Association of Lowering Low-Density Lipoprotein Cholesterol With Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis

Safi U. Khan, MD; Hammad Rahman, MD; Victor Okunrintemi, MD, MPH; Haris Riaz, MD; Muhammad Shahzeb Khan, MD; Sudhakar Sattur, MD; Edo Kaluski, MD; A. Michael Lincoff, MD; Seth S. Martin, MD, MHS; Michael J. Blaha, MD, MPH

***Background*—**The relationship between lowering LDL (low-density lipoprotein) cholesterol with contemporary lipid-lowering therapies and incident diabetes mellitus (DM) remains uncertain.

***Methods and Results*—**Thirty-three randomized controlled trials (21 of statins, 12 of PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors, and 0 of ezetimibe) were selected using Medline, Embase, and the Cochrane Central Register of Controlled Trials (inception through November 15, 2018). A total of 163 688 nondiabetic patients were randomly assigned to more intensive (83 123 patients) or less intensive (80 565 patients) lipid-lowering therapy. More intensive lipid-lowering therapy was defined as the more potent pharmacological strategy (PCSK9 inhibitors, higher intensity statins, or statins), whereas less intensive therapy corresponded to active control group or placebo/usual care of the trial. Metaregression and meta-analyses were conducted using a random-effects model. No significant association was noted between 1-mmol/L reduction in LDL cholesterol and incident DM for more intensive lipid-lowering therapy (risk ratio: 0.95; 95% CI, 0.87–1.04; P=0.30; R^2=14%) or for statins or PCSK9 inhibitors. More intensive lipid-lowering therapy was associated with a higher risk of incident DM compared with less intensive therapy (risk ratio: 1.07; 95% CI, 1.03–1.11; P<0.001; I^2=0%). These results were driven by higher risk of incident DM with statins (risk ratio: 1.10; 95% CI, 1.05–1.15; P<0.001; I^2=0%), whereas PCSK9 inhibitors were not associated with incident DM (risk ratio: 1.00; 95% CI, 0.93–1.07; P=0.96; I^2=0%; P=0.02 for interaction).

***Conclusions*—**Among intensive lipid-lowering therapies, there was no independent association between reduction in LDL cholesterol and incident DM. The risk of incident DM was higher with statins, whereas PCSK9 inhibitors had no association with risk of incident DM. **(*J Am Heart Assoc*. 2019;8:e011581. DOI: 10.1161/JAHA.118.011581.)**

Key Words: diabetes mellitus • LDL (low-density lipoprotein) cholesterol • PCSK9 (proprotein convertase subtilisin/kexin type 9) • statin

LDL (low-density lipoprotein) cholesterol (LDL-C) is a well-established modifiable risk factor for clinical atherosclerotic cardiovascular disease.[1,2] Incremental reductions in LDL-C levels by statins or intensifying statin therapy by adding ezetimibe or PCSK9 (proprotein convertase subtilisin/kexin type 9) have shown correspondingly higher cardiovascular risk reductions.[3–6] In contrast, several studies have shown a significant association between statins and a higher risk of incident diabetes mellitus (DM).[7,8] However, this association is not clear in case of PCSK9 inhibitors. The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial showed nonsignificantly higher numbers of incident DM among participants receiving evolocumab.[9] Conversely, the ODYSSEY OUTCOMES (Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome) trial showed lesser risk of

From the Department of Medicine, West Virginia University, Morgantown, WV (S.U.K.); Departments of Medicine (H.R.) and Cardiovascular Medicine (S.S., E.K.), Guthrie Health System/Robert Packer Hospital, Sayre, PA; Center for Health Care Advancement and Outcomes, Baptist Health South Florida, Miami, FL (V.O.); Department of Internal Medicine, East Carolina University, Greenville, NC (V.O.); Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH (H.R., A.M.L.); Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL (M.S.K.); Division of Cardiology, Johns Hopkins Medical Institutions, Baltimore, MD (S.S.M., M.J.B.).

Accompanying Tables S1 through S5 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011581

Correspondence to: Safi U. Khan, MD, Department of Medicine, West Virginia University, One Medical Center Drive, Morgantown, WV. E-mail: safinmc@gmail.com

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Clinical Perspective

What Is New?

- Statins and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors reduce cardiovascular risk by reducing LDL (low-density lipoprotein) cholesterol.
- Statins are known to increase the risk of incident diabetes mellitus (DM), whereas randomized controlled trials have shown numerically higher cases of incident DM with PCSK9 inhibitor therapy.
- It is not clearly known whether LDL cholesterol reduction is associated with risk of incident DM and whether this risk might vary across established LDL cholesterol–lowering drugs.

What Are the Clinical Implications?

- This meta-analysis shows that among intensive lipid-lowering drugs, there was no independent association between LDL cholesterol reduction achieved by these medications and risk of incident DM.
- The increased risk of incident DM was associated with statins only; PCSK9 inhibitors did not show any association with DM.
- The current study further adds to the safety of LDL cholesterol lowering with regard to the risk of DM.

new onset of DM with alirocumab compared with placebo (9.6% versus 10.1%).[10] In a meta-analysis, exposure to LDL-C–lowering alleles in or near *NPC1L1* (Niemann-Pick C1-like 1) or *HMGCR* (3-hydroxy-3-methylglutaryl-CoA reductase), *PCSK9*, *ABCG5/G8* (ATP-binding cassette subfamily G member), and *LDLR* (LDL receptor), which encode the molecular targets of lipid-lowering therapies (ie, statins, ezetimibe, and PCSK9 inhibitors) were associated with higher risk of type 2 DM.[11]

Although the beneficial effects of LDL-C reduction on cardiovascular outcomes are clearly established, the degree of risk associated with reduction in LDL-C in terms of new-onset DM is unclear,[7,8] as is the potential heterogeneity of this effect by LDL-C–lowering drug class. To assess whether lowering LDL-C has any association with risk of incident DM and whether this risk varies by different, established LDL-C–lowering drugs, we performed a meta-analysis and metaregression analysis.

Methods

Data Availability Statement

The authors declare that all supporting data are available within the article (and its online supplementary files).

Data Sources and Searches

This systematic review and meta-analysis was conducted according to Cochrane Collaboration guidelines[12] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] Two authors (S.U.K. and H.R.) devised a broad search strategy by using relevant keywords (*statins, proprotein convertase subtilisin/kexin type 9 inhibitors, PCSK9 inhibitors, ezetimibe, low-density lipoprotein cholesterol, LDL-C, diabetes mellitus*; Table S1). We searched Medline (PubMed), Embase, and the Cochrane Central Register of Controlled Trials from the inception of the databases to November 15, 2018. Although search restrictions were applied for clinical trials and humans, no restrictions were applied for language, year of publication, or text availability. Additional sources included websites (European Society of Cardiology, https://www.escardio.org/; American College of Cardiology, https://www.acc.org and https://www.cardiosource.org; ClinicalTrialResults.com, http://www.clinicaltrialresults.com/; ClinicalTrials.gov, https://www.clinicaltrials.gov/), proceedings of major cardiology meetings, and references of the relevant articles. The citations were downloaded in Endnote X7 (Thompson ISI Research Soft), and duplicates were identified and removed. Two authors (M.S.K. and H.R.) independently screened the records based on prespecified inclusion criteria. Any disagreements were resolved by mutual consensus or third-party review (S.U.K.).

