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Very low levels of atherogenic lipoproteins and risk of cardiovascular events; a meta-analysis of statin trials

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Statistical analysis: Boekholdt, Arsenault, Kastelein.

Administrative, technical, or material support: DeMicco, Kastelein.

Study supervision: Boekholdt, Kastelein.

Conflicts of interest

Drs Boekholdt, Hovingh and Arsenault report receipt of consultancy fees from Pfizer. Dr Hovingh received lecture honoraria from Pfizer, Genzyme, Merck Sharpe & Dohme, Amgen and Roche. Dr Mora reports receipt of research grant support through her institution from AstraZeneca, Atherotech Diagnostics and the National Heart Lung and Blood Institute (R01HL117861); consultancy fees from Pfizer, Quest Diagnostics, Cerenis and Genzyme; lecture honoraria from AstraZeneca and Abbott; and travel accommodations/meeting expenses from Pfizer. Dr Amarenco reports receipt of research grant support and lecture fees from Pfizer, Sanofi, Merck, AstraZeneca, Boehringer-Ingelheim, and consultancy fees from Pfizer, BMS, Merck, Boehringer-Ingelheim, AstraZeneca, Bayer, Daiichi-Sankyo, Lundbeck, Edwards, Boston Scientific, Kowa and research grants from the French government. Dr LaRosa reports receipt of consultancy fees from Pfizer and Amgen, and travel expenses from Pfizer. Dr Pedersen reports receipt of research grant support and lecture fees from Pfizer and Merck Sharp & Dohme and lecture fees from AstraZeneca and Roche. Dr Waters has received consultation fees from Anthera Pharmaceuticals, Genentech, Pfizer, Roche and Servier Laboratories; has received lecture honoraria from Pfizer and Zydus Medica; and has participated in committees of clinical trials sponsored by Aegerion Pharmaceuticals, Biosante, Merck Schering-Plough, Pfizer and Sanofi Aventis. Dr DeMicco reports being a full-time employee of Pfizer; and having stock/stock options with Pfizer. Dr Keech has received speaker and/or advisor honoraria or research support from Abbott, Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche Diagnostics, Solvay. Dr Hitman has received consultancy fees and lecture honoraria from GlaxoSmithKline, Eli Lily, Pfizer, NovoNordisk, Astra Zeneca, Merck Sharp & Dohme, Takeda and OSI Pharmaceuticals and grant income from Park Davies and Eli Lily. Dr Betteridge reports receipt of honoraria for lectures and advisory boards for Aegerion, Amgen, AstraZeneca, Kowa, Merck Sharpe & Dohme, Roche, and Takeda. Dr Clearfield reports provision of consulting services on advisory committees to Merck Sharp & Dohme and AstraZeneca. Dr Colhoun reports receipt of research grant support through the EU Innovative Medicines Initiative from Roche, Pfizer, Eli Lilly, Boehringer-Ingelheim, sanofi-aventis, and AstraZeneca; consultancy fees from Pfizer, sanofi-aventis, Novartis, and Eli Lilly; stocks from Roche; and lecture honoraria and travel expenses from Pfizer. Dr Gotto is a consultant for AstraZeneca, Janssen, KOWA, Merck, and Roche; a member of the Board of Directors for Aegerion Pharmaceuticals and Arisaph Pharmaceuticals; and a member of advisory boards for DuPont, Haptocure, VascuVis, and VateraCapital. Dr Ridker reports receipt of research grant funding from Novartis and AstraZeneca; serving as a consultant to ISIS, Vascular Biogenics, Merck Sharpe & Dohme, Abbott, and Boehringer-Ingelheim; board membership with Merck Sharp & Dohme; receipt of a grant or pending grant to his institution from Amgen; and being listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. Dr Kastelein reports receipt of lecture honoraria from Merck Sharpe & Dohme, Roche, Novartis, ISIS, Genzyme, Pfizer, Kowa, and AstraZeneca. Drs Simes, Colquhoun and Downs reported no conflict of interest.

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Abstract

Objectives—To evaluate (1) the inter-individual variability of reductions in low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) or apolipoprotein B (apoB) levels achieved with statin therapy, (2) the proportion of patients not reaching guideline-recommended lipid levels on high-dose statin therapy, and (3) the association between very low levels of atherogenic lipoproteins achieved with statin therapy and CVD risk.

Background—Levels of atherogenic lipoproteins achieved with statin therapy are highly variable, but the consequence of this variability for cardiovascular disease (CVD) risk is not well documented.

Methods—Meta-analysis of individual patient data from 8 randomized controlled statin trials in which conventional lipids and apolipoproteins were determined in all study participants at baseline and at 1-year follow-up.

Results—Among 38,153 patients allocated to statin therapy, a total of 6,286 major cardiovascular events occurred in 5,387 study participants during follow-up. There was large inter-individual variability in the reductions of LDL-C, non-HDL-C and apoB achieved with a fixed statin dose. Over 40% of trial participants assigned to high-dose statin therapy did not reach an LDL-C target below 70 mg/dL. Compared to patients who achieved an LDL-C > 175 mg/dL, those who reached an LDL-C 75-100 mg/dL, 50-75 mg/dL and < 50 mg/dL had adjusted hazard ratios for major cardiovascular events of 0.56 (95%CI 0.46-0.67), 0.51 (95%CI 0.42-0,62) and

0.44 (95%CI 0.35-0.55), respectively. Similar associations were observed for non-HDL-C and apoB.

