Published in final edited form as:

J Clin Lipidol. 2019 ; 13(4): 538–549. doi:10.1016/j.jacl.2019.05.014.

Association of baseline LDL-C with total and cardiovascular mortality in patients using proprotein convertase subtilisin-kexin type 9 inhibitors: A systematic review and meta-analysis

Safi U. Khan, MD*,

Department of Medicine, West Virginia University, Morgantown, WV, USA

Haris Riaz, MD,

Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, USA

Hammad Rahman, MD,

Department of Medicine, Guthrie Health System, Robert Packer Hospital, Sayre, PA, USA

Muhammad U. Khan, MD,

Department of Medicine, West Virginia University, Morgantown, WV, USA

Muhammad Shahzeb Khan, MD,

Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, USA

Mohamad Alkhouli, MD,

Department of Cardiovascular Medicine, West Virginia University, Morgantown, WV, USA

Edo Kaluski, MD,

Department of Cardiovascular Medicine, Guthrie Health System, Robert Packer Hospital, Sayre, PA, USA

Thorsten M. Leucker, MD, PhD,

Division of Cardiology, Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Michael J. Blaha, MD, MPH

Division of Cardiology, Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Abstract

*Corresponding author. Department of Medicine, West Virginia University, 1 Medical Center Drive, Morgantown, WV 26505, USA. safinmc@gmail.com.

Authors' contributions: Khan S.U. contributed to the conception and design of the work, data acquisition, analysis, data interpretation, and writing the manuscript. Riaz H. and Rahman H. contributed in drafting the manuscript. Khan M.U. and Khan M.S. were involved in data acquisition and quality assessment. Alkhouli M., Kaluski E., Leucker T.M., and Blaha M.J. all critically reviewed the manuscript.

Conflict of interests: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector. Michael J. Blaha is on advisory Boards for Amgen, Sanofi, Regeneron, Novartis, MedImmune, Medicure, and receives grants from Amgen Foundation.

Supplementary data

Supplementary data to this article can be found online at <https://dx.doi.org/10.1016/j.jacl.2019.05.014>.

BACKGROUND: The objective of this study was to investigate whether baseline low-density lipoprotein cholesterol (LDL-C) levels influence total and cardiovascular mortality reduction associated with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor therapy.

METHODS: In this meta-analysis, 9 randomized controlled trials were selected using Medline, Embase, and CENTRAL until November 2018. Analyses were stratified by mean baseline LDL-C (<100 mg/dL and ≥100 mg/dL). Stepwise prespecified sensitivity analyses were performed after excluding the SPIRE trials and by regrouping ODYSSEY OUTCOME mortality data according to the baseline LDL-C (< and ≥100 mg/dL).

RESULTS: In 83,321 patients, PCSK9 inhibitor therapy was not associated with a reduction in the risk of all-cause mortality (relative risk [RR], 0.94, 95% confidence interval [CI], 0.81–1.09, $P = .41$). These results remained consistent after excluding the SPIRE trials (RR, 0.89, 95% CI, 0.75–1.05, $P = .18$). However, the RR varied by baseline LDL-C, with significant RR reduction only in patients with LDL-C ≥100 mg/dL (RR, 0.39, 95% CI, 0.20–0.76) (P -interaction = .01). Meta-regression showed RR of 0.97 for all-cause mortality per 1 mg/dL higher baseline LDL-C (95% CI, 0.94–0.99). PCSK9 inhibitor therapy showed no significant effect on cardiovascular mortality, with no effect when excluding the SPIRE trials. However, after regrouping ODYSSEY OUTCOME estimates, there was a significant reduction in cardiovascular mortality restricted to patients with LDL-C ≥100 mg/dL (RR, 0.67, 95% CI, 0.51–0.87) (P -interaction = .006).

CONCLUSION: PCSK9 inhibitor therapy on a background statin treatment may reduce the risk of total and cardiovascular mortality in patients with baseline LDL-C ≥100 mg/dL. These results support current guidelines reserving PCSK9 inhibitors for high-risk patients with residually high LDL-C.