Study Selection

The following prespecified inclusion criteria were used. First, randomized controlled trials had to include at least 100 patients receiving the allocated pharmacological lipid-lowering therapy for a minimum of 12 weeks. Second, consistent with former reports,[1,2,6] we selected statin and nonstatin therapies in combination with statin that lower LDL-C levels via mechanisms that ultimately result in upregulation of LDL receptor (R) expression (ezetimibe and PCSK9 inhibitors [alirocumab and evolocumab]) compared with placebo or active controls. Third, studies had to report at least 1 clinical event for incident DM.

We excluded trials if (1) nonstatin therapy did not reduce LDL-C levels primarily via upregulation of LDLR expression (fibrates, niacin, and cholesteryl ester transfer protein inhibitors), (2) interventions showed concomitant effect on DM (bile acid sequestrants, ileal bypass surgery, exercise, and diet),[14–16] (3) findings of the study were reported as abstracts and do not have subsequent full-text publication (risk of having discrepancies between meeting abstract results and full-text publication),[17,18] and (4) trials assessing efficacy of bococizumab, which is not a therapeutic option because of immunogenicity.[19]

Data Extraction and Quality Assessment

Data extraction was performed by 2 independent authors (S.U.K. and H.R.) on a standard data collection form. The data abstraction was based on baseline characteristics of participants, treatment groups, events, total number of patients in each group, diabetic patients in each group, nondiabetic patients in each group (calculated as total patients minus diabetic patients), baseline LDL-C and reduction in LDL-C in each group, achieved LDL-C in each group and difference between the groups, and follow-up duration of each trial. We extracted data on incident DM using the methodology reported in a former study, namely, if the trial had clearly reported newly diagnosed DM as an adverse event or study participants had commenced antidiabetic drug treatment during the trial or if patients had 2 consecutive fasting blood glucose levels ≥126 mg/dL during the study period.[7]

The absolute change in LDL-C was calculated as mean or median difference, whichever was available, averaged over the course of follow-up between 2 groups. If not reported, then the achieved LDL-C value at the point closest to 50% of the median follow-up was used.[1] To assess the precision of calculated LDL-C values, we compared our results with the Cholesterol Treatment Trialists (CTT) collaboration meta-analysis[20] and a meta-analysis by Silverman et al.[1] In older studies, for which LDL-C was not available, we calculated the LDL-C from total cholesterol using the following regression equation: LDL-C=(total cholesterol)×[(total cholesterol)×0.0012+0.3793].[1] When available, we extracted data for intention to treat analysis. Any discrepancy related to data was resolved by discussion and referring to the original article. We also reviewed prior systematic reviews and meta-analyses for any additional information on the included studies in case the authors had reported further data beyond published trials in those meta-analyses.[1,7,8] The Cochrane Collaboration tool for bias risk assessment was used by 2 independent reviewers (V.O. and M.S.K.) to assess the quality of each trial (Table S2).[21]

More intensive lipid-lowering therapy was defined as a more potent pharmacological strategy, whereas *less intensive* lipid-lowering therapy corresponded to placebo/usual care or the active control group of the trial.[2,6] The group allocation was designated as such: (1) for statin versus placebo/usual care trials, statin therapy belonged to the more intensive therapy group and placebo/usual care was allocated to the less intensive therapy arm; (2) for higher intensive versus lower intensity statin trials, higher intensity statin was grouped with more intensive lipid-lowering therapy and less intensive statin was grouped with less intensive lipid-lowering therapy; and (3) for PCSK9 inhibitor trials, PCSK9 inhibitor therapy was grouped with more intensive lipid-lowering therapy and placebo/usual care or active control (ezetimibe) was grouped with less intensive lipid-lowering therapy.

Data Synthesis and Analysis

To account for potential between-study variance, estimates were pooled using a DerSimonian and Laird random-effects model.[22] The principal summary statistic was risk ratio (RR), supplemented by risk difference (RD) with 95% CI. Heterogeneity was assessed using Cochrane Q statistics and quantified by I^2 with values >25%, 50%, and 75% consistent with low, moderate, and high degrees of heterogeneity, respectively.[23] Publication bias was assessed using the funnel plot and Egger regression test.[24] Statistical significance was set at 5%.

Metaregression analyses were performed using random-effects models with the restricted maximum likelihood estimation. The Knapp and Hartung adjustment was applied for calculation of standard errors of the estimated coefficients to calculate summary effect estimates.[25] Metaregression analyses were conducted to estimate the associations among absolute amount of reduction in LDL-C (calculated as the difference in the achieved LDL-C between the 2 interventions),[1] percentage reduction in LDL-C (each 10%), baseline LDL-C, and absolute reduction in LDL-C adjusted for baseline LDL-C and incident DM. The index R^2 value (defined as the ratio of explained/total variance) was used to determine the proportion of variance accounted for by the change in LDL-C.

Subgroup analyses were conducted according to weighted between-group LDL-C differences observed at follow-up across the trials for particular lipid-lowering strategies as suggested by CTT collaboration meta-analysis[20] and interventions: statins, PCSK9 inhibitors, statins versus no statins, and high-intensity statins (atorvastatin 80 mg, simvastatin 80 mg, or rosuvastatin 40 mg) versus low-intensity statins (lesser doses of corresponding statin therapy [atorvastatin 10 mg, simvastatin 20–40 mg, and rosuvastatin up to 20 mg]). Additional sensitivity analyses included meta-analyses by fixed-effects model, analyses of trials with sample sizes of ≥500 patients that reported outcomes at follow-up ≥1 year, analyses according to year of publication,[6] and trials with the same definition for DM. Analyses were performed using Comprehensive Meta-Analysis software v3.0 (Biostat) and Metafor package v3.30 (R Project for Statistical Computing).

Results

The initial electronic search yielded 3711 citations, of which 1400 studies were removed as duplicates. Of the remaining 2311 articles, 1970 citations were excluded at title- and abstract-level screening. A total of 341 full-text articles were considered relevant, of which 308 were excluded based on a priori selection criteria. Ezetimibe data were presented as an abstract at the European Society of Cardiology Congress 2015 in subgroup analysis of IMPROVE IT (Improved

Reduction of Outcomes: Vytorin Efficacy International Trial), which showed no significant association of ezetimibe plus simvastatin versus simvastatin alone on incident DM (hazard ratio: 1.04; P=0.46).[26] This study was excluded based on a priori selection criteria, that is, if findings of that study were reported as abstracts and did not have subsequent full-text publication, the study would be excluded because of risk of discrepancies between abstract results and full-text publication. Ultimately, 33 trials met the criteria for the final list of studies (Figure 1).

Twenty-one trials of statins (124 755 patients) and 12 trials of PCSK9 inhibitors (38 933 patients) reported incident DM (Table 1).[9,10,27–56] The pooled mean baseline LDL-C was 3.37±0.71 mmol/L, and mean follow-up duration was 4.2±1.2 years. A total of 163 688 nondiabetic patients were randomly assigned to more intensive (83 123 patients) or less-intensive (80 565 patients) lipid-lowering therapy. A total of 9855 (6.0%) incident DM cases were reported in the total study population. Additional characteristics of included trials are reported in Table S3.

