

Trial-level surrogacy of non-high-density and low-density lipoprotein cholesterol reduction on the clinical efficacy of statins

Léa Liaigre ¹, Alicia Guigui^{1,2}, Marc Manceau¹, Jean-Luc Cracowski², Charles Khouri ^{1,2}, and Matthieu Roustit ^{1,2,*}

¹Univ. Grenoble Alpes, Inserm CIC1406, CHU de Grenoble, Grenoble, France; and ²Univ. Grenoble Alpes, Inserm U1300, HP2, Grenoble, France

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LDL cholesterol (LDL - c) and non-HDL cholesterol (non-HDL-c) are prognostic factors of cardiovascular risk. However, their validity as trial-level surrogates for cardiovascular outcomes is debated. This study aimed to determine whether LDL - c and non-HDL-c are reliable surrogates for cardiovascular events in statin trials, and to explore discrepancies in previous studies. We conducted an umbrella review of meta-analyses of randomized controlled trials (RCTs) assessing statin efficacy versus placebo or usual care on all-cause mortality and cardiovascular events. We search studies published between 1987 and August 2023 from PubMed, Embase, and the Cochrane Library. Baseline lipid levels, absolute risk differences (ARDs), and hazard ratios or risk ratios (RRs) for major cardiovascular events and all-cause or cardiovascular mortality were analysed. Weighted linear regressions between log RR or ARD, and absolute difference in non-HDL-c or LDL - c were performed. The coefficients of determination (R^2_{trial}) were calculated, with their 95% CI computed through bootstrapping. The surrogate threshold effect (STE) was also estimated. Twenty RCTs and 194 686 participants were included, with a median follow-up of 4.85 years. Statin treatment showed significant efficacy in improving all clinical outcomes. However, the association between treatment effects on LDL - c or non-HDL-c reduction and clinical outcomes was weak. The R^2_{trial} were ranging from 0 to 0.1 for LDL - c, and from 0 to 0.04 for non-HDL-c. The STE for major adverse cardiovascular event was 0.76 (0.36–1.69) mmol/L for LDL - c, and 0.87 (0.49–2.19) mmol/L for non-HDL-c. Neither LDL - c nor non-HDL-c demonstrated trial-level surrogacy for predicting treatment effects on mortality and cardiovascular events in statin trials. Although they are relevant biomarkers for the follow-up of patients treated with statins, their reduction does not reliably predict a similar reduction in cardiovascular risk. As such, they should not be used as pivotal evidence in drug trials.

Keywords

Surrogate • Cardiovascular disease • Statin • LDL - cholesterol • Non-HDL cholesterol

Introduction

LDL cholesterol (LDL - c) plasma level has long been used to guide statin treatment in the prevention of cardiovascular events. Indeed, most international guidelines (including those from the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the National Lipid Association) recommend using LDL - c as a primary target for reducing the risk of cardiovascular diseases.^{1,2} Moreover, LDL - c is considered by the FDA as a valid surrogate endpoint in patients with hypercholesterolaemia to assess lipid-lowering drugs,³ and is commonly cited as an example of surrogacy.⁴

Surrogacy refers to the validation of a substitution criterion that can replace a clinical endpoint for estimating the efficacy of a treatment.

To be considered valid, a surrogate must fulfil two main conditions: (1) the potential surrogate has to be associated with the endpoint, i.e. it is a prognostic factor for the clinical endpoint (cardiovascular events in the present situation); and (2) the effect of the treatment on the surrogate can be used to reliably predict the treatment effect on the clinical outcome.^{5,6} Regarding LDL - c and cardiovascular risk, the first condition, called 'individual-level surrogacy', has been shown to be fulfilled in previous, large studies.^{7–9} The second one, sometimes referred to as 'trial-level surrogacy',⁵ consists in estimating the correlation between the treatment effect on the surrogate outcome and the treatment effect on the clinical outcome, based on meta-analyses of randomized controlled trials (RCTs).

