies the summary estimate.

relative risk reduction (RRR) for MVE in favour of more-intensive treatment (RR 0.81, 95% CI 0.77–0.86; $P < 0.001$, I^2 79%; *Figure 1*). With respect to the type of intervention, the benefit was greater in trials comparing statin vs. no statin (RR 0.77, 95% CI 0.71–0.83) than in trials of more-statin vs. less-statin (RR 0.88, 95% CI 0.82–0.93) or trials of non-statin vs. placebo (RR 0.85, 95% CI 0.77–0.95) (P-interaction = 0.03).

Stratified meta-analyses are summarized in *Figure 2* and detailed in Supplementary material online, *Figures S2–S6*. The observed benefit was consistent in trials with statin[20–34] and those with a non-statin agent (i.e. ezetimibe or PCSK9 inhibitor)[9,35–37] as active treatment (P-interaction = 0.38, see Supplementary material online, *Figure S2*). The magnitude of benefit was greater in trials with mean baseline

LDL-C ≥3.0 mmol/L vs. <3.0 mmol/L (*P*-interaction = 0.004) and with LDL-C reduction ≥1.0 mmol/L vs. <1.0 mmol/L (*P*-interaction = 0.002). *Figure 3* provides a descriptive summary indicating greater RRR across higher baseline levels as well as greater achieved reduction of LDL-C (see Supplementary material online, *Table S4*).

Meta-regression analysis showed a significant, inverse association between the RR of the primary endpoint and LDL-C reduction (slope −0.19, 95% CI −0.28 to −0.10; *P* < 0.001; *Figure 4*). Each 1.0 mmol/L reduction in LDL-C was associated with a 19% RRR of MVE.

Using the observed rate of MVE in the control group of the largest of included studies as a baseline[9] (1512 events in 13 780 patients over 2.2 years corresponding to 53 events per 1000 patients per year), more-intensive LDL-lowering treatment was associated with 10 fewer MVE per 1000 patients per year (95% CI, 7–12 less events) (see Supplementary material online, *Table S5*).

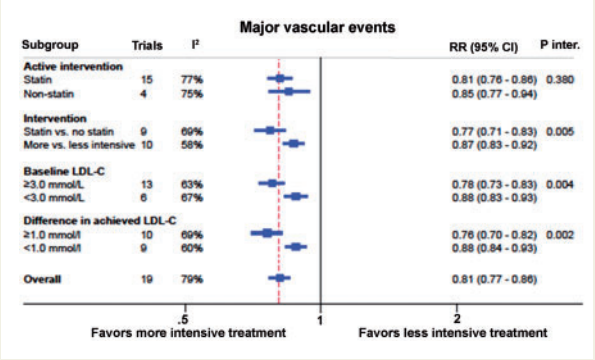

Figure 2 Stratified analyses for major vascular events. RR and corresponding CI for subgroups from individual trials were pooled and interactions were evaluated by random-effects meta-analyses. Boxes and horizontal lines represent the respective RR and 95% CI for each stratum. In the stratification by intervention, the 'more-intensive' vs. 'less-intensive' stratum includes trials comparing more-statin vs. less-statin ($n = 6$) and trials comparing non-statin vs. placebo ($n = 4$).

Sensitivity analyses for the primary outcome

In a sensitivity analysis of the primary outcome, we did not detect any variation in the clinical benefit of more-intensive treatment in trials of statins with follow-up ≤2.2 year[24,28,29] vs. trials of PCSK9 inhibitors (RR 0.87, 95% CI 0.80–0.94 vs. RR 0.81, 95% CI 0.80–0.89, respectively; *P*-interaction = 0.36) (see Supplementary material online, *Figure S7*). Similarly, in an analysis using data of statin trials with either follow-up duration ≤2.2 years[24,28,29] or with outcomes estimated up to 2.2 years as derived from the available Kaplan–Meier curves,[20,21,23,25,26,30–33] we found consistent risk reduction of MVE with statins and PCSK9 inhibitors (*P*-interaction = 0.72) (see Supplementary material online, *Figure S8*).