Keywords

Proprotein convertase subtilisin-kexin type 9 inhibitors; Mortality; Meta-analysis

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-established causal risk factor for atherosclerotic cardiovascular disease (ASCVD).¹ Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are new therapeutic agents approved for use as an adjunct to diet and maximally tolerated statin and ezetimibe therapy for treatment of clinical ASCVD, heterozygous familial hypercholesterolemia, or homozygous familial hypercholesterolemia.² The European Society of Cardiology guidelines suggest that these agents should be considered in high-risk patients with ASCVD having LDL-C of > 140 mg/dL, despite statin with or without ezetimibe or in those who are genuinely statin intolerant.³ The American College of Cardiology/American Heart Association guidelines recommend PCSK9 inhibitors to very-high-risk ASCVD patients (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions), whose LDL-C levels remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, and in patients with severe primary hypercholesterolemia whose LDL-C remains ≥100 mg/dL despite statin plus ezetimibe.⁴

Large outcomes trials, that is, FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) and ODYSSEY OUTCOMES (Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes [ACS]) have revealed that these drugs reduce major adverse cardiovascular events in patients with ≥ 70 mg/dL LDL-C on background therapy of moderate- to high-intensity statin.^{5,6} In the recent ODYSSEY OUTCOMES trial, there was 15% relative risk (RR) reduction in all-cause mortality among patients with recent ACS receiving alirocumab. However, because according to the prespecified statistical analysis plan, the reduction in coronary heart disease mortality did not achieve statistical significance, the reduction in total mortality was considered a nominal finding. Moreover, the absolute risk reduction in composite primary endpoint with alirocumab was most pronounced in patients with baseline LDL-C >100 mg/dL.⁶

Although the Cholesterol Treatment Trialists' Collaboration meta-analysis showed that statins are associated with 22% RR reduction for major vascular events per 1 mmol/L (38.7 mg/dL) LDL-C reduction, independent of baseline LDL-C⁷; a recent meta-analysis reported that mortality benefit with contemporary lipid-lowering drugs was confined to patients with higher baseline LDL-C.⁸ This hypothesis-generating observation led us to study the association of baseline LDL-C with total and cardiovascular mortality in relatively long-term clinical trials of PCSK9 inhibitors. To test this hypothesis, we conducted a meta-analysis and meta-regression of PCSK9 inhibitors and mortality stratified by baseline LDL-C levels.

Methods

This trial level meta-analysis was performed following the Cochrane Collaboration guidelines and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis.^{9,10}

Data sources and searches

Literature search was carried out by two investigators (M.U.K. and M.S.K.) independently using Medline, Embase, and Cochrane library (January 2005 to November 2018). A broad search was conducted using relevant search terms such as “proprotein convertase subtilisin-kexin type 9 inhibitor”, “antiPCSK9 antibody”, “pcsk9 inhibitors”, “evolocumab”, “AMG 145”, “alirocumab”, “bococizumab”, “myocardial infarction”, “cardiovascular events”, “all-cause mortality”, “cardiovascular mortality”. etc. (Table S1). We also searched online libraries of www.esccardio.org, www.acc.org, www.clinicaltrialresults.com, www.clinicaltrials.gov, www.cardiosource.org, major cardiovascular meetings, and references of the relevant articles. All citations were retrieved and transferred to Endnote X 7 (Thompson ISI Research Soft, Philadelphia, PA) and duplicates were identified and removed electronically and manually.

Study selection

The prespecified inclusion criteria were (1) randomized controlled trials of PCSK9 inhibitors reporting mortality and cardiovascular outcomes of interest, (2) studies with sample size of ≥ 500 patients (to avoid small study effects), and (3) follow-up duration of at

least 48 weeks (because limited follow-up duration was unlikely to demonstrate differences in hard estimates).^{1,8} Two authors (M.U.K. and M.S.K.) scrutinized the records based on a priori criteria. Any disagreements were resolved by mutual consensus or third-party review (S.U.K.).