Metaregression analysis did not demonstrate significant association between absolute reduction in LDL-C (for every 1 mmol/L) and incident DM for more intensive lipid-lowering therapy (RR: 0.95; 95% CI, 0.87–1.04; P=0.30; R^2=14%; RD: −0.002; 95% CI, −0.006 to 0.002; P=0.32; R^2=0; Figure 2), for statins (RR: 1.02; 95% CI, 0.91–1.14; P=0.67; R^2=0; RD: −0.002; 95% CI, −0.007 to 0.003; P=0.44; R^2=0), or for PCSK9 inhibitors (RR: 1.09; 95% CI, 0.60–1.99; P=0.74; R^2=0; RD: 0.009; 95% CI, −0.010 to 0.028; P=0.37; R^2=0). This effect remained consistent for change in baseline LDL-C values and absolute reduction in LDL-C adjusted for baseline LDL-C (Table 2). Similarly, more intensive lipid-lowering therapy (RR: 0.99; 95% CI, 0.97–1.01; P=0.48; R^2=0; RD: −0.0002; 95% CI, −0.0001 to 0.0001; P=0.74; R^2=0; Figure 3), statins (RR: 1.00; 95% CI, 0.99–1.00; P=0.18; R^2=0; RD: 0.00007; 95% CI, −0.0001 to 0.0003; P=0.52; R^2=0), or PCSK9 inhibitors (RR: 1.04; 95% CI, 0.98–1.11; P=0.12; R^2=0.27; RD: 0.0007; 95% CI, −0.0007 to 0.002; P=0.28; R^2=0.59) showed consistent nonsignificant association with risk of incident DM per 10% reduction in LDL-C values.

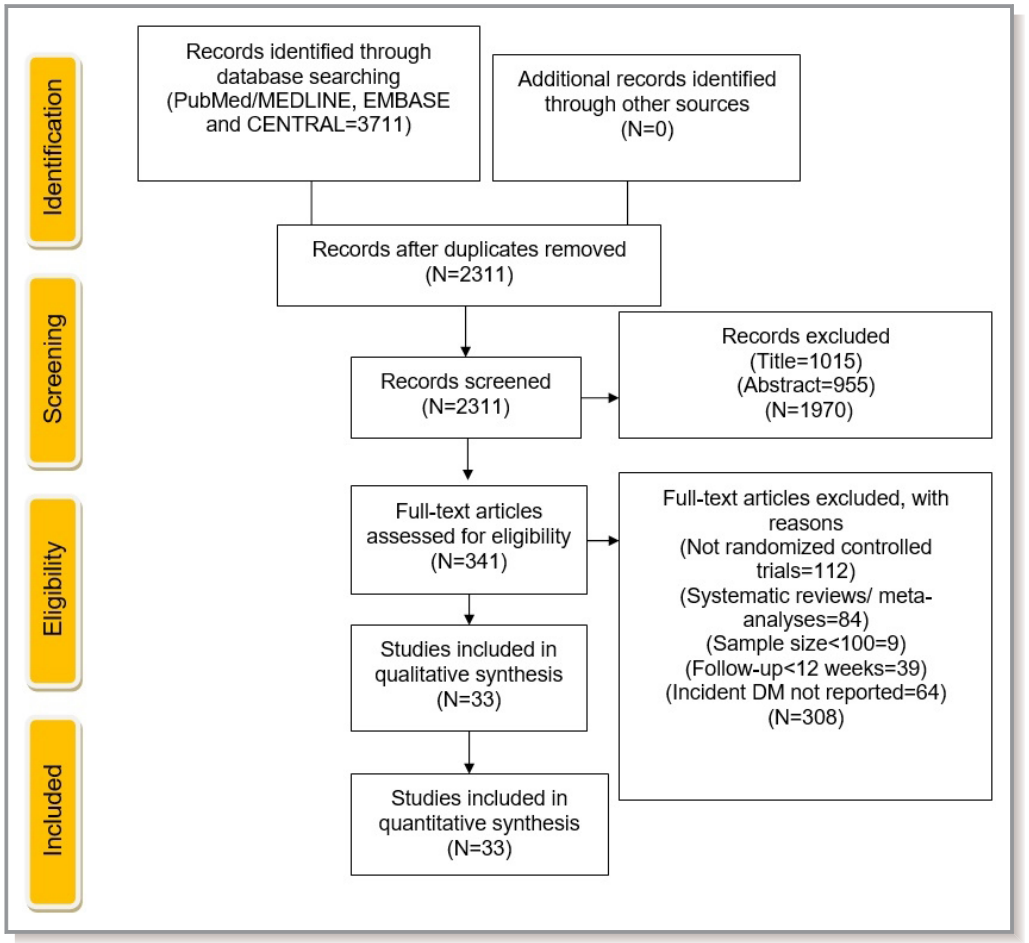

Figure 1. Study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. CENTRAL indicates Cochrane Central Register of Controlled Trials; DM, diabetes mellitus.

Table 1. Baseline Characteristics of Studies and Population Meeting Inclusion Criteria

Studies	Diabetic/Nondiabetic Patients, n (%)	Trial Population	Baseline LDL-C (mmol/L)	Between-Group Difference in Achieved LDL-C (mmol/L)	Diagnostic Criteria for Incident DM	Follow-up (wk)
Statin						
PMSGCRP (1993)[30]	1/1062 (0.1)	Hypercholesterolemia + ≥2 atherosclerotic CVD risk factors	4.68	2.01	Adverse event reported; medication	161
4S (1994)[56]	391/4242 (9.2)	Previous angina or MI	4.88	1.75	Adverse event reported; medication; 1 FBG ≥126 mg/dL	281
WOSCOPS (1995)[31]	168/5974 (2.8)	Hypercholesterolemia	4.96	0.98	Two FBG ≥126 mg/dL	250
LIPID (1998)[32]	264/6997 (3.8)	Unstable angina or MI within past 3 y	3.88	0.97	One FBG ≥126 mg/dL; medication	318
AFCAPS/TexCAPS (1998)[33]	146/6211 (2.4)	Hypercholesterolemia	3.89	1.08	Adverse event reported; medication; 1 FBG ≥126 mg/dL	271
GISSI PREV (2000)[34]	201/3460 (5.8)	MI within past 6 mo	3.92	0.35	Adverse event reported; 1 FBG ≥126 mg/dL	166
ALLHAT-LLT (2002)[29]	451/6087 (7.4)	CHD or risk factors for CHD	3.76	0.62	Adverse event reported; 1 FBG ≥126 mg/dL	250
GREACE (2002)[35]	54/1287 (4.2)	CHD	4.64	1.86	Adverse event reported; medication	156
PROSPER (2002)[36]	292/5181 (5.6)	Elderly patients with CHD or carrying high risk for CHD	3.79	1.03	One FBG ≥126 mg/dL; medication	156
HPS (2003)[37]	628/14 573 (4.3)	High risk of cardiovascular events	3.38	1.29	Adverse event reported; medication	260
ASCOT-LLA (2003)[38]	249/5860 (4.2)	Hypertension, risk factors for CHD	3.44	1.20	WHO 1999 criteria	172
A to Z (2004)[39]	112/3504 (3.2)	ACS	2.09	0.36	Adverse event reported; medication; 2 FBG ≥126 mg/dL; medication	104
PROVE IT (2004)[40]	200/3395 (5.9)	ACS	2.62	0.84	Adverse event reported; medication; 2 FBG ≥126 mg/dL; medication	156
IDEAL (2005)[41]	449/7461 (6.0)	History of previous MI	2.64	0.56	Adverse event reported; medication; 2 FBG ≥126 mg/dL; medication	250
TNT (2005)[42]	776/7595 (10.2)	CHD	2.52	0.62	Adverse event reported; medication; 2 FBG ≥126 mg/dL; medication	255
MEGA (2006)[43]	336/6086 (5.5)	Hypercholesterolemia without history of MI or stroke	4.05	0.59	Adverse event reported; medication; 2 FBG ≥126 mg/dL	276
CORONA (2007)[44]	188/3534 (5.3)	Elderly patients with systolic HF	3.55	1.61	Adverse event reported	140
GISSI-HF (2008)[45]	440/3378 (13.0)	Chronic HF	3.06	0.75	2 FBG ≥126 mg/dL	203
JUPITER (2008)[46]	486/17 802 (2.7)	No history of CHD	2.70	1.42	Adverse event reported; medication, OGTT positive, elevated random glucose with symptoms, 2 FBG ≥126 mg/dL	260