Conclusions—The reduction of LDL-C, non-HDL-C and apoB levels achieved with statin therapy displays large inter-individual variation. Among trial participants treated with high-dose statin therapy, over 40% do not reach an LDL-C target <70 mg/dL. Patients who achieve very low LDL-C levels have a lower risk of major cardiovascular events than those achieving moderately low levels.

Keywords

LDL-cholesterol; Non-HDL-cholesterol; Apolipoprotein B; Meta-analysis

Introduction

There is a wealth of evidence that high-dose statin therapy reduces both levels of atherogenic lipoproteins and cardiovascular disease (CVD) risk beyond that achieved with usual-dose statin therapy.[1] However, the interpretation of evidence on the efficacy of statin therapy is based on average LDL-C reductions and average reductions of CVD risk within randomized trials. There is large inter-individual variation in the extent of reduction of atherogenic lipoprotein levels achieved with statin therapy. Post-hoc analyses of randomized trials suggest that the benefits of statin therapy depend on the extent of achieved LDL-C reduction.[2,3] In addition, patients achieving very low LDL-C levels have been shown to be at very low CVD risk, although the number of patients achieving such very low levels in any given single trial is usually small.[4,5,6]

The guideline-recommended marker of atherogenic lipoproteins is low-density lipoprotein cholesterol (LDL-C), but we have recently shown that among patients treated with statin therapy non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) are at least as strongly associated with CVD risk.[7] Current guidelines consider the target LDL-C level to be in the range of 70 to 130 mg/dL, but observational evidence suggests that this range might be too conservative. Interestingly, novel lipid-lowering therapies including mipomersen and inhibitors of proprotein convertase subtilisin/kexin 9 (PCSK9) may allow the majority of patients to reach LDL-C levels below 70 mg/dL.[8,9,10] However, it is unclear whether pharmacological interventions resulting in atherogenic lipoprotein levels in this anticipated treatment range are beneficial in terms of CVD risk.

It was therefore our objective to assess (1) the variability of LDL-C, non-HDL-C or apoB reduction achieved with established statin therapy, (2) the proportion of patients not reaching guideline-recommended LDL-C, non-HDL-C or apoB levels despite being treated with high-dose statin therapy, and (3) the association between achieved very low LDL-C, non-HDL-C or apoB levels and risk of major cardiovascular events. We addressed these objectives by performing a meta-analysis of large randomized controlled statin trials in the setting of both primary and secondary prevention.

Methods

Study eligibility and data collection

The methods of this meta-analysis have been described previously.[7] The literature was searched to identify all randomized controlled trials that assigned study participants in at least 1 of the study groups to statin therapy, and that measured total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoproteins at baseline and during statin therapy in the entire study population. Trials with a mean follow-up for cardiovascular events shorter than 2 years and those including fewer than 1000 participants were excluded. The literature search was undertaken in PubMed using the following search terms: statin, hydroxymethylglutaryl coenzyme A reductase inhibitor, simvastatin, lovastatin, fluvastatin, pravastatin, atorvastatin, rosuvastatin, cholesterol, apolipoprotein, coronary heart disease, coronary artery disease and cardiovascular disease. The results were limited to randomized trials and English language. The first search was performed on January 4, 2009, and the updated search until December 31, 2011, was performed on January 20, 2012. Two authors (B.J.A. and S.M.B.) independently screened all abstracts for randomized controlled trials fulfilling the inclusion criteria. If an abstract described a subanalysis of a potentially relevant trial, the original publication was traced. Results were compared and inconsistencies were resolved by consensus.

Investigators were contacted and asked to provide individual patient data. The requested patient characteristics included sex, age, smoking status, body mass index, diabetes mellitus, systolic and diastolic blood pressure, fasting glucose, total cholesterol, LDL-C, HDL-C, triglycerides, and apolipoprotein A-I and B at baseline and at 1-year follow-up, study medication, and patient history of stable coronary heart disease (CHD), myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. The following outcomes (and time to event) were also collected: fatal and nonfatal myocardial infarction, fatal other CHD, hospitalization for unstable angina, fatal and nonfatal stroke, fatal and nonfatal hemorrhagic stroke, peripheral artery disease, and congestive heart failure. Data were harmonized into a pooled database and this database was independently validated against the original files. Quality of the included trials was assessed by the Delphi score.[11] This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a checklist was provided at the time of manuscript submission.[12]

Lipids, apolipoproteins, statins and outcome definition

Lipid and apolipoprotein levels at baseline and at 1-year follow-up were obtained from the participating trials. For on-statin measurements, the 1-year time point was chosen because this was the first uniform time point when apolipoproteins were measured in all participating trials. Cholesterol levels reported in mmol/L were converted to mg/dL by multiplying by 38.7, and triglycerides levels reported in mmol/L were converted to mg/dL by multiplying by 88.5. High-dose statin therapy was defined as either atorvastatin 80 mg or rosuvastatin 20 mg. Usual-dose statin therapy was defined as all other statin dosing regimens. The primary outcome of this meta-analysis was time to first major cardiovascular event, which was defined as fatal or nonfatal myocardial infarction, fatal other CHD, hospitalization for

unstable angina, and fatal or nonfatal stroke. Additional analyses were performed for the prediction of time to first major coronary events (fatal or nonfatal myocardial infarction, fatal other CHD, and hospitalization for unstable angina) and time to first major cerebrovascular event (fatal or nonfatal stroke).