There are discrepancies in the literature regarding the latter, which challenges whether or not LDL - c is a valid surrogate for clinical

* Corresponding author. Tel: +33 4 76 76 92 60, Email: MRoustit@chu-grenoble.fr

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outcomes. Indeed, a recent systematic review and meta-analysis suggested that there is no significant trial-level association between LDL-c reduction and the absolute and relative reductions in myocardial infarction (MI), stroke, or all-cause mortality.¹⁰ Even more recently, an umbrella review of meta-analyses assessing trial-level surrogacy of LDL-c found only one meta-analysis, among 11, reporting high-level evidence of LDL-c as a valid surrogate for major vascular events, major coronary events, and vascular mortality.¹¹

Other lipids could be evaluated as surrogate candidates. In 2021, the National Institute for Health and Care Excellence (NICE) updated its guideline on cardiovascular risk management and now recommends using non-HDL cholesterol (non-HDL-c) rather than LDL-c.¹² A meta-analysis using individual patient data showed that both LDL-c and non-HDL-c levels were associated with the risk of future major cardiovascular events, the strength of the association being greater for non-HDL-c.¹³ More recently, a meta-analysis compared the efficacy of statins on lipids in patients with diabetes and concluded that non-HDL-c could be a better target than LDL-c to predict cardiovascular disease.¹⁴ These findings thus suggest that non-HDL-c could be a good surrogate for cardiovascular events in trials.

The objective of this work is to confirm whether LDL-c is a valid trial-level surrogate for cardiovascular events in patients treated with statins, and to try to understand the discrepancies between previous studies. We further aimed at exploring the potential surrogacy of non-HDL-c and to compare it with that of LDL-c.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline to report study results.¹⁵ The protocol was prospectively published online (available at <https://osf.io/ufmc3>).

Literature searches and study selection

We conducted an umbrella review of meta-analyses of trials assessing the efficacy of statins vs. placebo or usual care on all-cause mortality and cardiovascular events. We searched MEDLINE, PubMed, and Embase, using the following combination of free words and MeSH terms relating to statins, mortality, and cardiovascular diseases endpoints: ((statins, hmg coa[MeSH Terms] AND (mortality[MeSH Terms])) OR (cardiovascular events[Text Word]) AND (clinicaltrial[Filter] OR randomized controlled trial [Filter])). The screening period was between 1987 (the year the first statin was approved by the FDA) and August 2023.

We screened all meta-analyses of RCTs assessing the efficacy of statins vs. placebo or usual care on all-cause or cardiovascular mortality and cardiovascular events. For each meta-analysis, we extracted the number of included studies, inclusion and exclusion criteria, outcomes, methods for statistical analyses, and results. We then screened all the trials included in these meta-analyses, and the following variables were extracted: title; journal name; publication date; study design; characteristics of the population, including statin indication (primary or secondary prevention); and type of statin, follow-up duration, dosage, type of comparator, and outcomes of interest (see below). Trials with at least 2 years of follow-up and exhaustive lipid data (total cholesterol, LDL-c, and HDL-c) were finally included.

Outcomes

For each trial, we extracted absolute rates and hazard or risk ratios (RRs), for major adverse cardiovascular events (MACEs, as defined in each study), all-cause mortality, cardiovascular mortality, MI, and stroke. Mean changes in LDL-c and non-HDL-c levels between groups from inclusion to the end of the study were also calculated to evaluate their potential surrogacy.

Assessment of the risk of bias and robustness of the results

Two authors (L.L. and A.G.) independently evaluated the methodological quality of included trials using the revised Cochrane 'Risk-of-bias' tool for randomized trials (RoB 2).¹⁶ Discrepancies were discussed with a third author (M.R.) until consensus. The quality of evidence for each outcome depending on the RoB was rated according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process.¹⁷

We reported the risk of bias as recommended for systematic reviews in the Cochrane Handbook for Systematic Reviews of Interventions and reported them in accordance with the PRISMA statement.

Statistical analysis

Non-HDL-c was calculated as total cholesterol minus HDL-c. When several LDL-c and non-HDL-c values were available throughout follow-up, they were weighted-averaged. For each included study, we calculated the absolute risk difference (ARD) and the log RR between statin treatment and control, as well as their 95% CI, for the four clinical outcomes. We also calculated the mean change in LDL-c and non-HDL-c levels between groups. We further calculated relative changes in LDL-c and non-HDL-c from baseline in the treated group to conduct sensitivity analyses (not planned in the protocol).