Continued

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Table 1. Continued

Studies	Diabetic/Nondiabetic Patients, n (%)	Trial Population	Baseline LDL-C (mmol/L)	Between-Group Difference in Achieved LDL-C (mmol/L)	Diagnostic Criteria for Incident DM	Follow-up (wk)
ASTRONOMER (2010)[47]	1/269 (0.4)	Mild to moderate aortic stenosis	3.15	1.67	Adverse event reported	182
SEARCH (2010)[27]	1212/10 797 (11.2)	History of previous MI	2.50	0.35	Adverse event reported; medication; 2 FBG ≥126 mg/dL; medication	349
PCSK9 inhibitor						
ODYSSEY OPTIONS I (2015)[48]	4/103 (3.9)	High risk for CVD	2.77	0.66	Adverse event reported; medication	32
ODYSSEY FH I (2015)[49]	10/429 (2.3)	Heterozygous FH	3.70	1.44	Adverse event reported; medication	78
ODYSSEY FH II (2015)[49]	10/239 (4.2)	Heterozygous FH	3.50	1.55	Adverse event reported; medication	78
ODYSSEY LONG TERM (2015)[50]	28/1503 (1.9)	Heterozygous FH or CHD or equivalent	3.16	1.83	Adverse event reported; medication	78
OSLER (2015)[51]	45/3866 (1.2)	Population from 12 different trials including patients with high risk for CHD; heterozygous FH	3.10	1.86	Adverse event reported; medication	56
GLAGOV (2016)[28]	35/766 (4.6)	CHD	2.39	1.46	Adverse event reported	78
ODYSSEY OPTIONS II (2016)[55]	4/103 (2.4)	Hypercholesterolemia; high risk for CVD	2.81	0.52	Adverse event reported	24
ODYSSEY CHOICE I (2016)[52]	14/586 (2.4)	High risk for CVD	3.24	2.02	Adverse event reported; diabetes mellitus or microvascular complications using coding system.	56
ODYSSEY JAPAN (2016)[53]	16/201 (8.0)	Heterozygous FH; high risk for CVD	3.70	2.25	Adverse event reported; medication	52
YUKAWA-2 (2016)[54]	1/207 (0.5)	High risk for CVD	3.6	2.30	Adverse event reported; medication	12
FOURIER (2017)[9]	1321/17 451 (7.6)	Atherosclerotic CVD	2.38	1.40	Adverse event reported; new-onset DM defined based on ADA and NDIC, ie, 2 FBG ≥126 mg/dL	115
ODYSSEY OUTCOMES (2018)[10]	1324/13 459 (9.8)	Recent ACS	2.38	1.70	Adverse event reported	146

Values are reported as mean or median, whichever was available. ADA. American Diabetes Association; ACS indicates acute coronary syndrome; A to Z, Aggrastat to Zocor; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trials; ASCOT-LLA, Prevention of Coronary and Stroke Events With Atorvastatin in Hypertensive Patients Who Have Average or Lower-Than-Average Cholesterol Concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; ASTRONOMER, Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin; CHD, coronary heart disease; CORONA, Controlled Rosuvastatin in Multinational Trial in Heart Failure; CVD, cardiovascular disease; DM, diabetes mellitus; FBG, fasting blood glucose; FH, familial hypercholesterolemia; 4S, Scandinavian Simvastatin Survival Study; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GISSI PREV, Gruppoltaliano per lo Studio dellaSopravvivenzanell'InfartoMiocardico; GISSI HF, The Gruppoltaliano per lo Studio dellaSopravvivenzanell'Insufficienza Cardiac–Heart Failure; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; GREACE, Greek Atorvastatin and Coronary-Heart-Disease Evaluation; HF, heart failure; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, LDL (low-density lipoprotein) cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group; MI, myocardial infarction; NDIC, National Diabetes Information Clearinghouse; ODYSSEY CHOICE I, Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia; ODYSSEY FH I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; ODYSSEY FH II, Study of Alirocumab (REGN727/SAR236553) in Patients With heFH (Heterozygous Familial Hypercholesterolemia) Who Are Not Adequately Controlled With Their LMT (Lipid-Modifying Therapy); 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 OPTIONS I, Study of the Efficacy and Safety of Alirocumab (REGN727/SAR236553) in Combination With Other Lipid-Modifying Treatment; ODYSSEY OPTIONS II, Study of Alirocumab (REGN727/SAR236553) Added-On to Rosuvastatin Versus Other Lipid Modifying Treatments; ODYSSEY OUTCOMES, Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome; OSLER, Open-Label Study of 12 Early Phase 2–3 Trials; PCSK9, proprotein convertase subtilisin/kexin type 9; PMSGCRP, Pravastatin Multinational Study Group for Cardiac Risk Patients; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; OGTT, Oral Glucose Tolerance Test; PROSPER, Pravastatin in Elderly Individuals at Risk of Vascular Disease; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets; WHO, World Health Organization; WOSCOPS, West of Scotland Coronary Prevention Study Group; YUKAWA-2, Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

