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Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

A Meta-Analysis of Statin Trials

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ABSTRACT

BACKGROUND Levels of atherogenic lipoproteins achieved with statin therapy are highly variable, but the consequence of this variability for cardiovascular disease risk is not well-documented.

OBJECTIVES The aim of this meta-analysis was to evaluate: 1) the interindividual 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 cardiovascular disease risk.

METHODS This meta-analysis used 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 interindividual variability in the reductions of LDL-C, non-HDL-C, and apoB achieved with a fixed statin dose. More than 40% of trial participants assigned to high-dose statin therapy did not reach an LDL-C target <70 mg/dl. Compared with patients who achieved an LDL-C >175 mg/dl, those who reached an LDL-C 75 to <100 mg/dl, 50 to <75 mg/dl, and <50 mg/dl had adjusted hazard ratios for major cardiovascular events of 0.56 (95% confidence interval [CI]: 0.46 to 0.67), 0.51 (95% CI: 0.42 to 0.62), and 0.44 (95% CI: 0.35 to 0.55), respectively. Similar associations were observed for non-HDL-C and apoB.

CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485–94) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

apo = apolipoprotein

CHD = coronary heart disease

CVD = cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

non-HDL-C = non-high-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin/kexin 9

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 evidence on the efficacy of statin therapy is interpreted on the basis of mean reductions of low-density lipoprotein cholesterol (LDL-C) and mean reductions of CVD risk within randomized trials. There is large interindividual 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 (4–6).

The guideline-recommended marker of atherogenic lipoproteins is 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 <70 mg/dl (8–10). However, it is unclear whether pharmacological interventions resulting in atherogenic lipoprotein levels in this anticipated treatment range are beneficial in terms of CVD risk.

SEE PAGE 495

It was therefore our objective with this study to assess: 1) the variability of LDL-C, non-HDL-C, and 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

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very low LDL-C, non-HDL-C, or apoB levels and the risk for major cardiovascular events.

METHODS

STUDY ELIGIBILITY AND DATA COLLECTION. The methods of this meta-analysis have been described previously (7). The published reports were 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 <2 years and those including <1,000 participants were excluded. The search of published reports 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 *CVD*. The results were limited to randomized trials in English. The first search was performed on January 4, 2009, and an updated search that extended until December 31, 2011, was performed on January 20, 2012. Two authors (S.M.B., B.J.A.) 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 status; systolic and diastolic blood pressure; fasting glucose, total cholesterol, LDL-C, HDL-C, triglycerides, and apo A-I and B concentrations at baseline and at 1-year follow-up; study medications; and patients' histories of stable coronary heart disease (CHD), myocardial infarction (MI), percutaneous coronary intervention, and coronary artery bypass grafting. The following outcomes (and times to events) were also collected: fatal and nonfatal MI, 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 that was independently validated against the original files. The Delphi score assessed the quality of the included trials (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 DEFINITIONS. Lipid and apo 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 it 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,* defined as fatal or nonfatal MI, fatal "other CHD," hospitalization for unstable angina, or fatal or nonfatal stroke. Subanalyses were performed for the prediction of time to first major coronary event (fatal or nonfatal MI, fatal "other CHD," and hospitalization for unstable angina) and time to first major cerebrovascular event (fatal or nonfatal stroke).