The I^2 statistic was used to assess heterogeneity between trials. Random-effects models were used since heterogeneity was considered significant (i.e. $I^2 > 50\%$) in most analyses. The DerSimonian and Laird random-effects model was used.¹⁸

Linear regressions, weighted on the sample size, were used to assess the associations between treatment effects on lipids and on clinical outcomes.¹⁹ The strength of association was expressed by its coefficient of determination (R^2_{trial}), with its 95% CI computed through bootstrapping ($n = 1000$). We also calculated the surrogate threshold effect (STE) from the 95% prediction interval of the weighted linear regressions, with its 95% CI computed through bootstrapping ($n = 1000$). The STE estimates the threshold level of a surrogate needed in a future clinical trial (of median sample size in the present case) to predict a benefit on the target outcome.²⁰ In other words, the STE represents the minimum treatment effect on the surrogate endpoint (e.g. reduction in LDL-c or non-HDL-c levels) required to predict a significant treatment effect on the clinical outcome (e.g. reduction in cardiovascular events).

Sensitivity analyses, initially unplanned in the protocol, were carried out using non-weighted linear regressions. Finally, we conducted *post hoc* analyses to assess how R^2_{trial} evolved over time, conducting an initial analysis with the first eight trials, and then updating the analysis each time new trial results were published.

Statistical analyses were performed using RStudio (version 4.0.2) and the meta and metafor packages. The dataset and codes in Rmarkdown format are available online (<https://osf.io/ufmc3>).

Patient and public involvement

Patients and the public were not involved in any way on this study.

Results

We identified 22 meta-analyses from the umbrella review, with a total of 89 RCTs. Among them, 20 RCTs were included in the final analysis (Figure 1). A total number of 194 686 participants were included (median per trial was 4614), and median follow-up time was 4.85 years. The median between-group difference in LDL-c at the end of follow-up was 0.99 mmol/L, and was 1.21 mmol/L for non-HDL-c. The most commonly studied statins were atorvastatin ($n = 7$), pravastatin ($n = 6$), and simvastatin ($n = 3$). Placebo was the comparator for most trials ($n = 15$). Statins were used for primary prevention ($n = 8$), secondary prevention ($n = 8$), or both ($n = 4$).

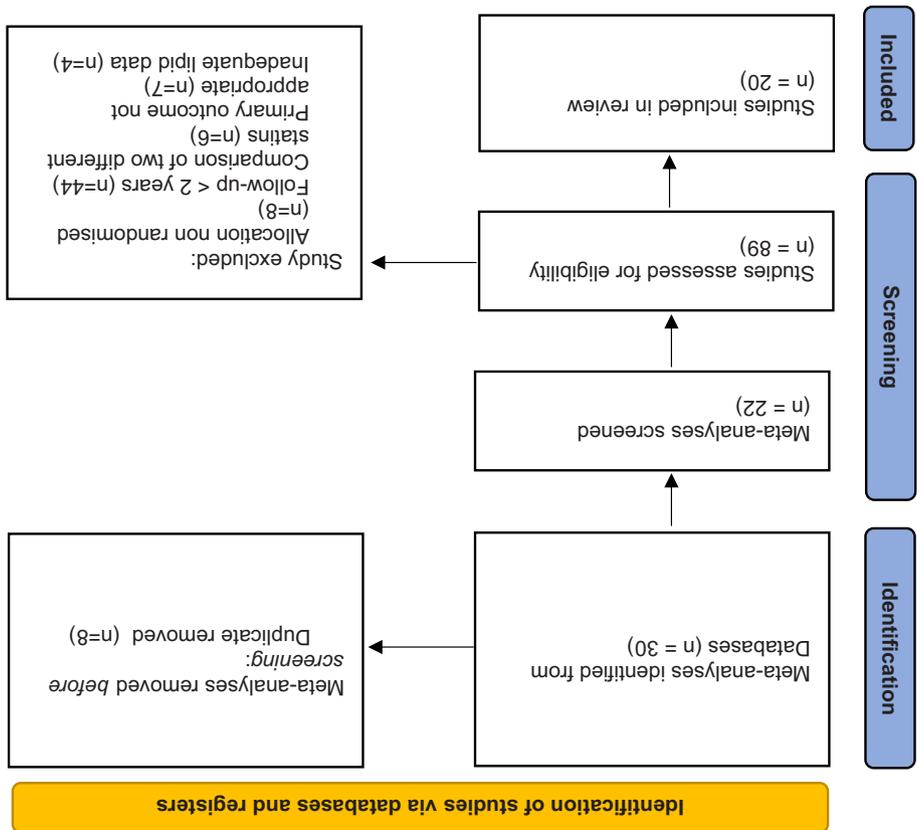


Figure 1 | Umbrella review flow diagram following PRISMA guidelines.