Statistical analysis

Baseline characteristics, levels of lipids and apolipoproteins at baseline and at 1-year, as well as absolute changes and percentage changes between on-trial and baseline levels were calculated for each trial separately. The distributions of percentage LDL-C, non-HDL-C or apoB reduction were displayed in waterfall plots for several examples of statin trial arms with a fixed dose increase, as well as for an example of patients enrolled in a placebo arm to represent the natural variability of these parameters. In order to limit the effect of potential outliers, patients with levels beyond 5 standard deviations of the mean were excluded. The proportion of study participants not achieving an on-trial LDL-C level of 100 mg/dL and 70 mg/dL was calculated among those randomized to high-dose statin therapy in one of the included trials. Similar proportions were calculated for the non-HDL-C targets 130 mg/dL and 100 mg/dL, and for the apoB targets 100 mg/dL and 80 mg/dL. The association between on-statin achieved levels of LDL-C, non-HDL-C or apoB and risk of cardiovascular events was evaluated using Cox proportional hazards models. For these analyses, study participants allocated to placebo were excluded. Hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) for the risk of cardiovascular events were calculated by categories of achieved LDL-C, non-HDL-C or apoB level, using the highest category as reference. The cut-off values between LDL-C categories were chosen to be 25 mg/dL, with subsequent increments of 25 mg/dL. We also specifically tested whether the risk of major cardiovascular events was lower among patients achieving very low LDL-C levels (< 50 mg/dL) compared to those achieving moderately low levels (75-100 mg/dL). Equivalent analyses using LDL-C cut-offs 50, 70, 100, 130, 160 and 190 mg/dL were also performed, as well as using non-HDL-C cut-offs 30 mg/dl higher. Analyses were adjusted for sex, age, smoking (current vs not), diabetes mellitus, systolic blood pressure, HDL-C and trial. Analyses were not additionally adjusted for prevalent CHD since all trials enrolled either 0% or 100% patients with prevalent disease, so adjustment for trial implies adjustment for prevalent CHD. It should however be noted that prevalent CHD as an inclusion criterion was documented less rigorously in some trials than in other trials. Separate analyses were performed for the outcomes major cardiovascular events, major coronary events, major cerebrovascular events, and hemorrhagic stroke.

Statistical heterogeneity across trials was quantified using the Cochran Q statistic and I^2 statistic. The I^2 statistic is derived from the Q statistic ($[Q-df/Q]*100$) and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity.[13] The potential for publication bias was addressed by drawing funnel plots and visual assessment. Proportionality of hazards over time was graphically checked by plotting the cumulative hazards over time for all categories against each other. A two-tailed p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 20.0).

Results

The results of the literature search are shown in Supplementary Figure 1, and have been published previously.[7] Briefly, 8 trials fulfilled all inclusion criteria: the Scandinavian Simvastatin Survival Study (4S),[14] the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS),[15] the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial,[16] the Collaborative Atorvastatin Diabetes Study (CARDS),[17] the Treating to New Targets (TNT) trial,[18] the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial,[19] the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial,[20] and the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).[21] Individual patient data were obtained from all 8 trials, with the exception of hemorrhagic stroke which was not available for the 4S and AFCAPS-TexCAPS trials. Study characteristics of these 8 trials are shown in Supplementary Table 1. Trials were of high quality with a median Delphi score of 9 (range 6-9). Heterogeneity between trials with regard to the association with risk of major cardiovascular events was low for LDL-C (Q=6.94, P=0.4, I^2=0%), non-HDL-C (Q=6.05, P=0.53, I^2=0) and apoB (Q=9.55, P=0.2, I^2=26%), as reported previously.[7] Visual assessment of funnel plots did not suggest strong evidence for bias. The proportionality assumptions were satisfied.

Baseline characteristics and events

Baseline characteristics of the study participants are shown in Supplementary Table 2. Levels of lipids and apolipoproteins at baseline and at 1-year on-trial, as well as the absolute and percentage changes between baseline and on-trial levels are shown in Supplementary Table 3. A total of 38,153 study participants were randomized to a statin arm and had a complete set of lipid and apolipoprotein levels during statin treatment available. During 155,573 person-years follow-up, 158 (0.4%) study participants developed a fatal myocardial infarction and 1,678 (4.4%) developed a non-fatal myocardial infarction. Fatal other CHD occurred in 615 study participants (1.6%) and fatal or nonfatal stroke occurred in 1,029 study participants (2.7%). A total of 2,806 participants (7.4%) were hospitalized for unstable angina. A total of 5,387 study participants (14.1%) developed at least one major cardiovascular event. Of these, 4,577 experienced 1 event, 728 experienced 2 events, 75 experienced 3 events, and 7 experienced 4 events.