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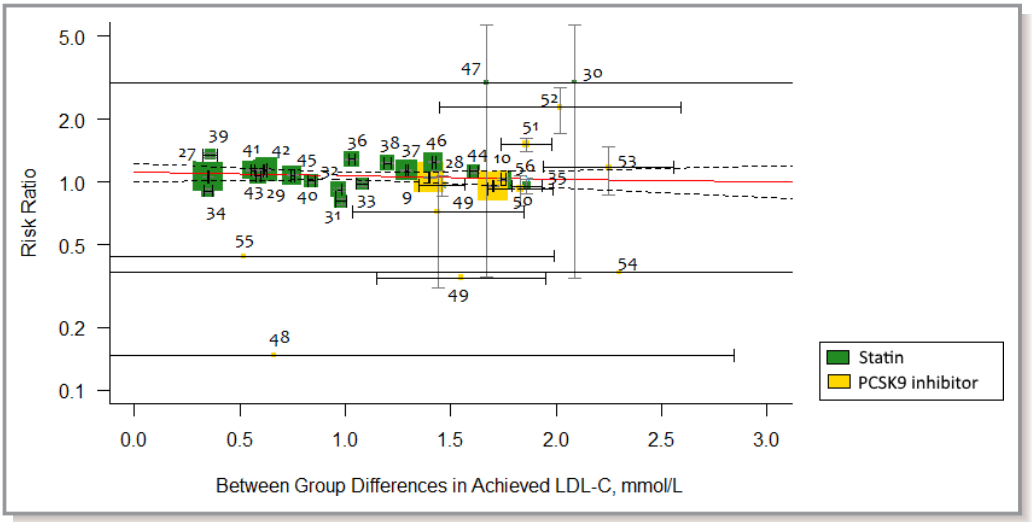

Figure 2. Metaregression showing association of between-group differences in achieved LDL (low-density lipoprotein) cholesterol (LDL-C) levels (mmol/L) and risk ratio of incident diabetes mellitus. Each trial is represented by a data marker, the size of which is proportional to the weight in the metaregression. The metaregression slope (predicted risk for degree of LDL-C reduction) is represented by a red line, and 95% CIs are presented as dashed lines. The horizontal lines through each square represent ±1 SE for the associated absolute change in LDL-C, and the vertical line through each square represents the 95% CI for relative risk. For converting millimoles to milligrams, multiply by 38.5. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

In sensitivity analysis for trials with ≥500 patients and follow-up ≥1 year, more intensive lipid-lowering therapy (RR: 0.96; 95% CI, 0.88–1.05; P=0.41; R^2=16%; RD: −0.002; 95% CI, −0.006 to 0.002; P=0.31; R^2=0), statins (RR: 1.02; 95% CI, 0.91–1.13; P=0.64; R^2=0; RD: −0.001; 95% CI, −0.007 to 0.003; P=0.49; R^2=0), and PCSK9 inhibitors (RR: 0.77; 95% CI, 0.48–1.20; P=0.26; R^2=0; RD: −0.001; 95% CI, −0.022 to 0.020; P=0.93; R^2=0) were not significantly associated with incident DM per 1-mmol/L decrease in LDL-C. Meta-analysis stratified according to between-group difference LDL-C achieved across lipid-lowering strategies did not show significant association (P=0.07 for interaction; Figure 4).

Meta-analysis of the entire population showed that 6.1% (5121/83 123) of patients had incident DM with the more intensive lipid-lowering therapy versus 5.8% (4734/80 565) with the less intensive lipid-lowering therapy. More intensive lipid-lowering therapy was associated with a higher risk of incident DM compared with less intensive therapy (RR: 1.07; 95% CI, 1.03–1.11; P<0.001; I^2=0%; RD: 0.003; 95% CI, 0.001–0.006; P=0.002; I^2=23%; Figure 5). These results were

Table 2. Metaregression Analyses for the Associations of LDL-C With Incident DM

	Studies	Patients	RR (95% CI)		
			Reduction of LDL-C, per 1 mmol/L	Increase in Baseline LDL-C, per 1 mmol/L	Reduction of LDL-C Adjusted for Baseline LDL-C
Total population					
More intensive lipid-lowering therapy	33	163 688	0.95 (0.87–1.04)	0.97 (0.91–1.03)	0.97 (0.87–1.07)
Statins	21	124 755	1.02 (0.91–1.14)	0.94 (0.88–1.01)	1.11 (0.98–1.28)
PCSK9 inhibitors	12	38 933	1.09 (0.60–1.99)	0.95 (0.62–1.43)	1.69 (0.71–4.05)
Trials with sample size of ≥500 patients which reported outcome at follow-up ≥1 y					
More intensive lipid-lowering therapy	25	161 531	0.96 (0.88–1.05)	0.98 (0.91–1.03)	0.97 (0.87–1.07)
Statins	20	124 486	1.02 (0.91–1.13)	0.94 (0.88–1.01)	1.11 (0.99–1.28)
PCSK9 inhibitors	5	37 045	0.77 (0.48–1.20)	1.28 (0.65–2.53)	0.71 (0.44–1.15)

DM indicates diabetes mellitus; LDL-C, LDL (low-density lipoprotein) cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; RR, risk ratio.

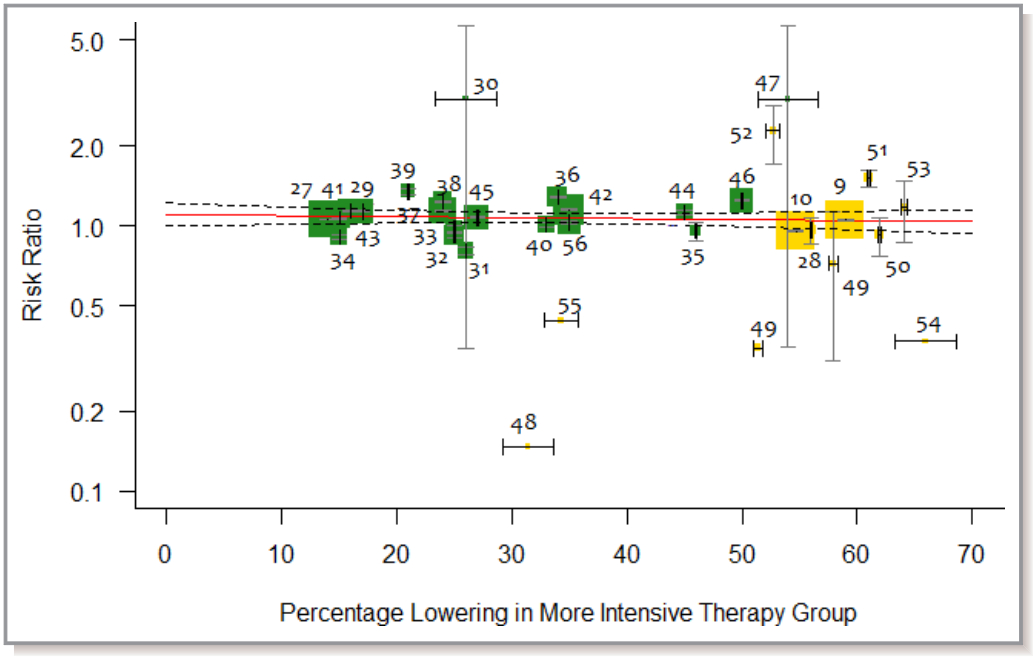

Figure 3. Metaregression showing association between percentage reduction of LDL (low-density lipoprotein) cholesterol (LDL-C) in the active arm and relative risk of incident diabetes mellitus. Each trial is represented by a data marker, the size of which is proportional to the weight in the metaregression. The metaregression slope (predicted risk for degree of LDL-C reduction) is represented by a red line, and 95% CIs are presented as dashed lines. The horizontal lines through each square represent ±1 SE for the associated absolute change in LDL-C, and the vertical line through each square represents the 95% CI for relative risk.