Secondary outcomes

Random-effects meta-analyses for secondary outcomes showed significant risk reduction for death (10%), cardiovascular death (14%), myocardial infarction (24%), stroke (19%), and coronary revascularization (19%) in favour of more-intensive treatment (*P* < 0.001 for all endpoints; see Supplementary material online, *Figures S9–S14*). The effect on mortality was significant in trials comparing statin vs. no statin (RR 0.85, 95% CI 0.78–0.92 for death and RR 0.78, 95% CI 0.73–0.84 for cardiovascular death), whereas no survival benefit of more-intensive treatment was observed with other two types of intervention (*Figure 5*).

Risk of bias assessment

Overall risk of bias was rated as low in all studies (see Supplementary material online, *Table S6*); four trials[24,27,30,32] were graded high risk

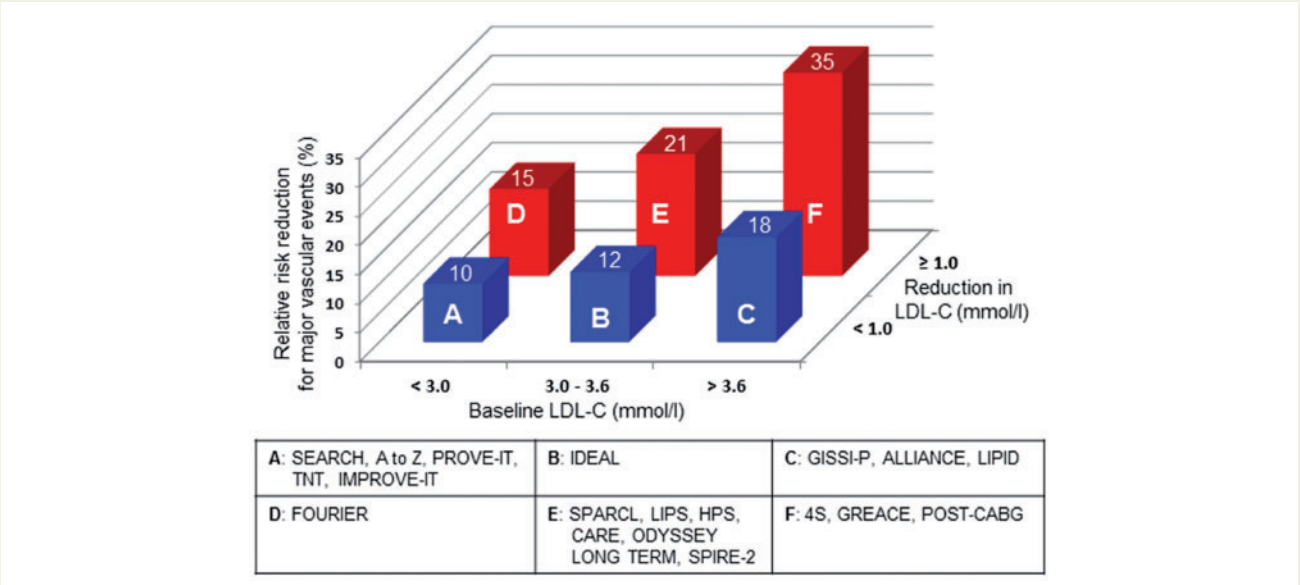

Figure 3 Relative risk reduction of the primary endpoint plotted against categories of baseline LDL-C (*x*-axis) and reduction in LDL-C (i.e. difference in achieved LDL-C between treatment arms; *z*-axis). Individual trials corresponding to each of the six groups are indicated below the graph.