Table 1 | Summary results of weighted linear regressions between treatment effect of statins on the risk of clinical outcomes [expressed as log risk ratio (RR)] and on lipid levels

Outcome	LDL - c			Non-HDL-c		
	Slope (95% CI)	R ² trial (95% CI)	STE (mmol/L) (95% CI)	Slope (95% CI)	R ² trial (95% CI)	STE (mmol/L) (95% CI)
MACE	-0.12 (-0.31, 0.07)	0.1 (0.0, 0.5)	0.76 (0.36, 1.69)	-0.04 (-0.21, 0.12)	0.02 (0.0, 0.36)	0.87 (0.49, 2.19)
All-cause mortality	-0.1 (-0.28, 0.07)	0.08 (0.0, 0.56)	ND ^a	-0.06 (-0.22, 0.1)	0.04 (0.0, 0.45)	ND ^a
Cardiovascular mortality	-0.02 (-0.29, 0.2)	0 (0.0, 0.22)	ND ^a	-0.05 (-0.25, 0.15)	0.02 (0.0, 0.23)	ND ^a
MI	-0.09 (-0.38, 0.2)	0.03 (0.0, 0.49)	1.49 (0.4, 1.9)	-0.03 (-0.28, 0.22)	0.0 (0.0, 0.44)	1.4 (0.56, 2.25)
Stroke	-0.12 (-0.44, 0.19)	0.04 (0.0, 0.39)	ND ^a	-0.01 (-0.29, 0.27)	0.0 (0.0, 0.34)	ND ^a

Clinical outcomes are major adverse cardiovascular events, all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke. Treatment effect on lipids is expressed as the mean difference in LDL cholesterol (LDL-c) or in non-HDL cholesterol (non-HDL-c) level. The surrogate threshold effect (STE) is the minimal change in non-HDL-c or LDL-c needed to observe a benefit on the clinical outcome.

MACE, major adverse cardiovascular event; MI, myocardial infarction; CI, confidence interval.

^a ND: not defined, i.e. STE was not reached when using the regression on the whole dataset.

The main characteristics of the trials included in the final analysis are reported in Supplementary material online, Table S1. Event rates in the treated and control groups, for each trial and each studied outcome, are reported in Supplementary material online, Table S2. Risk-of-bias assessment identified five trials with some concerns, all regarding a possible deviation from the intended intervention (see Supplementary material online, Figure S1).

We found a significant efficacy of statins on clinical outcomes with an RR of 0.75 (95% CI 0.70, 0.80), 0.88 (95% CI 0.83, 0.93), 0.81 or when non-weighted linear regressions were conducted as Supplementary material online, Table S3 and Figures S3 and S4), were obtained when considering absolute risk reduction (see Table 1 and Figure 2). Similar results of clinical outcomes was weak (Table 1 and Figure 2). The association between treatment effects on the reduction of non-HDL-c or LDL-c and on the relative reductions of clinical outcomes was weak (Table 1 and Figure 2). Similar results were obtained when considering absolute risk reduction (see Supplementary material online, Table S3 and Figures S3 and S4), or when non-weighted linear regressions were conducted as

