FULL TEXT

New Online | Views 7,262 | Citations 0 | Altmetric 78

PDF | More | Cite | Permissions

Original Investigation

ONLINE FIRST FREE

August 1, 2018

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

A Meta-analysis

Marc S. Sabatine, MD, MPH[1,2]; Stephen D. Wiviott, MD[1]; KyungAh Im, PhD[1]; et al

» Author Affiliations | Article Information

JAMA Cardiol. Published online August 1, 2018. doi:10.1001/jamacardio.2018.2258

Editorial Comment | Interviews

Key Points

Question Is the clinical benefit of low-density lipoprotein cholesterol (LDL-C) lowering preserved in patient populations starting with LDL-C levels averaging 1.8 mmol/L (70 mg/dL) or less, and is LDL-C lowering safe in such patients?

Findings In this meta-analysis, for statins and nonstatins, the risk of major vascular events was significantly reduced by 21% for each 1-mmol/L (38.7-

mg/dL) reduction in LDL-C, which was virtually the same magnitude as seen in the overall Cholesterol Treatment Trialists Collaboration analysis in which the starting LDL-C was nearly twice as high. No adverse safety signal was detected for LDL-C lowering.

FULL TEXT

lowest current targets is associated with further reduced cardiovascular risk with no offsetting safety risks.

Abstract

Importance In the Cholesterol Treatment Trialists Collaboration (CTTC), in patients starting with low-density lipoprotein cholesterol (LDL-C) levels of approximately 3.4 mmol/L (131.5 mg/dL), there was a 22% reduction in major vascular events per 1-mmol/L (38.7-mg/dL) lowering of LDL-C. The magnitude of clinical benefit of further LDL-C lowering in patients already with very low LDL-C levels remains debated.

Objective To evaluate efficacy and safety of further lowering LDL-C levels in patient populations presenting with median LDL-C levels of 1.8 mmol/L (70 mg/dL) or less.

Data Sources and Study Selection The CTTC was used for statin data. For nonstatin therapy, Medline database was searched (2015-April 2018). Key inclusion criteria were a randomized, double-blind, controlled cardiovascular outcome trial of LDL-C lowering with data in populations starting with LDL-C levels averaging 1.8 mmol/L (70 mg/dL) or less.

Data Extraction and Synthesis Two authors independently extracted data into standardized data sheets, and data were analyzed using meta-analysis.

Main Outcomes and Measures The risk ratio (RR) of major vascular events (a composite of coronary heart death, myocardial infarction, ischemic stroke, or coronary revascularization) per 1-mmol/L (38.7-mg/dL) reduction in LDL-C level.

Results In the subgroup of patients from the CTTC meta-analysis of statins with a mean LDL-C in the control arm of 1.7 mmol/L (65.7 mg/dL), 1922 major vascular events occurred and the RR for major vascular events per 1-mmol/L (38.7-mg/dL) reduction in LDL-C was 0.78 (95% CI, 0.65-0.94).

For 3 trials of nonstatin LDL-C–lowering therapies added to statins, there were 50 627 patients, the median LDL-C in the control arms ranged from 1.6 mmol/L to 1.8 mmol/L (63 mg/dL to 70 mg/dL), and 9570 major vascular events occurred. Nonstatin therapy lowered LDL-C by 0.3 to 1.2 mmol/L (11 events per 1-mmol/L 0.70-0.88). For statins and nonstatins combined, the RR was 0.79 (95% CI, 0.71-0.87; *P*<.001). Low-density lipoprotein cholesterol lowering was not associated with an increased risk of serious adverse events, myalgias and/or myositis, elevation in the level of aminotransferases, new-onset diabetes, hemorrhagic stroke, or cancer.

Conclusions and Relevance There is a consistent relative risk reduction in major vascular events per change in LDL-C in patient populations starting as low as a median of 1.6 mmol/L (63 mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg/dL), with no observed offsetting adverse effects. These data suggest further lowering of LDL-C beyond the lowest current targets would further reduce cardiovascular risk.