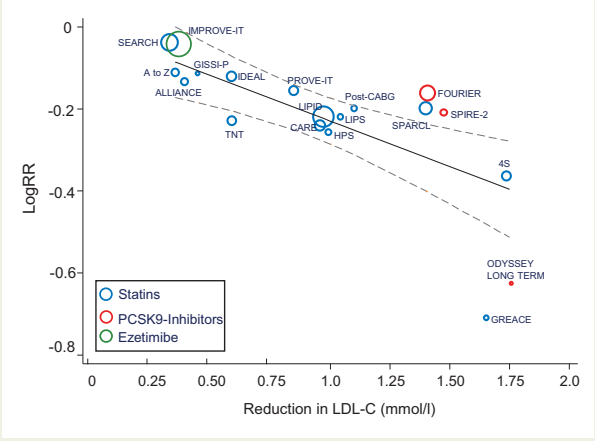

Figure 4 Meta-regression of major vascular events with reduction in LDL-C (mmol/L) in each trial as moderator. Circle size represents the weight each trial was given in the analysis. The meta-regression slope, derived from trial-level analysis of included trials, is indicated by the solid line and the 95% CI by the dashed lines.

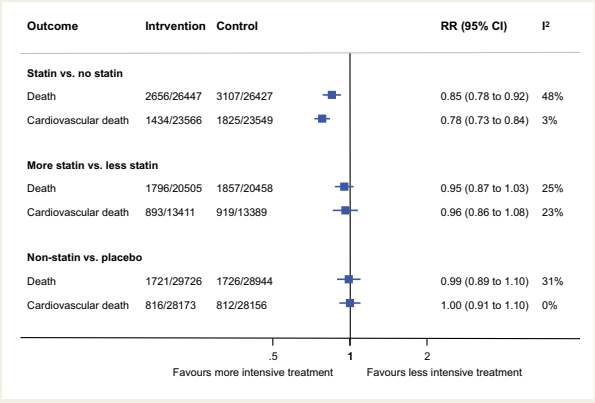

Figure 5 Summary estimates for secondary outcomes of all-cause and cardiovascular death. Trials are stratified by the type of intervention. RR and corresponding CI for subgroups from individual trials were pooled by random-effects meta-analyses. Boxes and horizontal lines represent the respective RR and 95% CI.

regarding blinding (open-label studies). There was no indication for small-study effect as suggested by visual assessment of funnel plots (see Supplementary material online, *Figure S15*) and Egger's test ($P = 0.10$). Sensitivity analyses with respect to trial quality showed no substantive differences (Supplementary material online).

Discussion

The salient findings of this meta-analysis of 19 RCTs including >152 000 patients and >25 000 primary outcome events can be summarized as follows. First, more-intensive vs. less-intensive LDL-C lowering by means of currently recommended medications resulted in 19% reduction of MVE in the context of secondary prevention. Second, each 1.0 mmol/L reduction in LDL-C was associated with 19% RRR for MVE across a broad spectrum of baseline and on-treatment LDL-C levels. Third, the clinical benefit was significant across varying modes of 'more-intensive' treatment but was more robust for the comparison of statin vs. no statin (when compared with the benefit yielded by statin intensification or addition of a non-statin agent). Statins and non-statin agents (PCSK9 inhibitors and ezetimibe) were associated with consistent clinical benefit (RR 0.81 vs. 0.85, respectively; *P*-interaction = 0.38). Fourth, the magnitude of derived benefit was greatest across higher baseline LDL-C levels and greater achieved LDL-C reductions. Fifth, more-intensive treatment resulted in decrease of all-cause and cardiovascular death, but the survival benefit was confined to studies comparing statin vs. no statin. These findings may have implications with respect to recommended first- and second-line LDL-lowering treatments in patients at very-high cardiovascular risk.

The beneficial cardiovascular impact of statin treatment is well established.[3,4] This meta-analysis provides an updated quantitative assessment of current evidence in the setting of secondary prevention by incorporating, for the first time to our knowledge, trials of non-statin agents—studies that included patients with lower baseline LDL-C levels, markedly decreased on-treatment levels, and more intense background cholesterol-lowering therapies (moderate-[35] or high-intensity statin[9,37]) compared with earlier RCTs of statins. Our findings extend previous evidence by demonstrating significant reductions in the risk of MVE across the spectrum of treatment modes, including medications that were recently introduced in clinical practice[9,36] or recently appreciated to improve prognosis.[35] Of note, the four non-statin trials included in this report contributed ~60 000 of all 152 500 patients—i.e. more than the sum of patients in 'more- vs. less-statin' trials included in the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis.[3]