Inter-individual variation of LDL-C, non-HDL-C and apoB reduction

Waterfall plots of the distribution of percentage LDL-C reduction (1-year minus baseline divided by baseline levels) achieved in various trials are shown in Figure 1. Displayed are typical examples for the initiation of usual-dose statin therapy (patients assigned to pravastatin 40 mg in the LIPID trial, n=3,936, plot A), the initiation of high-dose statin therapy (patients assigned to rosuvastatin 20 mg in the JUPITER trial, n=7,783, plot B), a dose increase from usual-dose to high-dose statin (patients increased dose from atorvastatin 10 mg to 80 mg in the TNT trial, n=4,636, plot C), and patients not treated with statin therapy (patients enrolled in the placebo arm of the AFCAPS-TexCAPS trial, n=2,802, plot D). The corresponding examples for non-HDL-C reduction and apoB reduction are shown in Supplementary Figures 2 and 3. These waterfall plots display a large inter-individual

variation with regard to the reductions in LDL-C, non-HDL-C and apoB achieved with a fixed-dose statin regimen.

Figure 2 presents the distribution of achieved levels of LDL-C, non-HDL-C and apoB among patients assigned to high-dose statin therapy, i.e. either atorvastatin 80 mg in the TNT, IDEAL, or SPARCL trials or rosuvastatin 20 mg in the JUPITER trial. Among 18,677 patients assigned to high-dose statin therapy, mean achieved LDL-C level was 69.6 mg/dL (standard deviation 27.0). A total of 2,364 (12.7%) did not reach an LDL-C target < 100 mg/dL, 7,546 (40.4%) did not reach an LDL-C target <70 mg/dL, and 14,600 (78.3%) did not reach an LDL-C target <50 mg/dL. A total of 2176 (11.7%) did not reach a non-HDL-C level of 130 mg/dL, whereas 6,285 (33.7%) did not reach a non-HDL-C level < 100 mg/dL/ The number of patients not reaching apoB < 100 mg/dL was 2,740 (14.7%), and the number not reaching apoB < 80 mg/dL was 6,662 (35.7%).

Very low levels of LDL-C, non-HDL-C and apoB and risk of major cardiovascular events—Risk estimates for cardiovascular events by categories of achieved LDL-C level are presented in Table 1. Patients achieving an LDL-C level < 50 mg/dL had a significantly lower risk of major cardiovascular events compared to those with an LDL-C level >175 mg/dL (adjusted hazard ratio 0.44; 95%CI 0.35-0.55). In fact, this category of patients achieving an LDL-C < 50 mg/dL even had a statistically significantly lower risk of major cardiovascular events when compared to patients achieving an LDL-C level between 75-100 mg/dL (adjusted hazard ratio 0.81; 95%CI 0.70-0.95). Similarly, the risk of major coronary events decreased with decreasing categories of achieved LDL-C, such that patients achieving an LDL-C level < 50 mg/dL had an adjusted hazard ratio of 0.47 (95%CI 0.36-0.61) compared to those with an LDL-C level >175 mg/dL. The association between achieved LDL-C categories and risk of major cerebrovascular events was less linear than for coronary events although with a similar overall trend, such that patients achieving an LDL-C level < 50 mg/dL had a adjusted hazard ratio of 0.36 (95%CI 0.22-0.59) compared to those in the highest category. Additional adjustment for baseline LDL-C levels did not change these results importantly. Corresponding results for non-HDL-C and apoB are shown in Tables 2 and 3, respectively. Supplementary tables 4 and 5 show equivalent analyses using the alternative LDL-C cutoffs 50, 70, 100, 130, 160 and 190 mg/dL and non-HDL-C cutoffs 80, 100, 130, 160, 190 and 220 mg/dL. Supplementary Table 6 shows the risk of hemorrhaghic stroke by categories of LDL-C, nonHDL-C or apoB, based on data available from 7 trials (4S, LIPID, CARDS, TNT, IDEAL, SPARCL, JUPITER). Although the absolute number of hemorrhagic strokes was low and therefore statistical power limited, the results suggest that risk of hemorrhagic stroke was somewhat higher among patients achieving very low levels of atherogenic lipoproteins compared to those achieving moderately low levels.

Discussion

Our results show that there is a large inter-individual variation with regard to the reduction of atherogenic lipoprotein levels achieved with statin therapy. As a consequence, over 40% of trial patients assigned to high-dose statin therapy did not reach an LDL-C level below 70 mg/dL. The clinical benefit of achieving even lower levels of atherogenic lipoproteins

appears to be considerable since patients achieving an LDL-C level < 50 mg/dL are at significantly lower risk of major cardiovascular events even when compared to those reaching LDL-C levels 75-100 mg/dL.