FULL TEXT

Advertisement

Introduction

A series of randomized clinical trials of statin therapy, first of statin vs no statin and then intensive vs less intensive statin therapy, demonstrated successive risk reduction, with experimental arms that achieved progressively lower levels of low-density lipoprotein (LDL) cholesterol.[1] Based on these data, National Cholesterol Education Program guidelines recommended progressively lower LDL-C targets.[2] A meta-analysis of 26 statin trials by the Cholesterol Treatment Trialists Collaboration (CTTC) quantified the magnitude of benefit. There was a 22% relative risk reduction in major vascular events per 1-mmol/L reduction in LDL-C that was consistent across baseline LDL-C levels, even down to less than 2 mmol/L (77.3 mg/dL), although only a small proportion of patients started at such low levels.[3]

We are now in a new era with nonstatin drugs that further lower LDL-C levels and further reduce cardiovascular risk when added to statins. Clinical trials with these drugs afford the opportunity to quantify the clinical benefit

of LDL-C lowering and to examine whether it remains consistent even in individuals starting with and achieving lower levels than were examined in the CTTC meta-analysis and lower than current guideline targets. Likewise, they offer the opportunity to explore any signals of harm in patients with

FULL TEXT

Methods

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] The CTTC meta-analysis provided data for statin therapy in a subset of patients starting with a mean LDL-C level of 1.7 mmol/L (65.7 mg/dL). We searched the medical literature via Medline database for and analyzed randomized, double-blind, controlled cardiovascular outcome clinical trials of adding LDL-C–lowering therapy to a statin that have published data on patients starting with a mean or median LDL-C level of 1.8 mmol/L (70 mg/dL) or less (a threshold for decision making in guidelines). For further details on the literature search and inclusion and exclusion criteria, see eMethods in the Supplement.

The CTTC outcome of major vascular events comprised of coronary heart death, myocardial infarction, ischemic stroke (if available, otherwise all stroke), or coronary revascularization was used. The risk ratio (RR) per 1-mmol/L (38.7-mg/dL) difference in LDL-C between treatment arms was calculated for each trial. A fixed-effects inverse-weighting model was used to meta-analyze the results. The association between achieved LDL-C and estimated 5-year rate of major vascular events was evaluated using fixed-effects meta-regression analysis of the data from each group (experimental and control). Safety outcomes of interest included serious adverse events, myalgias and/or myositis, elevation in the level of aminotransferases, new-onset diabetes, hemorrhagic stroke, and cancer. Risk ratios and 95% CI were extracted or calculated from raw counts for each trial and meta-analyzed using a fixed-effects inverse-weighting model. Statistical analyses were performed using Comprehensive Meta Analyses, version 3.3.070 (Biostat Inc) and R, version 3.2.2 (R Programming).

Results

In the CTTC meta-analysis of statin therapy,[3] within the subset of patients starting with a mean LDL-C level of 1.7 mmol/L (65.7 mg/dL), the RR for

major vascular events per 1-mmol/L (38.7-mg/dL) reduction in LDL-C was 0.78 (95% CI, 0.65-0.94). The literature search identified 32 studies (eFigure in the Supplement), of which data from 3 randomized, double-blind, placebo-controlled clinical trials of nonstatin LDL-C–lowering therapy