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STATISTICAL ANALYSIS. Baseline characteristics, levels of lipids and apolipoproteins at baseline and at 1 year, as well as absolute changes and percent changes between on-trial and baseline levels were calculated for each trial separately. The distributions of percent 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. To limit the effect of potential outliers, patients with levels >5 SDs of the mean were excluded. The proportion of study participants not achieving an on-trial LDL-C target of <100 mg/dl or <70 mg/dl was calculated among those randomized to high-dose statin therapy in 1 of the included trials. Similar proportions were calculated for a non-HDL-C target of <130 mg/dl or <100 mg/dl, and for an apoB target of <100 mg/dl or <80 mg/dl. The association between on-statin achieved levels of LDL-C, non-HDL-C, or apoB and the risk of cardiovascular events was evaluated using the Cox proportional hazards model. For these analyses, study participants allocated to placebo were excluded. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the risks for cardiovascular events were calculated by categories of achieved LDL-C, non-HDL-C, and apoB levels, using the highest category as reference. LDL-C category cut-offs were chosen as follows: 50, 75, 100, 125, 150, and 175 mg/dl. We also specifically tested whether the risk for major cardiovascular events was lower among patients achieving very low LDL-C levels (<50 mg/dl) compared with those achieving moderately low levels (75 to <100 mg/dl). Equivalent analyses using LDL-C cutoffs <50, <70, <100, <130, <160, and <190 mg/dl, as well as using non-HDL-C cutoffs 30 mg/dl higher, also were performed. Analyses were adjusted for sex, age, smoking status, diabetes mellitus status, systolic blood pressure, HDL-C, and trial. Analyses were not additionally adjusted for prevalent CHD because all trials enrolled either 0% or 100% patients with prevalent disease, so adjustment for trial implies adjustment for prevalent CHD. However, prevalent CHD as an inclusion criterion was documented less rigorously in some trials than in other trials. Separate analyses for the outcomes of major cardiovascular events, major coronary events, major cerebrovascular events, and hemorrhagic stroke were performed.

Statistical heterogeneity across trials was quantified using the Cochran Q statistic and the I^2 statistic. The I^2 statistic was derived from the Q statistic ($[Q - df/Q] \times 100$) 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 2-tailed p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

The results of the literature search are shown in Online Figure 1 and have been published previously (7). Individual patient data were obtained from all 8 trials (14–21), with the exception of those on hemorrhagic stroke, which were not available from AFCAPS-TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (15). The study characteristics of these 8 trials are shown in Online Table 1. Trials were of high quality, with a median Delphi score of 9 (range 6 to 9). Heterogeneity between trials with regard to the association with risk for 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.

The baseline characteristics of the study participants are shown in Online Table 2. Levels of lipids and apolipoproteins at baseline and at 1 year on-trial, as well as the absolute and percent changes between baseline and on-trial levels, are shown in Online Table 3. A total of 38,153 study participants were randomized to a statin arm and had a complete set of lipid and apo levels during statin treatment available. During 155,573 person-years of follow-up, 158 study participants (0.4%) developed a fatal MI, and 1,678 (4.4%) developed a nonfatal MI. 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 1 major cardiovascular event. Of these, 4,577 experienced 1 event, 728 experienced 2 events, 75 experienced 3 events, and 7 experienced 4 events.

Waterfall plots of the distribution of percent LDL-C reduction ([1 year - baseline]/[baseline]) achieved in various trials are shown in **Figure 1**. Displayed are typical examples of the initiation of usual-dose statin therapy (patients assigned to pravastatin 40 mg in