Stratified analyses provided additional important insights. The cardiovascular benefit of more-intensive LDL-C lowering was significant across baseline LDL-C levels but was comparatively more pronounced in the context of higher baseline levels. The CTTC patient-level meta-analysis previously showed no heterogeneity in risk reduction across baseline LDL-C levels ranging between <2.0 mmol/L and >4.0 mmol/L.[3] The discordant findings in our analysis should be viewed in light of the inclusion of a large number of patients with very low achieved LDL-C as well as our focus on secondary-prevention RCTs vs. inclusion also of primary-prevention trials in the CTTC meta-analysis.[3] As a result of our study design, this analysis included 13 of 26 trials (87 500 of 170 000 patients) analysed in the CTTC meta-analysis[3] and 6 additional RCTs not included in the CTTC report.

A major focus of this analysis was the assessment of cardiovascular outcomes associated with statins and non-statin medications. Risk reduction for MVE was significant with all types of intervention assessed, but was relatively more pronounced for statin vs. no statin when compared with either statin intensification or addition of a non-statin agent. The CTTC meta-analysis also showed greater reduction of the (unadjusted) risk of MVE in statin vs. control trials compared with more-statin vs. less-statin trials (RR 0.73 vs. 0.87).[3] Interpretation of our findings requires consideration of differences in study design and patient populations across trials that cannot be fully addressed in any trial-level meta-analysis. The findings of higher baseline LDL-C in trials comparing statin vs. no statin, as well more adverse cardiovascular risk profile (e.g. two-fold higher proportion of diabetic patients) and considerably shorter follow-up duration in trials of non-statin agents, are notable in this respect. Importantly, we

found no variation in clinical benefit afforded by statins (in aggregate) vs. non-statin agents as active, 'more-intensive' treatment. Thereby, against a background of established evidence of cardiovascular benefit conferred by statins, the findings of this study provide quantitative evidence of incremental clinical benefit with non-statin agents (PCSK9 inhibitors and ezetimibe). Collectively, our findings substantiate current statements recommending statins (up-titrated to the highest tolerable doses) as first-line treatment for LDL-C lowering in patients at very high risk,[5,6] and they support the use of PCSK9 inhibitors and ezetimibe as valuable add-on therapies in statin-treated patients requiring additional LDL-C lowering.

Meta-regression analysis showed 19% RRR of MVE per 1.0 mmol/L lowering of LDL-C across a broad range of achieved levels (see Supplementary material online, *Figure S16*), extending to levels lower than the currently recommended targets.[4–6] The magnitude of risk reduction with ezetimibe was consistent with the expected reduction based on the observed LDL-C lowering (i.e. within the CI of the regression line), whereas it was lower than expected for the given LDL-C decrease for the two largest PCSK9 inhibitor trials.[9,37] This finding requires cautious interpretation. First, the use of primarily high-intensity statin as background therapy in FOURIER[9] and SPIRE-2[37] (i.e. control treatment similar to the active treatment in earlier statin trials) may have resulted in relatively smaller potential for incremental clinical benefit in response to marked additional LDL-C reduction. Second, it has been postulated that a larger treatment effect might be expected if the follow-up duration of PCSK9 inhibitor trials had been longer.[9] This notion is substantiated in part by our sensitivity analyses showing consistent benefit with PCSK9 inhibitors and statins when adjusting for differing follow-up duration; however, in the absence of longer term outcomes data with PCSK9 inhibitors, these findings remain hypothesis generating. This analysis overall supports the concept that lower LDL-C is better with respect to clinical prognosis but cannot exclude the possibility that the proportional clinical benefit for a given degree of LDL-C reduction may be attenuated at relatively low baseline and extremely low achieved levels. Along these lines, Ference *et al.*[38] recently showed a log-linear association between LDL-C lowering and cardiovascular risk.