FULL TEXT

n the meta-analysis t enrolled patients with known atherosclerotic cardiovascular disease. Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[5] studied ezetimibe in 18 144 patients stabilized after a recent acute coronary syndrome.[5] The median LDL-C in the control arm was 1.8 mmol/L (70 mg/dL). Ezetimibe reduced LDL-C levels by 0.3 mmol/L (13 mg/dL) and the relative risk of major vascular events by 7.5%. Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER)[6] studied the PCSK9 inhibitor evolocumab in 27 564 patients with stable atherosclerotic cardiovascular disease (either prior myocardial infarction, prior stroke, or symptomatic peripheral artery disease).[6] Among 2034 patients with a baseline LDL-C level less than 1.8 mmol/L (70 mg/dL), the median LDL-C level in the control arm was 1.7 mmol/L (66 mg/dL), and evolocumab reduced LDL-C levels by 1.1 mmol/L (42 mg/dL) and the relative risk of major vascular events by 22%.[7] Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) studied the cholesteryl ester transfer protein (CETP) inhibitor anacetrapib in 30 449 patients with stable atherosclerotic cardiovascular disease (either prior myocardial infarction, prior stroke or carotid revascularization, prior peripheral artery revascularization, or diabetes with symptomatic coronary heart disease).[8] The median LDL-C level in the control arm was 1.6 mmol/L (63 mg/dL). Anacetrapib reduced LDL-C by 0.3 mmol/L (11 mg/dL) and the relative risk of major vascular events by 7%.

A meta-analysis of the RR for major vascular events from each trial normalized for the LDL-C reduction achieved in that trial is shown in Figure 1A. The data from the prior CTTC meta-analysis showed an RR of 0.78 (95% CI, 0.65-0.94) per 1-mmol/L (38.7-mg/dL) lowering of LDL-C for statins. For nonstatin therapies, the RR was 0.79 (95% CI, 0.70-0.88; $P<.001$). Data for the individual components of the composite outcome were consistent (Figure 2). The overall effect for statins and nonstatins was an RR of 0.79 (95% CI, 0.71-0.87; $P<.001$).

Trial reports that did not provide the necessary information were excluded. Specifically, Heart Outcomes Prevention Evaluation 3 (HOPE-3) studied rosuvastatin but was excluded because the lowest reported starting LDL-C subgroup was only 2.9 mmol/L (112 mg/dL) or less. Assessment of Clinical

FULL TEXT

on With Evacetrapib in ELERATE) studied the CETP inhibitor evacetrapib but was excluded because LDL-C was not measured by β quantification, and it has been shown that in patients receiving CETP inhibitors, both Friedewald estimation and direct LDL-C assays underestimate LDL-C and therefore would overestimate LDL-C reduction. The ODYSSEY Outcomes trial studied the PCSK9 inhibitor alirocumab but was excluded because the lowest reported starting LDL-C subgroup was only less than 2.1 mmol/L (80 mg/dL). However, sensitivity analyses that included data extrapolated from these trials did not materially affect the results, with point estimates that shifted by no more than 0.01 (eResults in the Supplement). The plot of achieved LDL-C vs the estimated 5-year rates of major vascular events in the experimental and control arms of the 3 nonstatin trials (Figure 1B) shows a significant association, down to 0.5 mmol/L (21 mg/dL) (β, 0.35; 95% CI, 0.25-0.45; $P < .001$).

In terms of safety, LDL-C lowering was not associated with an increased risk of serious adverse events, myalgias and/or myositis, elevation in the level of aminotransferases, new-onset diabetes, hemorrhagic stroke, or cancer in any of the trials individually or when meta-analyzed (Table 2 and Figure 3).

Discussion

Extending observations made with statins, we found consistent clinical benefit from further LDL-C lowering in patient populations starting as low as a median of 1.6 mmol/L (63 mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg/dL). Specifically, when examining 11 492 major vascular events, there was a 21% relative risk reduction per 1-mmol/L (38.7-mg/dL) reduction in LDL-C through this range. This relative risk reduction is virtually the same as the 22% reduction seen in the overall CTTC analysis in which the starting LDL-C was nearly twice as high.[3] Moreover, these data parallel observational data showing progressively greater coronary atherosclerotic plaque regression and progressively lower adjusted risk of major vascular events with progressively LDL-C levels down to less than 0.2 mmol/L (7 mg/dL).[9,10] Furthermore, there was no evidence of an increased

incidence of adverse events with lowering LDL-C to such levels. These levels are considerably lower than the targets or thresholds for additional nonstatin LDL-C–lowering therapy in current cholesterol guidelines that, for high-risk patients, range from 1.8 mmol/L to 2.6 mmol/L (70 mg/dL to 100