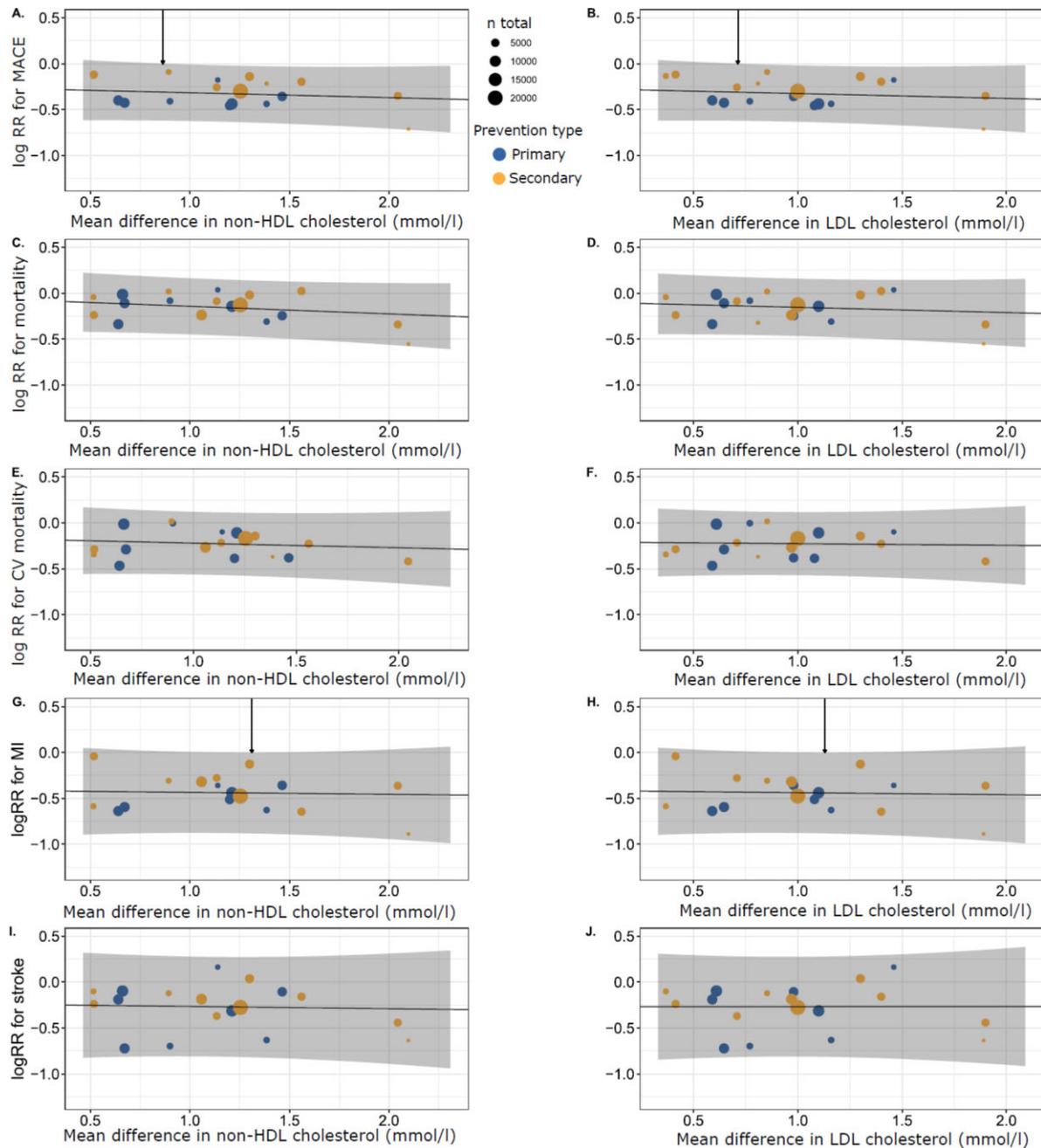


Figure 2 Weighted regressions between the log risk ratio (RR) for major adverse cardiovascular events (MACEs), all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), and stroke, and the between-group difference in non-HDL cholesterol (non-HDL-c) or LDL cholesterol (LDL-c) level (in mmol/L). Shaded areas represent the 95% prediction intervals for the log RR. Vertical arrows represent the surrogate threshold effect (STE) (when computable), i.e. the minimal change in non-HDL-c or LDL-c needed to observe a benefit on the clinical outcome.

sensitivity analyses (see [Supplementary material online, Table S4](#)). *Post hoc* sensitivity analyses using relative changes in lipids also provided very weak associations with relative (see [Supplementary material online, Table S5](#)) or absolute (see [Supplementary material online, Table S6](#)) treatment effects on clinical outcomes.