driven by higher risk of incident DM with statins (RR: 1.10; 95% CI, 1.05–1.15; $P<0.001$; $I^2=14\%$; RD: 0.004; 95% CI, 0.002–0.006; $P=0.001$; $I^2=13\%$), whereas PCSK9 inhibitors were not associated with significant risk of incident DM (RR: 1.00; 95% CI, 0.93–1.07; $P=0.96$; $I^2=0\%$; RD: 0.001; 95% CI, −0.004 to 0.006; $P=0.75$; $I^2=11\%$; $P=0.02$ for interaction). The higher risk of DM remained consistent when statins were compared with no statins (RR: 1.09; 95% CI, 1.03–1.16; $P=0.01$; $I^2=8\%$; RD: 0.003; 95% CI, 0.001–0.006; $P=0.01$; $I^2=0\%$) or high-intensity statins versus low-intensity statins (RR: 1.11; 95% CI, 1.03–1.19; $P<0.001$; $I^2=0\%$; RD: 0.009; 95% CI, 0.003–0.014; $P=0.002$; $I^2=16\%$; $P=0.72$ for interaction; Figure 6). Sensitivity analysis for trials with ≥500 patients and follow-up ≥1 year showed consistent results ($P=0.03$ for interaction; Figure 7). Meta-analysis according to the fixed-effects model (Table S4) or sensitivity analyses according to year of publication and definition of DM showed consistent results (Table S5). The Egger regression test did not detect publication bias (Figure S1).

Discussion

In this meta-analysis we report that over a mean follow-up duration of 4 years, metaregression analysis did not show significant association between reduction in LDL-C by more intensive lipid-lowering therapy and risk of incident DM. The 7% RR and 0.3% absolute risk of incident DM across more intensive lipid-lowering strategy was driven by 10% higher RR and 0.4% absolute risk with statins. Conversely, PCSK9 inhibitors in the setting of background statin therapy were not associated with significant risk of incident DM. These results suggest that among the intensive lipid-lowering strategies, the modest risk of incident DM may be prominent with statins only.

Statin-induced DM is a much discussed phenomenon.[7,8,57] The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial showed a 25% increase in incident DM (physician reported) over a median follow-up of 1.9 years with rosuvastatin 20 mg compared with placebo.[58] This conclusion was also supported by Sattar and colleagues (13 trials, 91 140 patients), showing 9% increased relative risk of incident DM with statins over a mean duration of 4 years,[8] and Preiss et al in their comparison of more intensive statin therapy with moderate-intensity statin therapy.[7]

The exact mechanism of statin-induced DM remains unclear, and various mechanisms have been postulated to explain this association. First, statins may derange the glucose metabolism by negative effects on both β-cell secretion and insulin sensitivity. For example, the METSIM (Metabolic Syndrome in Men) study (9749 patients) showed 46% increased relative risk of type 2 DM, 24% reduction in insulin sensitivity, and 12%

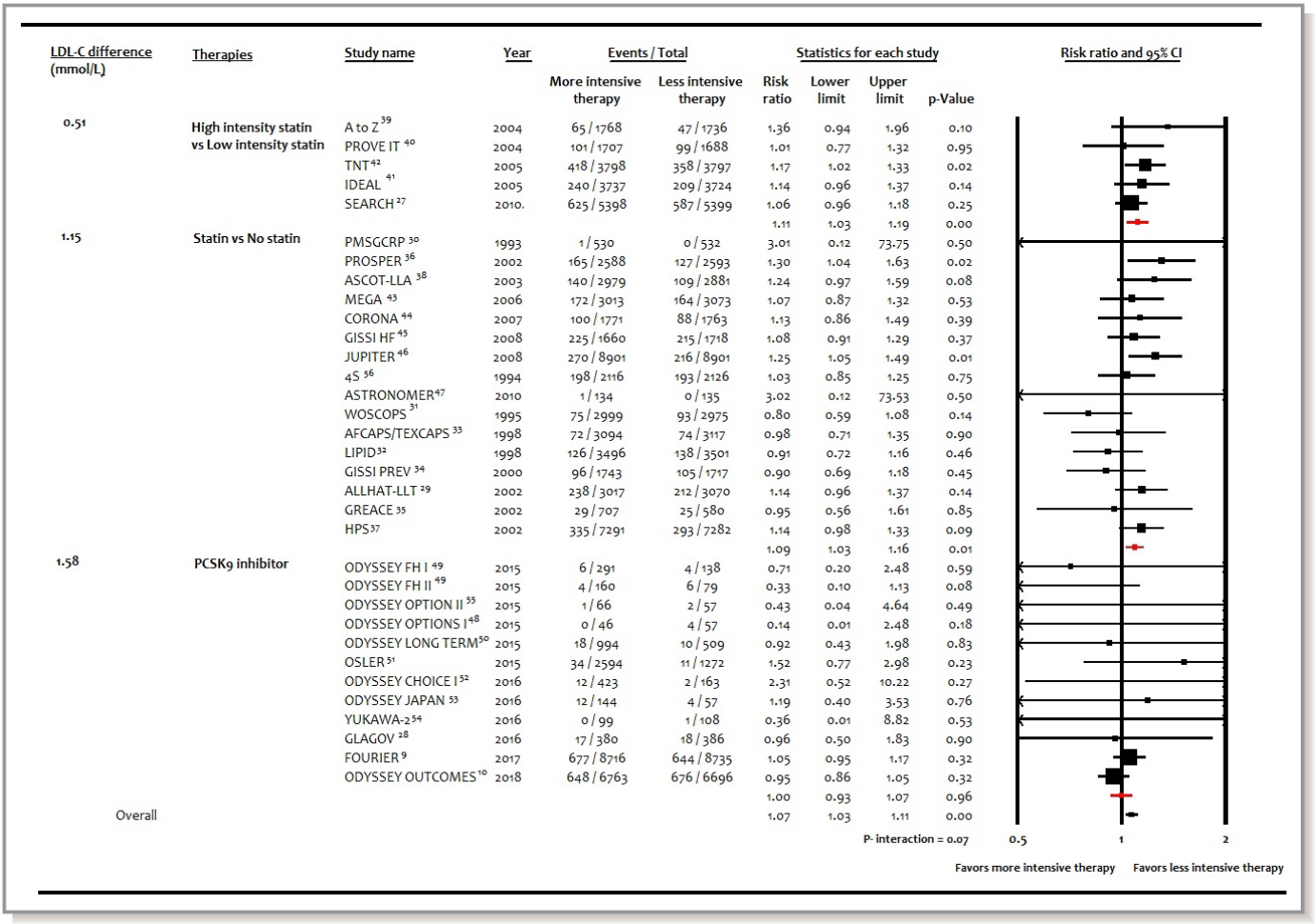

Figure 4. Forest plot showing subgroup analysis according to weighted between-group difference in LDL (low-density lipoprotein) cholesterol (LDL-C) achieved (mmol/L) among interventions and risk of incident diabetes mellitus. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

reduction in insulin secretion in patients taking statins.[59] It is proposed that β-cell dysfunction might be related to LDLR-mediated increased levels of intracellular cholesterol. Studies with murine experimental models have shown that the addition of LDL-C to culture medium of rat islet β cells resulted in cell death.[60,61] To further explore this concept, Besseling et al conducted a study in patients with familial hypercholesteremia (63 320 patients) and showed that prevalence of type 2 DM was significantly lower in familial hypercholesteremia patients than unaffected relatives (1.75% versus 2.93%, $P<0.001$).[62] Hypercholesteremia in familial hypercholesteremia is caused by genetically impaired LDLR-mediated transcellular cholesterol transport, whereas, conversely, HMGCR inhibition by statins promotes transmembranous cholesterol uptake by increasing expression of LDLR; therefore, the authors proposed that there might be a causal relationship between LDLR-mediated increased internalization of cholesterol into pancreatic β cells and impaired insulin secretion.[62]