Quality assessment and data extraction

Data abstraction was performed by two investigators (M.U.K. and M.S.K.) using a prespecified data collection form incorporating baseline characteristics of the participants, number of events, sample size, crude point estimates, baseline LDL-C, reduction in LDL-C in each group, achieved LDL-C in each group and difference between the groups (magnitude of LDL-C reduction), and follow-up duration of each trial. The absolute difference in LDL-C (mg/dL) was calculated as mean difference averaged over the course of follow-up between two groups. If not available, then the mean achieved LDL-C value at the point closest to 50% of the median follow-up was used.¹ When possible, estimates were extracted based on intention to treat principle. The accuracy of data was appraised by S.U.K. and any discrepancies were resolved by discussion and referring to original study. The assessment of risk was done at study level by the Cochrane bias risk assessment tool (Table S4).¹¹

Outcome measures

The coprimary outcomes were all-cause mortality and cardiovascular mortality. The supportive secondary endpoints were myocardial infarction (MI), stroke, coronary revascularization, congestive heart failure exacerbation, neurocognitive adverse events, incident diabetes mellitus (DM), and cancer.

Statistical analysis

Outcomes were combined according to DerSimonian and Laird random effects models.¹² The summary estimates were reported as RR with 95% confidence interval (CI). Heterogeneity was assessed using Q statistics with $I^2 > 75\%$ being consistent with a high degree of heterogeneity¹³ (Table S5). In prespecified subgroup analyses, the ODYSSEY OUTCOMES trial reported key endpoints according to the following categories of baseline LDL-C: <80 mg/dL, 80 to <100 mg/dL, and ≥100 mg/dL. Because neither of the included trials had mean baseline LDL-C <80 mg/dL, we stratified the analyses at the baseline LDL-C <100 mg/dL and ≥100 mg/dL. The following stepwise prespecified sensitivity analyses were performed: (1) removal of the SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) trials (the study was terminated early and the development of bococizumab was stopped subsequently owing to the immunogenicity)¹⁴ followed by (2) meta-analyses of mortality outcomes by regrouping ODYSSEY OUTCOMES data in patients with baseline LDL-C <100 mg/dL.

Because ODYSSEY OUTCOMES reported estimates at the baseline LDL-C ≥70 mg/dL, we pooled these outcomes with trials having baseline LDL-C <100 mg/dL for primary meta-analysis. For sensitivity analyses, we regrouped mortality estimates corresponding to baseline LDL-C ≥100 mg/dL in subgroups of ODYSSEY OUTCOMES and pooled them accordingly with trials having baseline LDL-C <100 mg/dL.

Additional analyses for primary and secondary cardiovascular outcomes were performed according to the identity of drug and by magnitude of LDL-C reduction (Table S2). Subgroup analyses were conducted for primary endpoints according to type of control, age, use of background intensive statin therapy, events, sample size, and follow-up duration (Table S3). To evaluate whether the effect differed significantly between the subgroups, a formal subgroup-treatment effect interaction was calculated.

The random effects meta-regression analyses were conducted using the restricted maximum likelihood approach. The intercept was set at 0 to calculate log RR per each 1 mg/dL change in baseline LDL-C and 38.7 mg/dL reduction in LDL-C levels. The index R^2 value was used to determine the proportion of variance accounted for by the change in LDL-C. Publication bias was not assessed because of lesser number of studies (<10). For all analyses, statistical significance was set at 5%. Meta-analyses were performed using Comprehensive Meta-Analysis Software Version 3.0 (Biostat, Englewood, NJ) and Metafor Package Version 3.30 (R Project for Statistical Computing).

Results

Of 1,159 citations, 607 were duplicates, 441 were removed at title and abstract level, and further 102 were removed based on prespecified criteria. Finally, nine trials met inclusion criteria (Fig. 1). A total of 83,321 patients were randomized to PCSK9 inhibitors (43,057 patients) or control (40,264 patients). Mean age was 60 ± 2.3 year, 34% were women, 70% had coronary heart disease, and 30% had DM. The baseline LDL-C varied from 92 to 134 mg/dL with a weighted mean level of 107 ± 15 mg/dL. Ninety-three percent of patients were on statin, whereas 63% were on high-intensity statins. The weighted mean follow-up was 1.6 ± 0.6 years (Table 1).