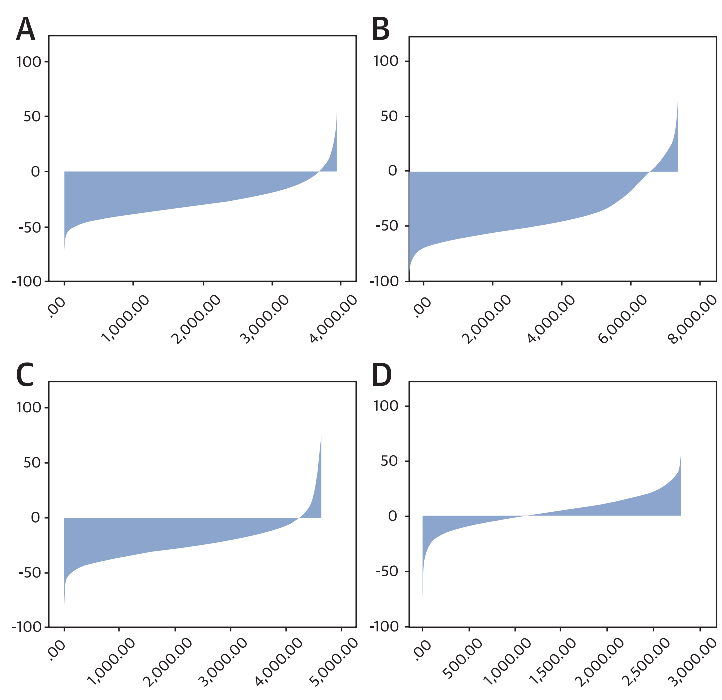


FIGURE 1 Waterfall Plots of Percent LDL-C Reduction

Waterfall plots presenting the distribution of percent reduction in low-density lipoprotein cholesterol (LDL-C) ([1 year − baseline]/baseline) achieved in trials. Displayed are typical examples of usual-dose statin therapy (pravastatin 40 mg in the LIPID [Long-Term Intervention With Pravastatin in Ischemic Disease] trial [3]) **(A)**, high-dose statin therapy (rosuvastatin 20 mg in the JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin] trial [6]) **(B)**, a dose increase from usual-dose to high-dose statin therapy (atorvastatin, from 10 to 80 mg, in the TNT [Treating to New Targets] trial [5]) **(C)**, and a placebo arm (AFCAPS-TexCAPS [Air Force/Texas Coronary Atherosclerosis Prevention Study] [15]) **(D)**.

the LIPID [Long-Term Intervention With Pravastatin in Ischemic Disease] trial [3]; n = 3,936) (**Fig. 1A**), the initiation of high-dose statin therapy (patients assigned to rosuvastatin 20 mg in the JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin] trial [6]; n = 7,783) (**Fig. 1B**), a dose increase from usual-dose to high-dose statin (patients with atorvastatin dose increased from 10 to 80 mg in the TNT [Treating to New Targets] trial [5]; n = 4,636) (**Fig. 1C**), and patients not treated with statin therapy (patients enrolled in the placebo arm of AFCAPS-TexCAPS; n = 2,802) (**Fig. 1D**). The corresponding examples of non-HDL-C reduction and apoB reduction are shown in Online Figures 2 and 3, respectively. These waterfall plots display a large interindividual 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 (e.g., either atorvastatin 80 mg in TNT [5], IDEAL [High-Dose Atorvastatin Vs. Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction] [19], or SPARCL [Stroke Prevention by Aggressive Reduction in Cholesterol Levels] [20] or rosuvastatin 20 mg in JUPITER [6]). Among 18,677 patients assigned to high-dose statin therapy, the mean achieved LDL-C level was 69.6 ± 27.0 mg/dl. 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 2,176 (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%).

The 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 for major cardiovascular events compared with those with an LDL-C level ≥175 mg/dl (adjusted hazard ratio [HR] 0.44; 95% CI: 0.35 to 0.55). In fact, this category of patients achieving an LDL-C <50 mg/dl had a statistically significantly lower risk for major cardiovascular events even when compared with patients achieving an LDL-C level between 75 and <100 mg/dl (adjusted HR: 0.81; 95% CI: 0.70 to 0.95). Similarly, the risk for major coronary events lowered with decreasing categories of achieved LDL-C, such that patients achieving an LDL-C level <50 mg/dl had an adjusted HR of 0.47 (95% CI: 0.36 to 0.61) compared with those with an LDL-C level ≥175 mg/dl. The association between achieved LDL-C categories and the risk for 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 an adjusted HR of 0.36 (95% CI: 0.22 to 0.59) compared with those in the highest category. Additional adjustment for baseline LDL-C levels did not change these results importantly. The corresponding results for non-HDL-C and apoB are shown in **Tables 2 and 3**, respectively. Online Tables 4 and 5, respectively, show equivalent analyses using the alternative LDL-C cutoffs of <50, <70, <100, <130, <160, and <190 mg/dl and non-HDL-C cutoffs of <80, <100, <130, <160, <190, and <220 mg/dl. Online Table 6 shows the risk for hemorrhagic stroke, by categories of LDL-C, non-HDL-C, and apoB, on the basis of data available from 7 trials (excepting AFCAPS-TexCAPS). Although the absolute number