Inter-individual variation of statin response

It is well known that there is a large inter-individual variation in the response to statin therapy. However, our current results highlight an underappreciated aspect, namely that some patients achieve a very large reduction of atherogenic lipoprotein levels, whereas others respond very poorly. Therefore, current management of dyslipidemia continues to be suboptimal, with a substantial proportion of patients failing to achieve guideline-recommended lipid targets.[22,23] Multiple patient characteristics including sex, age, smoking status, body weight, diet, and physical activity have been reported to contribute to variations in statin-induced LDL-C reduction but the impact of these factors is very modest.[24,25,26] However, non-adherence is probably one of the most important factors in the failure of patients to reach their lipid targets. Non-adherence is a complex entity and is affected by several factors including dose-related toxicity and side-effects, doctor-related issues such as failure to initiate therapy, inadequate patient education, inappropriate drug or dose selection, and inadequate dose titration, as well as patient-related issues such as depression.[27,28,29]

Several studies have investigated the association between genetic variants and the magnitude of LDL-C reduction achieved with a fixed statin dose. For instance, among patients treated with pravastatin 40 mg, two common variants in the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) gene were shown to be associated with lower efficacy of pravastatin treatment.[30] In a genetic substudy of the TNT trial variants in APOE, PCSK9 and HMGCR were also associated with statin efficacy, in this case atorvastatin.[31] A genome-wide association study in the JUPITER trial identified variants in ABCG2, LPA, APOE, and PCSK9 to be involved in response to rosuvastatin.[32] Voora et al. reported that variants in the APOE and ABCA1 genes were also associated with statin efficacy.[33] A genetic substudy of the Heart Protection Study also identified several genetic variants associated with statin efficacy, but the authors concluded that these did not alter lipid response by more than a few percent.[34] Overall, the lack of strong genetic effects on statin-induced lipid response in these large trials is likely a reflection of the complexity of lipid homeostasis and suggests that variability in response is due to a range of small effects superimposed on non-adherence.[31] Thus, the most important causes of inadequate lipid lowering achieved with statin therapy are largely unexplained.

Very low levels of atherogenic lipoproteins and risk of major cardiovascular events

The U.S. ATP-III guidelines recommend that for patients with CHD or a CHD risk equivalent, the LDL-C goal should be <100 mg/dL.[35] The more recently published European guidelines recommend that for people at high CVD risk the LDL-C goal is <2.5 mmol/L (~100 mg/dL).[36] These guidelines also suggest a target below 70 mg/dL or 1.8 mmol/L respectively, for patients at very high CVD risk, but these recommendations are not evidence-based. Our results suggest that even in the optimal setting of a randomized controlled trial, over 40% of patients assigned to high-dose statin therapy do not reach an LDL-C level <70 mg/dL. However, phase 2 data from trials with PCSK9 inhibitors suggest

that the large majority of patients treated with those agents may be able to reach LDL-C levels < 70 mg/dL.[8]

Whether achieving very low levels of atherogenic lipoproteins is indeed beneficial in terms of CVD risk is unclear. Post-hoc analyses from several statin trials have shown that patients achieving very low LDL-C levels on statin therapy are at lower CVD risk than those achieving moderately low levels, although the number of patients achieving very low LDL-C levels in individual trials is usually small. In the PROVE IT – TIMI-22 trial, there was no adverse effect and even an apparently lower cardiovascular risk in patients who reached LDL-C levels lower than the target 80-100 mg/dL.[4] A post-hoc analysis of the TNT trial showed that there was a highly significant reduction in the rate of major cardiovascular events with descending quintiles of achieved on-treatment LDL-C, even down to the lowest quintile which was defined as <64 mg/dL.[5] In JUPITER, statin-allocated participants attaining LDL-C <50 mg/dL had a lower risk of cardiovascular events than those not reaching LDL-C <50 mg/dL.[6] Our large-scale meta-analysis confirms the results of these studies and suggests that achieving very low levels of atherogenic lipoproteins seems to provide cardiovascular benefit beyond just treatment with a statin. With regard to the safety of very low levels of atherogenic lipoproteins, we observed that the risk of hemorrhagic stroke appeared to be somewhat higher among patients achieving very low levels of atherogenic lipoproteins than among those achieving moderately low levels. It should be stressed however that the number of hemorrhagic strokes was low, so statistical power was insufficient to draw definite conclusions. It should also be stressed that this small potential relative increase in hemorrhagic stroke was outweighed by a much lower risk of other cerebrovascular events. Thus, the overall risk of major cerebrovascular events was still lowest among patients achieving very low levels of atherogenic lipoproteins.

Limitations

Several aspects need to be taken into account when interpreting the results of this analysis. An important strength of this study is the availability of individual patient data, which enabled individual-level patient analyses, which provides more appropriate and accurate results than study-level analyses. A second strength is the fact that the dataset contained a large number of patients and major cardiovascular events. This enabled more reliable analyses of the relatively small group of patients reaching very low levels of atherogenic lipoproteins, which in individual trials is usually a small number. The most important limitation is the fact that this was a post-hoc analysis based on observational data, which cannot be extrapolated to treatment recommendations. A second limitation is the fact that the participating trials had different inclusion criteria. The different distributions of baseline characteristics may have affected the results of our meta-analysis. In particular, inclusion based on lipid criteria may have led to the selection of specific subpopulations of patients in some trials. In addition, outcome definitions may have differed slightly between trials. It should also be noted that the results are based on patients included in trials and that these results cannot necessarily be extrapolated to patients in routine clinical practice. Another limitation is the use of on-statin lipid and apolipoprotein levels measured at 1-year follow-up. This time point was chosen because it was the first uniform time point when lipids and apolipoproteins were measured in all participating trials. Therefore, fatal cardiovascular

events occurring in the first year of therapy are not accounted for in this analysis. Finally, it should be noted that part of the variability of LDL-C reductions observed in the trials may not have a strict biological explanation, but could also be explained by drug interactions or other factors like noncompliance, a factor that could not be accounted for in the present analysis.