FULL TEXT

The clinical benefit per millimoles per liter reduction in LDL-C was virtually identical for statins, ezetimibe, PCSK9 inhibition, and CETP inhibition, despite these drugs having different effects on other risk markers such as high-density lipoprotein cholesterol, lipoprotein(a), and high-sensitivity C-reactive protein. This observation reinforces the notion that the reduction in LDL-C (or more broadly, atherogenic apolipoprotein B–containing particles) is the primary driver of clinical benefit.

Because LDL-C–lowering therapies tend to produce the same relative percentage lowering of LDL-C regardless of starting levels, the absolute lowering of LDL-C and therefore the relative and absolute risk reductions will mathematically be a function of the baseline LDL-C. For example, in patients starting with an LDL-C level of 2.6 mmol/L (100 mg/dL), a 60% decrease in LDL-C (what a PCSK9 inhibitor typically achieves) should lower LDL-C by 1.6 mmol/L (60 mg/dL), reduce the relative risk of major vascular events by 31%, and, assuming a 5-year major vascular event rate of 25% in a secondary prevention population, yield an absolute risk reduction of 7.8%. If the same patients started with an LDL-C level of 1.8 mmol/L (70 mg/dL), LDL-C should be lowered by 1.1 mmol/L (42 mg/dL) and the relative risk of major vascular events by 23%, which would yield an absolute risk reduction of 5.8%.

However, because there were no offsetting safety concerns with LDL-C lowering through this range, the benefit-risk ratio from a medical perspective should always remain favorable (assuming longer-term safety data of very low LDL-C in larger numbers of individuals are equally reassuring). Assessment of cost-effectiveness is more complicated,[14,15] and whereas statins and ezetimibe are generic, PCSK9 inhibitors are not. If one wishes to target a minimum absolute risk reduction in major vascular events to justify the cost of therapy, a nomogram exists to identify patients based on baseline risk and LDL-C.[16]

Limitations

This analysis included data from a small number of randomized clinical trials with different entry criteria and durations of follow-up. Nonetheless, the risk reduction per 1-mmol/L reduction in LDL-C was remarkably consistent. The cut point of 1.8 mmol/L (70 mg/dL) was post hoc but was selected given the

FULL TEXT

Conclusions

In summary, there is a consistent relative risk reduction in major vascular events per further reduction in LDL-C in patient populations starting as low as a median of 1.6 mmol/L (63 mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg/dL), with no offsetting adverse effects. These data suggest further lowering of LDL-C thresholds for initiating more intensive therapy, or simply targeting LDL-C at least as low as approximately 0.5 mmol/L or 20 mg/dL, would further reduce cardiovascular risk.

Article Information

Back to top

Corresponding Author: Marc S. Sabatine, MD, MPH, TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Bldg for Transformative Medicine, 60 Fenwood Rd, 7th Floor, Boston, MA 02115 (msabatine@bwh.harvard.edu).

Accepted for Publication: June 8, 2018.

Published Online: August 1, 2018. doi:*10.1001/jamacardio.2018.2258*

Author Contributions: Dr Sabatine had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Sabatine.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Sabatine.

Critical revision of the manuscript for important intellectual content: Wiviott, Im, Murphy, Giugliano.

Statistical analysis: Im, Murphy.