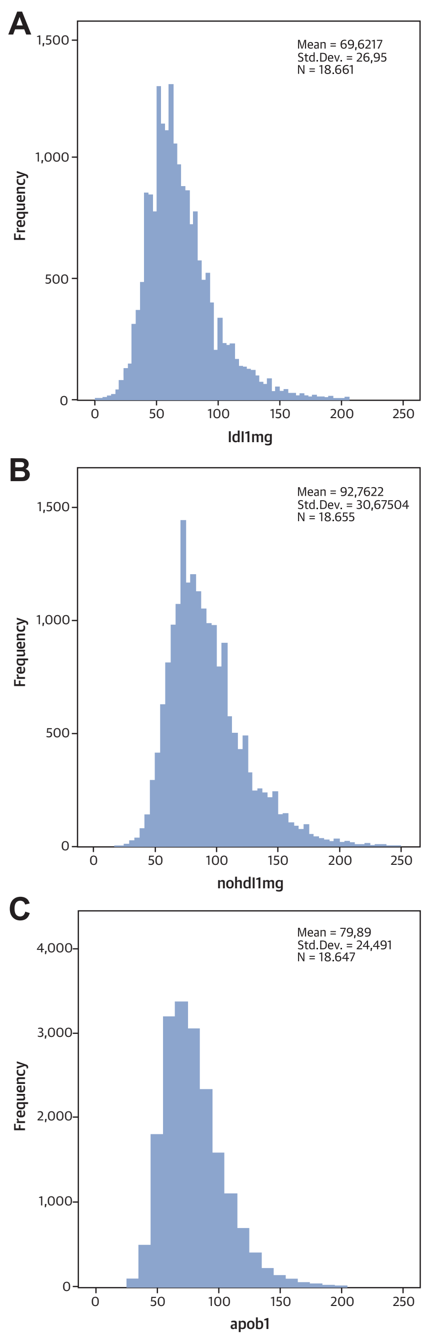


FIGURE 2 **Distribution of Achieved Levels of LDL-C, Non-HDL-C, and ApoB**

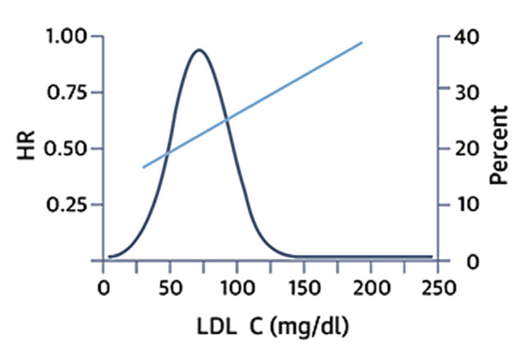
Histograms displaying the distribution of achieved levels of low-density lipoprotein cholesterol (LDL-C) **(A)**, non-high-density lipoprotein cholesterol (non-HDL-C) **(B)**, and apolipoprotein B (apoB) **(C)** among patients treated with high-dose statin therapy. The results are on the basis of patients assigned to atorvastatin 80 mg in the TNT (Treating to New Targets) (5), IDEAL (High-Dose Atorvastatin Vs. Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction) (19), and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) (20) trials, and those assigned to rosuvastatin 20 arm in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial.

of hemorrhagic strokes was low and, therefore, statistical power was limited, the results suggest that the risk for hemorrhagic stroke was somewhat higher among patients achieving very low levels of atherogenic lipoproteins compared with that in those achieving moderately low levels.

DISCUSSION

Our results show that there is large interindividual variation with regard to the reduction of atherogenic lipoprotein levels achieved with statin therapy. As a consequence, >40% of trial patients assigned to high-dose statin therapy did not reach an LDL-C level <70 mg/dl (**Central Illustration**). The clinical benefit of achieving even lower levels of atherogenic lipoproteins appears to be considerable because patients achieving an LDL-C level <50 mg/dl are at significantly lower risk for major cardiovascular events, even when compared with those reaching LDL-C levels 75 to <100 mg/dl.

It is well-known that there is large interindividual variation in the response to statin therapy. However, our results highlight an underappreciated aspect, namely, that some patients achieve a large reduction of atherogenic lipoprotein levels, whereas others respond poorly. Therefore, the current management of dyslipidemia continues to be suboptimal (22). 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 modest (23–25). However,



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 for Major Cardiovascular Events, by Achieved LDL-C Concentration

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

Values are n (%) unless otherwise indicated. *Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol concentration, and trial. The highest low-density lipoprotein cholesterol (LDL-C) category was used as the reference category.
CI = confidence interval; HR = hazard ratio.

nonadherence is probably one of the most important factors in the failure of patients to reach their lipid targets. Nonadherence is a complex entity and is affected by several factors, including dose-related toxicity and adverse effects, physician-related issues, and patient-related issues such as depression (26–28).