In patients with ASCVD and inadequately controlled hypercholesterolaemia despite evidence-based statin therapy, add-on treatment with non-statin agents is currently recommended in appropriate patients based on the anticipated incremental LDL-C reduction as well associated reduction in cardiovascular risk.[4,5] Ezetimibe is associated with comparable risk reduction for MVE per unit of LDL lowering (*Figure 4*) but more potently reduces LDL-C levels (20–24%[5,35]) than up-titration of a potent satin from moderate dose to high dose (around 6–10% on average[5]). Along these lines, PCSK9 inhibitors (rather than ezetimibe) might be a reasonable second-line option in patients with markedly elevated LDL-C levels, despite high-intensity (or maximally tolerated) statin treatment. In this context, the associated risk reduction with PCSK9 inhibitors would be greater in absolute terms (albeit proportionally smaller per unit of LDL-C lowering) than that conferred by ezetimibe, given the considerably larger LDL-C reduction achieved by means of PCSK9 inhibition (50–60%).

In this data set, 100 patients would need to be treated with more-intensive LDL-C lowering over a period of 1 year to prevent one MVE. It should be noted that this calculation depends largely on the absolute risk of the reference population. Although our approach of using event rates of the largest—and one of the most contemporary—of included studies[9] for baseline risk estimates is consistent with previous reports,[15] inherent limitations of such assumptions (including marked heterogeneity in absolute risk across trials) need to be considered.

The survival benefit associated with more-intensive LDL-C lowering was overall significant but confined to trials comparing statin vs. no statin. This observation is along the lines of the CTTC meta-analysis[3] showing an effect of additional LDL-C lowering on coronary heart disease mortality only in trials of statin vs. control. This finding might relate to evidence-based therapies that reduce cardiovascular mortality in more recent ('more-statin vs. less-statin', PCKS9 inhibitior, or ezetimibe) trials compared with earlier trials that compared statin vs. no statin (see Supplementary material online, *Figure S17*).

This study has several limitations. As in all trial-level meta-analyses, lack of individual patient data precluded analyses in pre-specified patient subgroups or full evaluation to identify patient characteristics associated with maximal clinical benefit. Meta-regression techniques on a trial level require cautious interpretation and are presented as hypothesis generating. There is a risk of confounding factors, ecological bias, and the multiple subgroup analyses increase the probability of type I error.[39] Although random-effects pooling reduces heterogeneity, the heterogeneity observed among studies with different baseline cardiovascular risk and background therapy is substantial and acknowledged as a notable limitation. The composite primary endpoint was not identical across trials; however, our definition of MVE closely resembles the respective endpoint selection in previous meta-analyses.[7] Only four trials of non-statin agents were included; these studies, however, contributed 40% of patients one-third of primary-outcome events to the meta-analysis. One of the included PCSK9 inhibitor trials was terminated early due to antidrug antibodies and attenuation of LDL lowering over time[37]; development of bococizumab has therefore been discontinued. Although our sensitivity analyses sought to address the shorter follow-up of current trials with PCSK9 inhibitors, studies with longer follow-up are warranted to definitively evaluate long-term clinical efficacy of these medications. In view of the high cost of monoclonal antibody treatments, cost-effectiveness aspects for PCSK9 inhibitors not addressed in the present analysis will be essential for future recommendations regarding their clinical use.[40,41] Assessment of safety of LDL-C-lowering interventions was not the focus of this analysis but has been addressed in previous meta-analyses of statins[3] and RCTs of non-statin agents. Finally, patient enrolment and follow-up in the included trials extended from 1988 to 2017, a time frame during which medical treatment, non-medical therapies (e.g. revascularization), and cardiovascular event rates have changed in patients with established ASCVD.

Supplementary material

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

Conflict of interest: LR has received research contracts to the institution from Abbott, Sanofi and Regeneron and speaker fees by Amgen and Biotronik. FM received honoraria from Amgen, AstraZeneca, BMS, Eli Lilly, MSD, Sanofi, and Pfizer. SW has received research contracts to the institution from Abbott, Astra Zeneca,

Boston Scientific, Biosensors, Biotronik, Cordis, Eli Lilly, Medtronic, and St Jude. All other authors have no conflicts of interest to report.

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Corrigendum

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The authors of the above paper wish to inform readers that sacubitril was misspelled as sacubril as originally published. The paper has now been corrected online.