The STE was computable for MACE and MI only and was ≥ 0.87 mmol/L for non-HDL-c and ≥ 0.76 mmol/L for LDL-c ([Table 1](#)). When treatment effect was expressed as absolute risk reduction, STE was also computable for MACE and MI only for

non-HDL-c, and was ≥ 1.49 mmol/L, and was computable for MACE, MI, and stroke for LDL-c, and was ≥ 1.32 mmol/L (see [Supplementary material online, Table S3](#)).

Sensitivity analyses separating primary prevention and secondary prevention trials also show weak associations for both types of statin use, whether considering relative (see [Supplementary material online, Figure S5](#) and [Tables S7](#) and [Table S8](#)) or absolute (see [Supplementary material online, Figure S6](#) and [Tables S9](#) and [S10](#)) treatment effects on clinical outcomes.

Finally, the cumulative estimation of R^2_{trial} over time shows variations as new studies are added. However, the 95% CIs remain extremely wide (see [Supplementary material online, Figure S7](#)).

Discussion

Our results suggest that the treatment effect of statins on non-HDL-c or on LDL-c similarly correlates with their treatment effect on all-cause mortality and major cardiovascular events, but these correlations are too weak to fulfil one of the conditions required for a surrogate to be considered as valid. Indeed, it is commonly admitted that trial-level surrogacy is reached when the lower limit of the 95% CI of R^2_{trial} is ≥ 0.65 .^{21–23} In our study, all lower limits of the 95% CI of R^2_{trial} were far below this threshold (close to zero), suggesting the absence of trial-level surrogacy. Sensitivity analyses suggest that expressing treatment effect on clinical outcomes and on lipid levels as relative or absolute changes do not change this conclusion.

Previous meta-analyses of clinical trials aimed at assessing the relationship between the treatment effect of statins on lipid-level reduction, and on cardiovascular outcomes, with discrepant conclusions. These discrepancies are unlikely to be related to the studies included, since the degree of overlap in the RCT included in these different meta-analyses is important. In addition, cumulative evaluation of R^2_{trial} does not suggest any trend towards a greater association over time. Differences in conclusions are more likely to be due to the methods used to assess the relationship between intermediate and clinical endpoints, and the results on which conclusions are made. Indeed, significant associations are often reported, but they are not sufficient to fulfil the 'trial-level surrogacy' condition.

Byrne *et al.*¹⁰ have shown weak correlations between the mean reduction in LDL-c and the absolute or relative reduction of MI, and an R^2 of 0 for all-cause mortality and stroke,¹⁰ using random-effects metaregression. The authors concluded that the benefit of statins may not be strongly mediated through the degree of LDL-c reduction. On the contrary, a meta-analysis conducted by Silverman *et al.*²⁴ on a very similar set of trials concluded that lower achieved LDL-c levels were associated with lower rates of major coronary events, which is supported by the significant reduction of major vascular events for each 1 mmol/L reduction in LDL-c, with an RR of 0.77 (95% CI 0.71, 0.84; $P < 0.001$). The value of R^2 was as high as 0.98, i.e. very different from those of Byrne *et al.*,¹⁰ but again no 95% CI was provided. Marston *et al.*²⁵ have published one of the only meta-analyses studying the association between the treatment effect of different lipid-lowering drugs on non-HDL-c, and their effect on major events. Their results are very consistent with those of the previous study, with an RR of 0.80 (95% CI 0.77, 0.82) per 1 mmol/L reduction in non-HDL-c. In both cases, conclusions are drawn from the slope of the regression line, which is significantly different from zero. Nonetheless, a significant slope does not mean that the lower limit of the 95% CI of R^2_{trial} will fulfil the criteria of a valid surrogate, as shown by another, similar meta-analysis, which showed significant log RR per mg/dL change in LDL-c, with an R^2 of 0.4 (without its 95% CI).²⁶ Finally, Delahoy *et al.*, through a similar approach, found R^2 ranging between 0.47 and 0.87, depending of the outcome [26]. In other words, while all studies explored associations on similar datasets and methods, the R^2 ranges between 0 and 0.98. A source of heterogeneity might be the time point chosen for the surrogate measurement, and the method used when several times points were available (e.g. average of the different value, or latest value only). Differences in follow-up duration may also induce heterogeneity, some meta-analyses including trials with shorter follow-up durations (e.g. 1 year or even 6 months). These differences may affect the number of participants at risk. In addition, some meta-analyses have used RR while others have used log RR to estimate the treatment effect on events.