All-cause mortality

A total of nine trials (1876 events/83,318 patients) were included. In the total population, PCSK9 inhibitor therapy did not reduce the risk of all-cause mortality (RR, 0.94, 95% CI, 0.81–1.09, $P=.41$), and this effect did not vary according to baseline LDL-C (P -interaction = .10) (Fig. 2). After exclusion of the SPIRE trials, PCSK9 inhibitor therapy had no significant effect on all-cause mortality (RR, 0.89, 95% CI, 0.75–1.05, $P=.18$). However, the RR varied by baseline LDL-C, with significant RR reduction in patients only with baseline LDL-C ≥ 100 mg/dL (RR, 0.39, 95% CI, 0.20–0.76) (P -interaction = .01) (Fig. 3). Similarly, there was a significant 40% RR reduction after regrouping the ODYSSEY OUTCOME data for patients with LDL-C >100 mg/dL (P -interaction = .006) (Fig. S1).

Meta-regression did not show an association between baseline LDL-C and all-cause mortality (Table 2). After exclusion of the SPIRE trials, metaregression showed that PCSK9 inhibitor therapy was associated with an RR of 0.97 (95% CI, 0.94–0.99) for total mortality per 1 mg higher baseline LDL-C (Fig. 4). This benefit persisted after regrouping ODYSSEY OUTCOMES data for LDL-C >100 mg/dL or after adjusting for magnitude of LDL-C reduction (Table 2). Baseline LDL-C accounted for 89% of the between-study variability (R^2) in the reduction of all-cause mortality. A model comprised baseline LDL-C and magnitude of LDL-C reduction resulted in R^2 of 98%.

In subgroup analyses, trials having <50% background intensive statin therapy had higher-risk reduction (RR, 0.42, 95% CI, 0.20–0.87) compared with trials using >50% intensive statin therapy (RR, 0.95, 95% CI, 0.83–1.10) (P -interaction = .03; Table S3).

Cardiovascular mortality

A total of nine trials (1162 events/83,318 patients) were included. PCSK9 inhibitor therapy did not reduce the risk of cardiovascular mortality (RR, 0.95, 95% CI, 0.85–1.07, P = .40), and the risk did not vary according to baseline LDL-C (Fig. 5). The exclusion of the SPIRE trials showed a consistent effect (RR, 0.94, 95% CI, 0.84–1.07, P = .36) (Fig. S2). However, an analysis regrouping ODYSSEY OUTCOME data (LDL-C > 100 mg/dL), patients with baseline LDL-C ≥ 100 mg/dL had RR of 0.67 (95% CI, 0.51–0.81, P < .001), with no benefit in baseline LDL-C < 100 mg/dL (RR, 1.04, 95% CI, 0.87–1.24, P = .65) (P -interaction = .006) (Fig. S3).

Metaregression analysis did not show an association between baseline LDL-C and cardiovascular mortality (Table 2). After removal of the SPIRE trials, and adjusting for magnitude of LDL-C reduction, metaregression showed an RR of 0.97 (95% CI, 0.94–0.99) per unit increase in baseline LDL-C (Fig. 6). This benefit was consistent after regrouping ODYSSEY OUTCOMES data for LDL-C ≥ 100 mg/dL or after adjusting for magnitude of LDL-C reduction (Table 2). Baseline LDL-C accounted for 71% of R^2 in the reduction of cardiovascular mortality. A model comprised baseline LDL-C and magnitude of LDL-C reduction resulted in R^2 of 98%.

Secondary endpoints

PCSK9 inhibitor therapy reduced the risk of MI (RR, 0.83, 95% CI, 0.71–0.98, P = .02), stroke (RR, 0.75, 95% CI, 0.66–0.86, P < .001), and coronary revascularization (RR, 0.83, 95% CI, 0.77–0.89, P < .001), regardless of baseline LDL-C (P -interaction > .05). Whereas, PCSK9 inhibitors had no significant effect on congestive heart failure exacerbation (RR, 0.99, 95% CI, 0.88–1.10, P = .81), neurocognitive adverse events (RR, 1.00, 95% CI, 0.85–1.18, P = .99), incident DM (RR, 1.00, 95% CI, 0.93–1.08, P = .32), or cancer (RR, 0.54, 95% CI, 0.12–2.50, P = .43), regardless of baseline LDL-C. (Figs. S4–S10).

Discussion

In this systematic review and meta-analysis, while PCSK9 inhibitors reduced the risk of major adverse cardiovascular outcomes independent of baseline LDL-C, the potential total or cardiovascular mortality benefit appeared to be confined to patients with baseline LDL ≥ 100 mg/dL. Metaregression showed a linear association between baseline LDL-C and mortality benefit even after adjustment for the magnitude of LDL-C reduction. Sensitivity analyses suggested that all-cause mortality, at least in large part, was driven by reduction in cardiovascular death.