Second, animal studies have suggested that statin-induced myopathy occurs because of development of muscle insulin resistance[63]; using this evidence, Preiss et al hypothesized that the risk might be related to the effect of statins on insulin sensitivity in muscle and liver.[7]

Third, weight gain may play a causal role in development of DM by increasing insulin resistance. Swerdlow et al studied single-nucleotide polymorphism in *HMGCR* genes and used rs17238484 and rs12916 as proxies for HMGCR inhibition by statins.[57] This meta-analysis of 43 genetic studies (223 463 patients) showed that these *HMGCR* single-nucleotide polymorphisms were associated with higher body weight, waist circumference, lower LDL-C, and increased plasma glucose concentration.

Finally, genetic data have shown a potential association between LDL-C lowering and incident DM. Lotta et al demonstrated that LDL-C–lowering alleles in or near *HMGCR* were associated with higher risk of type 2 DM (odds ratio: 1.39; $P=0.03$).[11] Although the possibility of other mechanisms cannot be excluded, the pooled analyses of randomized controlled trials could not strongly demonstrate an association between lowering LDL-C and incident DM.[8,64]

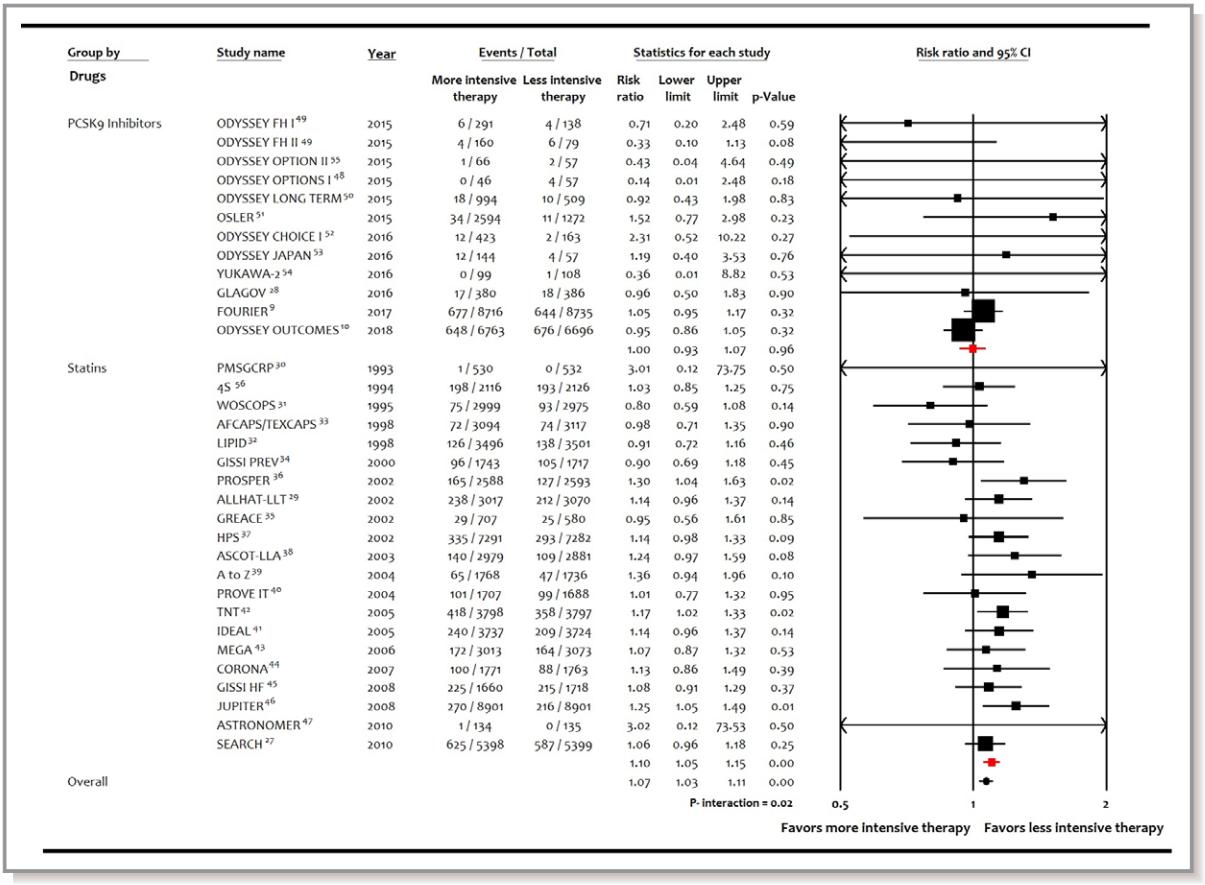

Figure 5. Forest plot comparing risk of incident diabetes mellitus among interventions. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

Lotta and colleagues reported that genetic variants in PCSK9 were associated with a 19% (95% CI, 2–38%) higher RR for DM per 1-mmol/L reduction in LDL-C.[11] On the same note, PCSK9 inhibitor trials also hinted at a potential association of PCSK9 inhibitors with new-onset DM. In FOURIER, the risk of incident DM was numerically higher