Besides these differences, none of these meta-analyses has provided confidence intervals for R^2 , which is commonly used to reach a conclusion on the validity of the surrogate.^{5,23} In the present study, we observe large confidence intervals around R^2_{trial} using bootstrapping, which could be explained by the small number of available studies, and possibly the heterogeneity between these studies.

A more intuitive appreciation of the validity of a surrogate is to use the STE approach. To our knowledge, only one study has used this method to assess the surrogacy of LDL-c in patients treated with statins.²⁷ This study used both weighted and non-weighted models, and the STE for cardiovascular mortality is >1.4 mmol/L, i.e. very close to what we found in the present study for MI when using unweighted regression. The use of weighted models decreased the STE, but it also highlights its variability. The wide 95% CI of STE, calculated using bootstrapping, reflects the lack of precision of our prediction model.

A key message of this work is to distinguish between the practical implications of individual surrogacy and trial-level surrogacy. Overall, evidence demonstrates the individual-level surrogacy of LDL-c and non-HDL-c, i.e. their prognostic value on the occurrence of cardiovascular events.^{7–9} As such, they are relevant biomarkers for the follow-up of patients treated with statins. This is why the recent NICE guideline on cardiovascular risk management now recommends a 40% reduction in non-HDL-c after 3 months of high-intensity statin treatment.¹² On the other hand, the present work shows that trial-level surrogacy is not met. Although previous studies have shown a significant association between the reduction of LDL-c or non-HDL-c with statins and their clinical benefit, this association is too weak for the mean reduction in lipid levels to reliably predict a similar reduction in cardiovascular events and all-cause mortality. This finding does not challenge clinical guidelines, but has important consequences for policymaking. Indeed, it strongly suggests that future trials should not rely on the average reduction in lipid levels to predict statin efficacy on clinical outcomes. Thus, neither LDL-c nor non-HDL-c is sufficient to be used as pivotal evidence for the authorization of medicines.

Our study presents some limitations. First, we conducted an umbrella review, with the risk of replicating or amplifying study selection bias if the original systematic reviews were not performed properly. However, considering the number and the overall quality of the systematic reviews, we consider that this risk is low. Another limitation is that we had to exclude studies for which we could not calculate non-HDL-c, because of missing data. Therefore, our results are not exhaustive for non-HDL-c. We added a *post hoc* analysis to assess the association between treatment effect on clinical outcomes and on relative variations in lipid levels, which is in line with the above-mentioned NICE recommendations. Yet, we only had access to aggregated data, and therefore we could not calculate the mean of individual relative changes in lipids, which is not equal to the percentage change of the means. We thus used the mean per cent change from baseline in the treated groups, which is of course a rough approximation of treatment effect that does not take into account variations in the control groups.

Conclusions

Our findings do not support stronger trial-level surrogacy between the effects of statins on all-cause mortality or MACEs and reductions in non-HDL-c compared with LDL-c. Neither non-HDL-c nor LDL-c should be relied upon as surrogate markers for predicting treatment effects on clinical endpoints in pivotal clinical trials. While our results may appear to contradict those of previous meta-analyses, this discrepancy likely reflects differences in methodologies and interpretations of the conditions necessary to establish trial-level surrogacy.

Supplementary material

Supplementary material is available at [European Heart Journal—Cardiovascular Pharmacotherapy](#) online.

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Conflict of interest: none declared.

Data availability

The full dataset is available at <https://osf.io/ufmc3>.

Author contributions

L.L. collected and analysed the data and wrote the manuscript; A.G. collected and analysed the data and critically reviewed and approved the manuscript; M.M. analysed the data critically reviewed and approved the manuscript; J.-L.C. critically reviewed and approved the manuscript; C.K. conceived the study, analysed the data, and critically reviewed and approved the manuscript; and M.R. conceived the study and wrote the manuscript.

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