Patients with higher baseline LDL-C carry higher risk of adverse cardiovascular events and mortality. Because the magnitude of LDL-C lowering depends on baseline LDL-C and efficacy of drug,⁸ the incremental LDL-C reductions will be higher at higher baseline LDL-C, consequently translating into higher event rate reductions. This concept was evident in

ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy) and OSLER (Open Label Study of Long-Term Evaluation Against LDL-C) trials, where both trials showed numerically lower mortality events in participants with baseline LDL-C levels of ~120 mg/dL and LDL-C reductions of ~70 mg/dL using PCSK9 inhibitors.^{17,18}

In the same framework, secondary prevention trials of statin therapy have consistently shown mortality benefit in patients with higher baseline LDL-C. For instance, 4S trial (4444 patients) showed 29% RR reduction in all-cause mortality in patients with mean baseline LDL-C of 188.3 ± 25.5 mg/dL at 5.4 years.²⁰ Similarly, GREACE (The GREek Atorvastatin and Coronary-heart-disease Evaluation Study) trial (1600 patients) showed 43% RR reduction at mean baseline LDL-C of 180 ± 27 mg/dL over 3 years.²¹ Other trials, such as LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease),²² HPS (Heart Protection Study),²³ and PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy)²⁴ showed similar results.

The FOURIER and the ODYSSEY OUTCOMES contain most of the weight in the analysis; therefore, the baseline population differences among these trials should be considered while interpreting the results.^{5,6} In FOURIER, patients with stable ASCVD (mean 2–3 years after the most recent event) and LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on maximally tolerated statin therapy received evolocumab or placebo.⁵ Conversely, in ODYSSEY OUTCOMES, patients with relatively higher risk for recurrent cardiovascular events—that is, subjects with recent ACS event (median duration of 2.6 months since index ACS) having suboptimal lipid control (defined as LDL-C ≥ 70 , non-HDL ≥ 100 , or apolipoprotein B ≥ 80 mg/dL while on a statin)—were randomized to alirocumab or placebo.⁶ Another key difference from FOURIER was that in ODYSSEY OUTCOMES, alirocumab dose was titrated between 75 and 150 mg to contain the LDL-C between 25 and 50 mg/dL but ≥ 15 mg/dL.^{5,6} In ODYSSEY OUTCOMES, ~90% patients were on high-intensity statin therapy compared with ~70% in FOURIER trial and ~3% patient received ezetimibe in ODYSSEY OUTCOMES compared with ~5.2% in FOURIER.

Among the large outcome trials, the SPIRE trials were terminated prematurely because of development of antidrug antibodies attenuating the substantial reduction in LDL-C.¹⁴ There was 54.2% reduction in LDL-C at 12 weeks with bococizumab, which was attenuated to 43% at 52 weeks. There was a direct association between reduction in LDL-C and antibody levels. This dampening effect, lower baseline LDL-C (93.7 mg/dL) and short follow-up (7 months) consequently translated into lack of cardiovascular benefit in the SPIRE-1 trial. However, in the SPIRE-2 trial, there was a 21% reduction in the primary endpoint in patients having LDL-C ~ 133.7 mg/dL at 12 months. Because the lack of mortality benefit by bococizumab was most likely secondary to the limited follow-up duration and suboptimal LDL-C reduction due to immunogenicity, exclusion of these trials explains the mortality reduction with PCSK9 inhibitors in the current analyses.

It is noteworthy to discuss the subgroup analyses showing mortality benefit with PCSK9 inhibitors in patients receiving $<50\%$ intensive statin therapy. In clinical trials, both

evolocumab and alirocumab have shown 50% to 60% reductions in LDL-C in the setting of statin intolerance.^{25–28} Current professional guidelines favor ezetimibe, bile acid sequestrant, or other nonstatin therapies over PCSK9 inhibitors to achieve target goals in statin intolerant patients^{29,30}; however, because there is no outcome trial data of PCSK9 inhibitors in this setting, these observations suggest consideration of antiPCSK9 therapy in this subset.