In summary, we show that a large inter-individual variability exists with regard to the reduction of atherogenic lipoprotein levels achieved with statin therapy, and that despite treatment with high-dose statin therapy over 40% of trial patients do not reach guideline-recommended targets. Importantly, patients who achieve an LDL-C level < 50 mg/dL are at lower CVD risk than those achieving an LDL-C level 75-100 mg/dL. Whether a strategy targeting very low levels of atherogenic lipoproteins provides clinical benefit compared to a strategy targeting moderately low levels needs to be established in randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

List of abbreviations

LDL-C	Low-density lipoprotein cholesterol
Non-HDL-C	Non-high-density lipoprotein cholesterol
ApoB	Apolipoprotein B
4S	Scandinavian Simvastatin Survival Study
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
CARDS	Collaborative Atorvastatin Diabetes Study
TNT	Treating to New Targets
IDEAL	Incremental Decrease in Endpoints through Aggressive Lipid Lowering
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels

| JUPITER | Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin |

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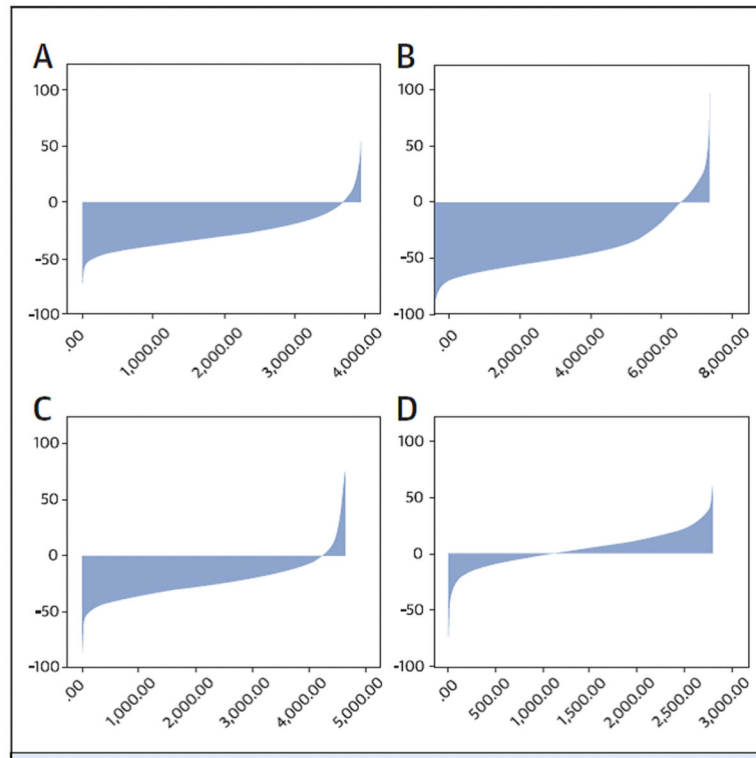
Figure 1. Waterfall plots of percentage LDL-C reduction

Waterfall plots present the distribution of percentage LDL-C reduction (1-year minus baseline divided by baseline levels) achieved in trials. Displayed are typical examples of usual-dose statin therapy (pravastatin 40 mg in the LIPID trial, plot A), high-dose statin therapy (rosuvastatin 20 mg in the JUPITER trial, plot B), a dose increase from usual-dose to high-dose statin (atorvastatin 10 mg to 80 mg in the TNT trial, plot C), and a placebo arm (AFCAPS-TexCAPS trial, plot D). LDL-C indicates low-density lipoprotein cholesterol.
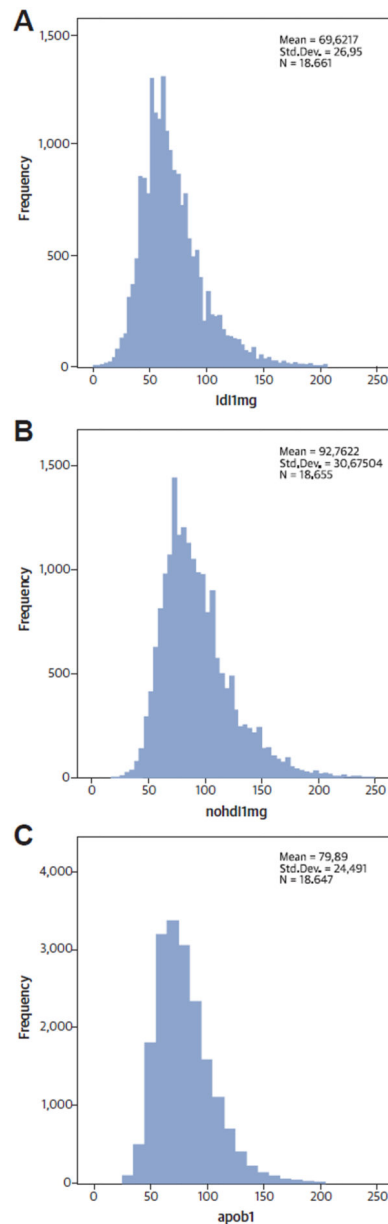
Figure 2. Distribution of achieved levels of LDL-C, non-HDL-C and apoB
Histograms displaying the distribution of achieved levels of LDL-C, non-HDL-C and apoB among patients treated with high-dose statin therapy. The results are based on patients assigned to atorvastatin 80 mg in the TNT, IDEAL, and SPARCL trials, and those assigned to rosuvastatin 20 arm in the JUPITER trial. LDL-C indicates low-density lipoprotein cholesterol, non-HDL-C indicates non-high-density lipoprotein cholesterol, apoB indicates apolipoprotein B.
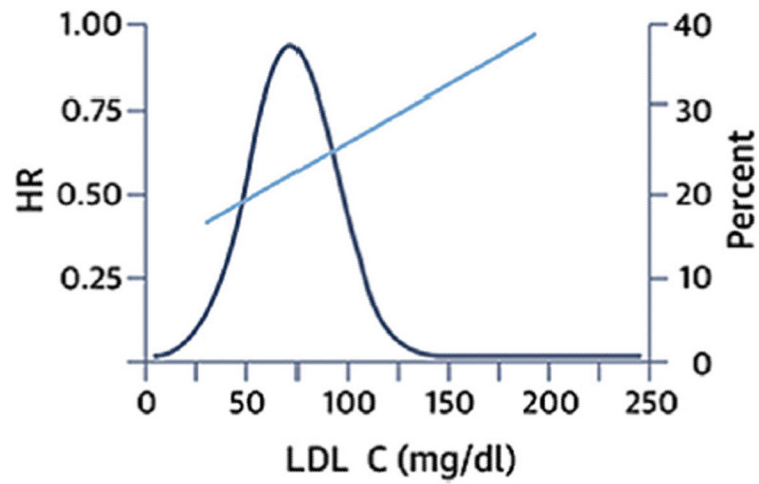
CENTRAL ILLUSTRATION. On-Statin LDL-C Levels and Risk for Major Cardiovascular Events