Supervision: Sabatine.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The TIMI

tt Laboratories; Amgen; sai; Genzyme; Gilead; GlaxoSmithKline; Intarcia; Janssen Research and Development; Medicines Company; MedImmune; Merck; Novartis; Poxel; Pfizer; Roche Diagnostics; and Takeda. Dr Sabatine reports receiving honoraria for consulting from Alnylam; Amgen; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; Dyrnamix; Esperion; Intarcia; Ionis; Janssen Research and Development; Medicines Company; MedImmune; Merck; MyoKardia; and Novartis. Dr Wiviott reports receiving consultant/advisory board fees from Angelmed, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Aegerion, Janssen, Merck, Arena, Xoma, Amgen, and ICON Clinical and Boston Clinical Research Institute. Dr Wiviott's spouse is employed by Merck. Ms Murphy reports receiving consultant/advisory board fees from Amgen. Dr Giugliano reports receiving honoraria for continuing medical education activities from Amgen, Daiichi Sankyo, and Merck; and consulting/advisory board fees from Amarin, Amgen, Daiichi-Sankyo, Lexicon, Bristol Myers Squibb, CVS Caremark, GlaxoSmithKline, and Pfizer. No other disclosures were reported.

Disclaimer: Dr Sabatine is Deputy Editor of *JAMA Cardiology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

References

1. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561. doi:10.1016/S0140-6736(16)31357-5
PubMed | Google Scholar | Crossref

2. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239. doi:10.1161/01.CIR.0000133317.49796.0E
PubMed | Google Scholar | Crossref

3. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*.

FULL TEXT

40-6736(10)61350-5

4. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64. doi:10.7326/0003-4819-151-4-200908180-00135
PubMed | Google Scholar | Crossref

5. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489
PubMed | Google Scholar | Crossref

6. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
PubMed | Google Scholar | Crossref

7. Giugliano RP, Keech A, Murphy SA, et al. Clinical efficacy and safety of evolocumab in high-risk patients receiving a statin: secondary analysis of patients with low LDL cholesterol levels and in those already receiving a maximal-potency statin in a randomized clinical trial. *JAMA Cardiol*. 2017;2(12):1385-1391. doi:10.1001/jamacardio.2017.3944
PubMed | Google Scholar | Crossref

8. Bowman L, Hopewell JC, Chen F, et al; HPS3/TIMI55-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377(13):1217-1227. doi:10.1056/NEJMoa1706444
PubMed | Google Scholar | Crossref

9. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the

GLAGOV randomized clinical trial. *JAMA*. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951
PubMed | Google Scholar | Crossref

FULL TEXT
FOURIER Investigators. low LDL-cholesterol ocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390(10106):1962-1971. doi:10.1016/S0140-6736(17)32290-0
PubMed | Google Scholar | Crossref

11. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70(14):1785-1822. doi:10.1016/j.jacc.2017.07.745
PubMed | Google Scholar | Crossref

12. Landmesser U, Chapman MJ, Stock JK, et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J*. 2018;39(14):1131-1143. doi:10.1093/eurheartj/ehx549
PubMed | Google Scholar | Crossref

13. Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an expert panel of the National Lipid Association. *J Clin Lipidol*. 2017;11(4):880-890. doi:10.1016/j.jacl.2017.05.001
PubMed | Google Scholar | Crossref

14. Kazi DS, Penko J, Coxson PG, et al. Updated Cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. *JAMA*. 2017;318(8):748-750. doi:10.1001/jama.2017.9924
PubMed | Google Scholar | Crossref

15. Fonarow GC, Keech AC, Pedersen TR, et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*.

2017;2(10):1069-1078. doi:10.1001/jamacardio.2017.2762
PubMed | Google Scholar | Crossref

16. Sabatine MS, Giugliano RP. Low-density lipoprotein cholesterol lisin/kexin type 9 ardiol. 017.2293
PubMed | Google Scholar | Crossref

FULL TEXT

JAMA Cardiology

JAMA Network™

Help

Get the latest from JAMA Cardiology

Email address

Sign Up

JAMA Network™

© 2018 American Medical Association. All Rights Reserved.

Terms of Use | Privacy Policy | Accessibility Statement

POWERED BY SILVERCHAIR INFORMATION / SYSTEMS