Various cost-effectiveness analyses have suggested that PCSK9 inhibitors cost considerably more than the value they provide.^{31,32} The Institute for Clinical and Economic Review report proposed a reduction in the cost of these agents to between \$5300 and \$7,600.³³ These recommendations were further amended to suggest that evolocumab should be priced at \$1725 to \$2242 per annum following the cardiovascular benefit demonstrated in the FOURIER trial.⁵ In 2018, drug companies cut the price of these agents by 60%.³⁴ Given the financial considerations of prescribing PCSK9 inhibitors, our findings might have direct clinical and financial relevance. While current results support the current professional cholesterol guidelines to consider the use of these drugs in high-risk patients with higher residual baseline LDL-C after maximally tolerated statin (with or without ezetimibe) therapy,^{3,4} the mortality benefit with these agents should initiate a debate regarding the true net value of these therapies.

We critically compared our findings with previous meta-analyses. Navarese et al.³⁵ (24 trials, 10,159 patients) published the first meta-analysis, which reported a mortality benefit with PCSK9 inhibitors. However, this study was limited by inclusion of trials with low event rates and short follow-up duration (17 trials had follow-up of less than 6 months duration). In addition, because this study was published in 2015, authors could not include data sets of contemporary large outcomes trials.^{5,6,14} The subsequent meta-analyses incorporating the FOURIER trial⁵ had failed to demonstrate a mortality benefit,^{36,37} although ODYSSEY OUTCOMES result were unavailable at that time for analysis.⁶

Our study is subject to certain limitations. Most importantly, this was a study level analysis and we could not adjust our results for individual-level characteristics including diabetes, stable coronary heart disease vs acute coronary syndrome, gender, BMI, high density lipoprotein cholesterol, blood pressure thresholds, or estimated GFR. Therefore, an individual patient analysis of contemporary PCSK9 inhibitor trials stratified by baseline LDL-C would still be valuable. The current findings are somewhat influenced by early-phase 2/3 data. These trials had variable, relatively short follow-up periods (48 weeks to 146 weeks) compared with various statin trials.⁷ In the GLAGOV trial, there was greater reduction in percentage atheroma volume after 76 weeks of treatment with PCSK9 inhibitor therapy, suggesting a potential for greater plaque regression over time, which might translate into a later mortality benefit.¹⁹ Therefore, it is possible that with longer follow-up duration, these agents might show a statistically significant mortality reduction similar to statin trials.⁷ Thus, it is important to note that even in trials comparing high-intensity vs moderate-intensity statins, there was lack of cardiovascular or total mortality benefit in patients with baseline LDL-C 100 mg/dL at median follow-up of ~5.1 years.⁷ Most trials were not powered for total or cardiovascular mortality endpoints. Finally, some of these trials

included patients with low risk of coronary heart disease who were inherently at lower risk of mortality; this observation can further lower the magnitude of mortality benefit.^{15,18}

In summary, over a mean follow-up of 1.6 years, while PCSK9 inhibitor therapy on a background statin therapy reduced major adverse cardiovascular outcomes regardless of baseline LDL-C, the potential mortality benefit may be limited to patients with baseline LDL-C < 100 mg/dL. Because baseline LDL-C is directly related to absolute risk of recurrent cardiovascular events, physicians should consider the initial LDL-C levels while prescribing these drugs in high-risk patients. While these findings support the current European Society of Cardiology and American College of Cardiology/American Heart Association guide-lines, our study also argues for future randomized controlled trials of patients with higher baseline LDL-C to validate our observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289–1297. [PubMed: 27673306]
2. Repatha Fala L. (evolocumab): second PCSK9 inhibitor approved by the FDA for patients with familial hypercholesterolemia. *Am Health Drug Benefits*. 2016;9:136–139. [PubMed: 27668060]
3. 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;39:1131–1143. [PubMed: 29045644]
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73:3168–3209. [PubMed: 30423391]
5. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376:1713–1722. [PubMed: 28304224]
6. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379: 2097–2107. [PubMed: 30403574]
7. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376: 1670–1681. [PubMed: 21067804]
8. Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA* 2018;319:1566–1579. [PubMed: 29677301]
9. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. *Spine* 2003;28:1290–1299. [PubMed: 12811274]
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535. [PubMed: 19622551]
11. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928. [PubMed: 22008217]
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin trials*. 1986;7:177–188. [PubMed: 3802833]