Distribution of achieved on-statin LDL-C levels (**dark blue curve**; right *y*-axis) and the risk of major cardiovascular events (**light blue line**; left *y*-axis). The *x*-axis represents achieved on-statin LDL-C levels. LDL C = low-density lipoprotein cholesterol; HR = hazard ratio.

Table 1

Risk of cardiovascular events by categories of achieved LDL-C level

On-trial LDL-C, mg/dL	< 50	50-75	75-100	100-125	125-150	150-175	> 175
On-trial LDL-C, mmol/L	<1.29	1.29-1.94	1.94-2.58	2.58-3.23	3.23-3.88	3.88-4.52	>4.52
Number of patients	4,375	10,395	10,091	8,953	3,128	836	375
Major cardiovascular events							
Number	194	1,185	1,664	1,480	557	184	123
Event rate	4.4%	11.4%	16.5%	16.5%	17.8%	22.0%	32.8%
Unadjusted hazard ratio	0.20	0.40	0.50	0.48	0.51	0.64	1.00
95% confidence interval	(0.16-0.25)	(0.33-0.48)	(0.42-0.60)	(0.40-0.58)	(0.42-0.62)	(0.51-0.81)	
Adjusted hazard ratio	0.44	0.51	0.56	0.58	0.64	0.71	1.00
95% confidence interval	(0.35-0.55)	(0.42-0.62)	(0.46-0.67)	(0.48-0.69)	(0.53-0.79)	(0.56-0.89)	
Major coronary events							
Number	129	918	1,431	1,336	492	170	107
Event rate	2.9%	8.8%	14.2%	14.9%	15.7%	20.3%	28.5%
Unadjusted hazard ratio	0.15	0.36	0.50	0.51	0.53	0.69	1.00
95% confidence interval	(0.12-0.20)	(0.29-0.43)	(0.41-0.61)	(0.42-0.62)	(0.43-0.65)	(0.54-0.88)	
Adjusted hazard ratio	0.47	0.53	0.58	0.62	0.67	0.78	1.00
95% confidence interval	(0.36-0.61)	(0.43-0.65)	(0.48-0.71)	(0.51-0.75)	(0.55-0.83)	(0.61-0.99)	
Major cerebrovascular events							
Number	72	315	302	205	91	21	23
Event rate	1.6%	3.0%	3.0%	2.3%	2.9%	2.5%	6.1%
Unadjusted hazard ratio	0.47	0.62	0.52	0.38	0.47	0.41	1.00
95% confidence interval	(0.29-0.74)	(0.41-0.95)	(0.34-0.79)	(0.25-0.58)	(0.30-0.75)	(0.23-0.74)	
Adjusted hazard ratio	0.36	0.46	0.49	0.45	0.58	0.43	1.00
95% confidence interval	(0.22-0.59)	(0.30-0.71)	(0.32-0.75)	(0.29-0.69)	(0.36-0.91)	(0.24-0.78)	

Adjusted hazard ratios and corresponding 95% confidence intervals are adjusted for sex, age, smoking, diabetes mellitus, systolic blood pressure, HDL cholesterol, and trial. The highest LDL-C category was used as reference category. LDL-C indicates low-density lipoprotein cholesterol.