Several studies have investigated the association between genetic variants and the magnitude of LDL-C reduction achieved with a fixed-dose statin. For instance, among patients treated with pravastatin 40 mg, 2 common variants in the 3-hydroxy-3-methylglutaryl coenzyme A reductase gene (*HMGCR*) were shown to have been associated with lower efficacy of pravastatin treatment (29). In a genetic substudy of the TNT trial, variants of *APOE, PCSK9,* and *HMGCR* also were associated with statin efficacy, in this case atorvastatin (30). A genome-wide association study in the JUPITER trial identified variants of *ABCG2, LPA, APOE,* and *PCSK9* to be involved in response to rosuvastatin (31). Voora et al. (32) reported that variants in the *APOE* and *ABCA1* genes also were associated with statin efficacy. 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 nonadherence (30). Thus, the most important causes of inadequate lipid lowering achieved with statin therapy are largely unexplained.

The U.S. Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults guideline (33) recommends that for patients with CHD or

TABLE 2 Risk for Major Cardiovascular Events, by Achieved Non-HDL-C Concentration

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

Values are n (%) unless otherwise indicated. *Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C) concentration, and trial. The highest non-HDL-C category was used as the reference category.
Abbreviations as in Table 1.

JACC VOL. 64, NO. 5, 2014
AUGUST 5, 2014:485–94

TABLE 3 Risk for Major Cardiovascular Events, by Achieved ApoB Concentration

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

Values are n (%) unless otherwise indicated. *Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, HDL-C concentration, and trial. The highest apolipoprotein B (apoB) category was used as the reference category.

Abbreviations as in Tables 1 and 2.

a CHD risk equivalent, the LDL-C goal should be <100 mg/dl. 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) (34). These guidelines also suggest a target of <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, >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 of 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 of data from several statin trials have shown that patients achieving very low LDL-C levels on statin therapy are at lower CVD risk than are those achieving moderately low levels, although the number of patients achieving very low LDL-C levels in individual trials is usually small. As reported in a substudy of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 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 to <100 mg/dl (4). A post-hoc analysis of data from the TNT trial showed that there was a 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 (6), statin-allocated participants attaining LDL-C <50 mg/dl had a lower risk for cardiovascular events than did those not reaching LDL-C <50 mg/dl. Our large-scale meta-analysis supports the results of those 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 for hemorrhagic stroke appeared to be somewhat higher among patients achieving very low levels of atherogenic lipoproteins than among those achieving moderately low levels. However, the number of hemorrhagic strokes was low, so statistical power was insufficient to draw definite conclusions, and this small potential relative increase in hemorrhagic stroke was outweighed by a much lower risk for other cerebrovascular events. Thus, the overall risk for major cerebrovascular events was still lowest among patients achieving very low levels of atherogenic lipoproteins.

Several aspects need to be taken into account when interpreting the results of this analysis. An important strength of this study was the availability of individual patient data, which enabled individual-level patient analyses, which in turn provide more appropriate and accurate results than do study-level analyses. A second strength was the fact that the dataset contained large numbers of patients and major cardiovascular events, allowing for 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.

STUDY LIMITATIONS. The most important limitation was the fact that this was a post-hoc analysis on the basis of observational data, which cannot be extrapolated to treatment recommendations. A second limitation was 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 on the basis of 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. The results were on the basis of patients included in trials, and these results cannot necessarily be extrapolated to patients in routine clinical practice. Another limitation was 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, part of the variability of LDL-C reductions observed in the trials may not have a strict biological explanation but also could be explained by drug interactions or other factors, such as noncompliance—a factor that could not be accounted for in the present analysis.

CONCLUSIONS

We show that large interindividual variability exists with regard to the reduction of atherogenic lipoprotein levels achieved with statin therapy, and that despite treatment with high-dose statin therapy, >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 are those achieving an LDL-C level 75 to <100 mg/dl. Whether a strategy targeting very low levels of atherogenic lipoproteins provides clinical benefit compared with a strategy targeting moderately low levels needs to be established in randomized controlled trials.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: High-dose statin therapy reduces blood levels of atherogenic lipoproteins and the risk for cardiovascular events more than does intermediate-dose therapy, but the value of targeting specific lipoprotein levels is uncertain.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to test the efficacy and safety of targeting specific blood levels of lipoproteins to reduce cardiovascular risk.

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APPENDIX For supplemental tables and figures, please see the online version of this article.