13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560. [PubMed: 12958120]
14. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med* 2017;376: 1527–1539. [PubMed: 28304242]
15. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;370: 1809–1819. [PubMed: 24678979]
16. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J* 2015;36:1186–1194. [PubMed: 25687353]
17. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489–1499. [PubMed: 25773378]
18. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500–1509. [PubMed: 25773607]
19. 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;316:2373–2384. [PubMed: 27846344]
20. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atheroscler Suppl* 2004;5:81–87. [PubMed: 15531279]
21. Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus ‘usual’ care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002;18: 220–228. [PubMed: 12201623]
22. Group TL-TIwPiIDS. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339: 1349–1357. [PubMed: 9841303]
23. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22. [PubMed: 12114036]
24. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504. [PubMed: 15007110]
25. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA* 2016; 315:1580–1590. [PubMed: 27039291]
26. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA* 2012;308: 2497–2506. [PubMed: 23128163]
27. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;63:2541–2548. [PubMed: 24694531]
28. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin re-challenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015;9:758–769. [PubMed: 26687696]
29. Guyton JR, Bays HE, Grundy SM, Jacobson TA, The National Lipid Association Statin Intolerance P. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol* 2014;8: S72–S81. [PubMed: 24793444]
30. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016; 253:281–344. [PubMed: 27594540]
31. 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;318:748–750. [PubMed: 28829863]

32. 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: 1069–1078. [PubMed: 28832867]
33. AJMC Managed Markets Network. PCSK9 inhibitors should cost 85% less, ICER reports. Available at: <https://www.ajmc.com/newsroom/pcsk9-inhibitors-should-cost-85-less-icer-reports>. Accessed May 15, 2019.
34. Regeneron. Regeneron and Sanofi offer Praluent (alirocumab) at a new reduced U.S. list price. Available at: <https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-offer-praluent-alirocumab-new-reduced-us>. Accessed May 15, 2019.
35. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med* 2015;163:40–51. [PubMed: 25915661]
36. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017;4:Cd011748. [PubMed: 28453187]
37. Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc* 2017;6.

Figure 1. Study selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Figure 2.
Forest plot showing relative risk of all-cause mortality.

Figure 3.
Forest plot showing relative risk of all-cause mortality after removal of SPIRE trials.

Figure 4.

Metaregression analysis for all-cause mortality. Change in relative risk of all-cause mortality and 95% confidence intervals of PCSK9 inhibitor vs control plotted against baseline LDL-C levels. Each trial is represented by one circle, the size of which is proportional to the weight in the meta-regression. (A): metaregression for all included PCSK9 inhibitor trials; (B): metaregression of PCSK9 inhibitors trials after excluding SPIRE trials; (C): metaregression of PCSK9 inhibitors trials after regrouping ODYSSEY OUTCOMES estimates reported for baseline LDL-C ≥ 100 mg/dL. PCSK9, proprotein convertase subtilisin-kexin type 9; LDL-C, low-density lipoprotein cholesterol; ODYSSEY OUTCOMES, Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes.

Figure 5.
Forest plot showing relative risk of cardiovascular mortality.

Figure 6.

Metaregression analysis for cardiovascular mortality. Change in relative risk of cardiovascular mortality and 95% confidence intervals of PCSK9 inhibitor vs control plotted against baseline LDL-C levels. Each trial is represented by one circle, the size of which is proportional to the weight in the meta-regression. (A): metaregression for all included PCSK9 inhibitor trials; (B): metaregression of PCSK9 inhibitors trials after excluding SPIRE trials; (C): metaregression of PCSK9 inhibitors trials after regrouping ODYSSEY OUTCOMES estimates reported for baseline LDL-C > 100 mg/dL. PCSK9, proprotein convertase subtilisin-kexin type 9; LDL-C, low-density lipoprotein cholesterol; SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events; ODYSSEY OUTCOMES, Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes.