Table 2

Risk of cardiovascular events by categories of achieved non-HDL-C level

On-trial non-HDL-C, mg/dL	<75	75-100	100-125	125-150	150-175	175-200	>200
On-trial non-HDL-C, mmol/L	<1.94	1.94-2.58	2.58-3.23	3.23-3.88	3.88-4.52	4.52-5.17	>5.17
Number of patients	6,341	8,318	9,764	7,956	3,992	1,178	604
Major cardiovascular events							
Number	390	970	1,555	1,349	697	259	167
Event rate	6.2%	11.7%	15.9%	17.0%	17.5%	22.0%	27.6%
Unadjusted hazard ratio	0.31	0.48	0.59	0.60	0.61	0.80	1.00
95% confidence interval	(0.26-0.38)	(0.41-0.57)	(0.50-0.69)	(0.51-0.71)	(0.52-0.72)	(0.66-0.97)	
Adjusted hazard ratio	0.57	0.60	0.64	0.69	0.75	0.89	1.00
95% confidence interval	(0.47-0.69)	(0.51-0.71)	(0.54-0.75)	(0.59-0.81)	(0.63-0.89)	(0.73-1.08)	
Major coronary events							
Number	260	760	1,338	1,220	627	232	146
Event rate	4.1%	9.1%	13.7%	15.3%	15.7%	19.7%	24.2%
Unadjusted hazard ratio	0.24	0.44	0.59	0.63	0.64	0.82	1.00
95% confidence interval	(0.20-0.29)	(0.37-0.52)	(0.49-0.69)	(0.53-0.75)	(0.53-0.76)	(0.67-1.01)	
Adjusted hazard ratio	0.58	0.61	0.66	0.73	0.79	0.94	1.00
95% confidence interval	(0.47-0.72)	(0.51-0.73)	(0.56-0.79)	(0.62-0.87)	(0.66-0.94)	(0.76-1.15)	
Major cerebrovascular events							
Number	145	246	278	191	100	38	31
Event rate	2.3%	3.0%	2.8%	2.4%	2.5%	3.2%	5.1%
Unadjusted hazard ratio	0.72	0.71	0.59	0.47	0.49	0.64	1.00
95% confidence interval	(0.49-1.06)	(0.49-1.03)	(0.41-0.86)	(0.33-0.69)	(0.33-0.73)	(0.40-1.02)	
Adjusted hazard ratio	0.49	0.55	0.54	0.54	0.59	0.68	1.00
95% confidence interval	(0.33-0.73)	(0.37-0.80)	(0.37-0.79)	(0.37-0.79)	(0.40-0.89)	(0.42-1.10)	

Adjusted hazard ratios and corresponding 95% confidence intervals are adjusted for sex, age, smoking, diabetes mellitus, systolic blood pressure, HDL cholesterol, and trial. The highest non-HDL-C category was used as reference category. Non-HDL-C indicates non-high-density lipoprotein cholesterol.

Table 3

Risk of cardiovascular events by categories of achieved apoB level

On-trial apoB, mg/dL	<50	50-75	75-100	100-125	125-150	150-175	>175
Number of patients	1,278	10,085	12,989	9,769	2,969	824	239
Major cardiovascular events							
Number	43	942	1,846	1,676	606	209	65
Event rate	3.4%	9.3%	14.2%	17.2%	20.4%	25.4%	27.2%
Unadjusted hazard ratio	0.21	0.41	0.51	0.61	0.72	0.94	1.00
95% confidence interval	(0.14-0.30)	(0.32-0.52)	(0.40-0.66)	(0.47-0.78)	(0.56-0.93)	(0.71-1.25)	
Adjusted hazard ratio	0.59	0.55	0.59	0.64	0.71	0.91	1.00
95% confidence interval	(0.40-0.88)	(0.43-0.71)	(0.46-0.76)	(0.50-0.82)	(0.55-0.92)	(0.69-1.20)	
Major coronary events							
Number	30	723	1,573	1,483	531	186	57
Event rate	2.3%	7.2%	12.1%	15.2%	17.9%	22.6%	23.8%
Unadjusted hazard ratio	0.16	0.36	0.51	0.62	0.73	0.96	1.00
95% confidence interval	(0.11-0.25)	(0.27-0.47)	(0.39-0.66)	(0.47-0.80)	(0.55-0.96)	(0.71-1.29)	
Adjusted hazard ratio	0.59	0.54	0.58	0.64	0.70	0.91	1.00
95% confidence interval	(0.37-0.93)	(0.41-0.70)	(0.45-0.76)	(0.49-0.83)	(0.53-0.92)	(0.68-1.22)	
Major cerebrovascular events							
Number	14	256	347	264	102	31	15
Event rate	1.1%	2.5%	2.7%	2.7%	3.4%	3.8%	6.3%
Unadjusted hazard ratio	0.34	0.52	0.44	0.43	0.53	0.60	1.00
95% confidence interval	(0.16-0.70)	(0.31-0.87)	(0.26-0.73)	(0.25-0.72)	(0.31-0.92)	(0.32-1.11)	
Adjusted hazard ratio	0.45	0.49	0.51	0.52	0.61	0.61	1.00
95% confidence interval	(0.21-0.95)	(0.29-0.83)	(0.31-0.86)	(0.31-0.88)	(0.35-1.04)	(0.33-1.13)	

Adjusted hazard ratios and corresponding 95% confidence intervals are adjusted for sex, age, smoking, diabetes mellitus, systolic blood pressure, HDL cholesterol, and trial. The highest apoB category was used as reference category. ApoB indicates apolipoprotein B.