Baseline characteristics of the trials and participants

Table 1

Studies (y)	Phase	Arms	N	Age (y)	Women (%)	Baseline LDL-C (mg/dL)	CHD (%)	HTN (%)	DM (%)	Statin therapy (%)	Intensive statin therapy (%)	Follow-up (wk)
DESCARTES (2014) ¹⁵	3	Evolocumab Placebo	599 302	55.9 56.7	51.6 53.6	104.2 104.0	15.7 13.9	48.2 49.3	10.4 13.9	87.6 87.7	45.2 45.0	52
ODYSSEY COMBO II (2014) ¹⁶	3	Alirocumab Ezetimibe	479 241	61.7 61.3	24.8 29.5	108.2 104.4	91.2 88	— —	30.7 31.5	99.8 100	66.8 66.4	104
ODYSSEY LONG TERM (2015) ¹⁷	3	Alirocumab Placebo	1553 788	60.4 60.6	36.7 39.8	122.7 121.9	67.9 70.1	— —	34.9 33.9	99.9 99.9	46.8 46.7	78
OSLER (2015) ¹⁸	2/3	Evolocumab Standard therapy	2976 1489	57.8 58.2	49.9 48.6	120.0 121.0	19.8 20.6	51.9 52.2	12.8 14.6	69.7 70.9	26.7 27.9	48
GLAGOV (2016) ¹⁹	3	Evolocumab Placebo	484 484	59.8 59.8	27.7 27.9	92.4 92.6	100 100	83.7 82.2	21.5 20.2	98.3 98.8	59.9 57.9	76
FOURIER (2017) ⁵	3	Evolocumab Placebo	13,784 13,780	62.5 62.5	24.6 24.5	92.0 92.0	100 100	80.1 80.1	36.7 36.5	100 100	69.5 69.1	113
SPIRE 1 (2017) ¹⁴	3	Bococizumab Placebo	8408 8409	63.3 63.3	26.3 26.5	93.8 93.7	NA NA	81.2 80.9	48.3 47.4	99.1 99.2	91.7 91.4	* ₃₀
SPIRE 2 (2017) ¹⁴	3	Bococizumab Placebo	5312 5309	62.2 62.6	34.1 35.1	133.9 133.4	NA NA	81.3 89.6	47.8 46.1	83.2 83.1	73.3 73.5	52
ODYSSEY OUTCOMES (2018) ⁶	3	Alirocumab Placebo	9462 9462	58.5 58.6	25.3 25.1	92.0 92.0	100 100	65.6 63.9	28.5 29.1	97.6 97.5	88.6 89.1	146

CHD, Coronary Heart Disease; DM, diabetes mellitus; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; LDL-C, low-density lipoprotein cholesterol; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) vs Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia; ODYSSEY LONG TERM, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; ODYSSEY OUTCOMES, Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes; OSLER, Open Label Study of Long-term Evaluation Against LDL-C Trial; SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events.

Values are provided as mean ± SD or median (Q1–Q3) whichever were available.

* Median duration.

Table 2

Multivariate meta regressions analyses

Outcome	RR [95% CI] per unit increase in baseline LDL-C (mg/dL)	RR [95% CI] for magnitude of LDL-C lowering	RR [95% CI] per unit increase in baseline LDL-C adjusted for magnitude of LDL-C lowering
All-cause mortality	0.99 [0.98, 1.01]	0.68 [0.30, 1.50]	0.99 [0.98, 1.01]
Cardiovascular mortality	0.99 [0.98, 1.00]	0.71 [0.30, 1.64]	0.99 [0.98, 1.01]
Sensitivity analyses after excluding SPIRE 1 and 2 trials			
All-cause mortality	0.97 [0.94, 0.99]	0.68 [0.19, 2.41]	0.96 [0.94, 0.99]
Cardiovascular mortality	0.97 [0.94, 1.00]	0.70 [0.22, 2.33]	0.97 [0.94, 0.99]
Sensitivity analyses after incorporating ODYSSEY OUTCOMES estimates in subgroup with baseline LDL-C 100 mg/dL			
All-cause mortality	0.96 [0.94, 0.98]	0.81 [0.20, 3.22]	0.97 [0.95, 0.98]
Cardiovascular mortality	0.97 [0.94, 0.99]	0.85 [0.20, 3.52]	0.97 [0.94, 0.99]

ODYSSEY OUTCOMES, effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes; SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events; LDL-C, low-density lipoprotein cholesterol.

Change in baseline LDL-C refers to each 1 mg/dL change and magnitude of LDL-C lowering refers to each 38.7 mg/dL reduction.