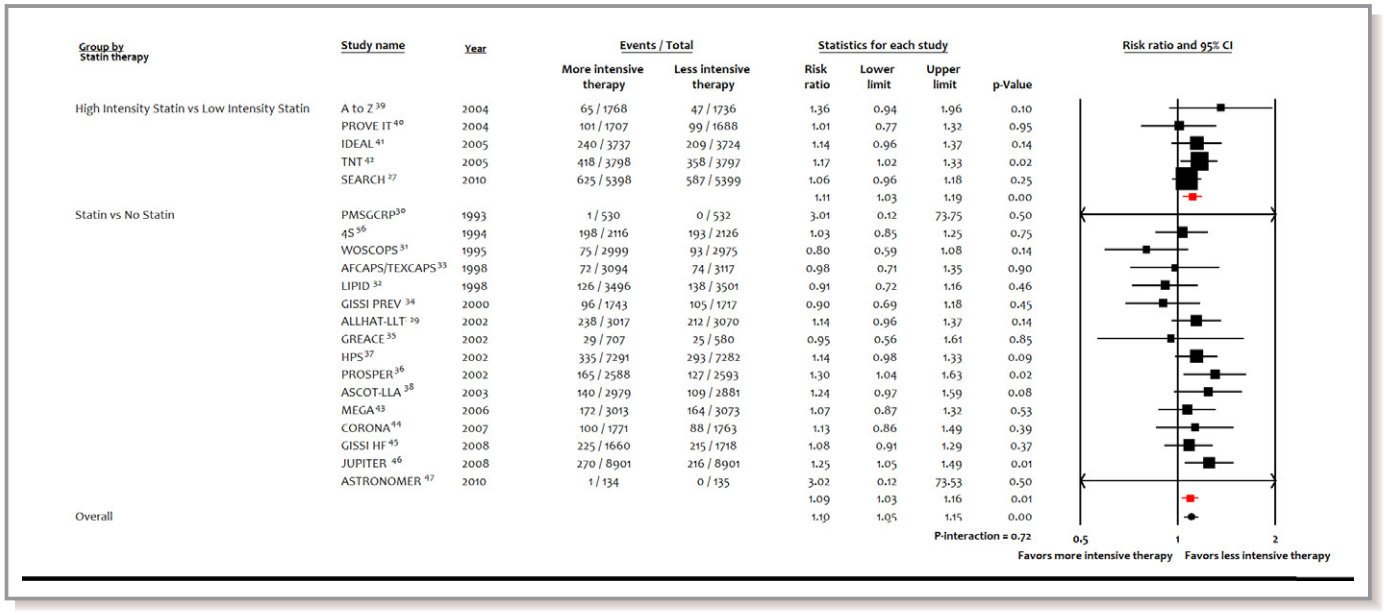

Figure 6. Sensitivity analysis, forest plot showing subgroup analysis of statin therapy on incident diabetes mellitus.

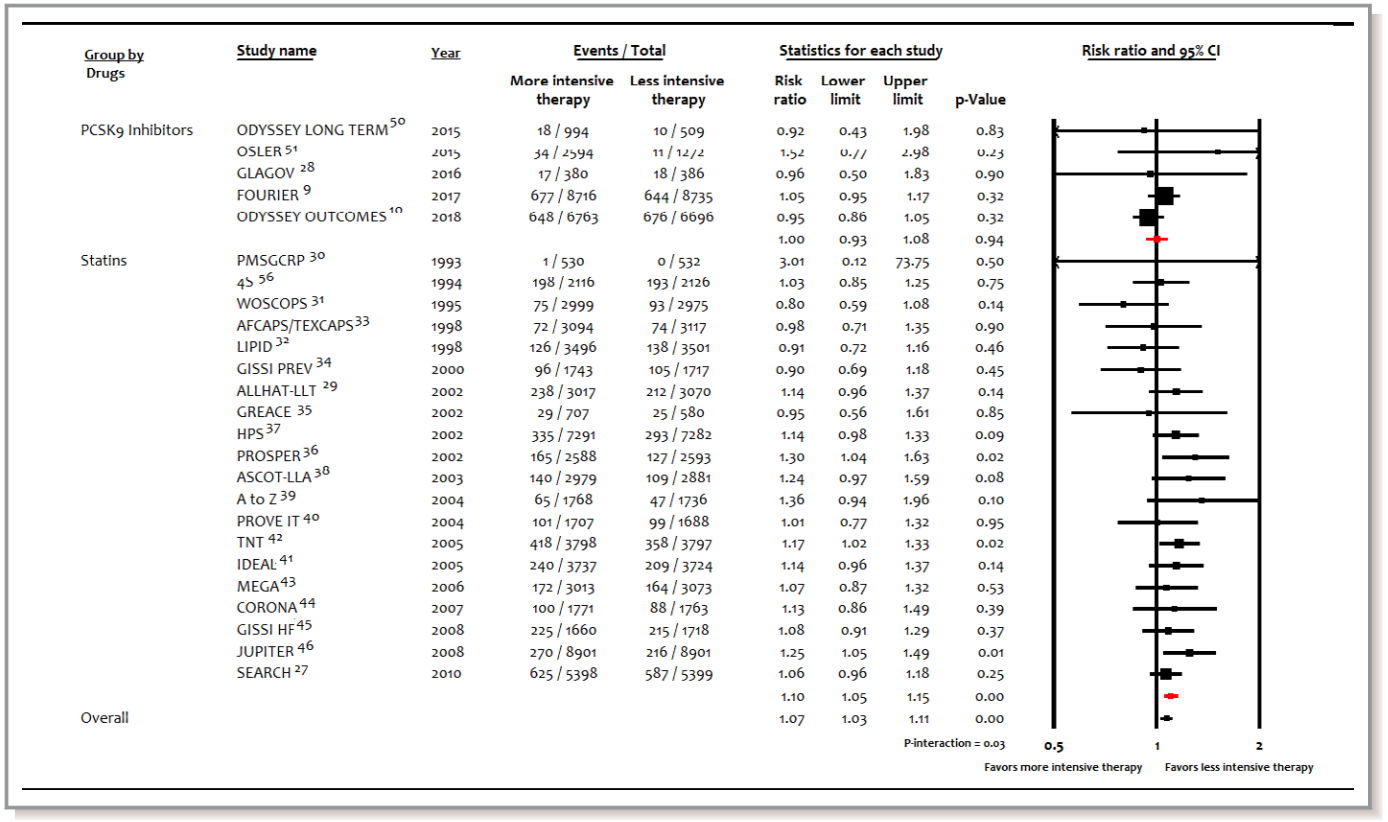

Figure 7. Sensitivity analysis, forest plot comparing risk of incident diabetes mellitus among interventions in trials with sample sizes ≥500 patients and follow-up ≥1 year. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

with PCSK9 inhibitors (hazard ratio: 1.05; *P*=0.34).[9] However, in a prespecified analysis of the FOURIER trial, evolocumab did not increase the risk of new-onset DM in nondiabetic patients (hazard ratio: 1.05; 95% CI, 0.94–1.17) or those with prediabetes (hazard ratio: 1.00; 95% CI, 0.89–1.13).[65] Similarly, the ODYSSEY OUTCOME trial showed fewer participants with incident DM with PCSK9 inhibitor use compared with placebo.[10]

We critically compared our results with prior meta-analyses. Sattar and colleagues showed significantly higher risk of incident DM with statins, but metaregression analysis did not demonstrate an association between change in LDL-C and risk of incident DM.[8] Meta-analysis by Preiss et al (5 statin trials, 32 752 patients) showed 12% relative risk of incident DM with intensive-dose statin therapy compared with moderate-dose statin therapy.[7] De Carvalho et al meta-analyzed 20 randomized controlled trials (68 123 patients) of PCSK9 therapy to investigate its association with incident type 2 DM.[66] They reported that during a median follow-up of 78 weeks, PCSK9 inhibitors increased fasting blood glucose by 1.88 mg/dL and HbA1c by 0.032%; however, this effect did not translate into increased incidence of DM (RR: 1.04; *P*=0.42). In a metaregression analysis, they showed a 3.8% increase in DM for each 10% lowering of LDL-C levels; however, this study included the SPIRE trial, which does not reflect contemporary PCSK9 inhibitor therapy. Conversely, findings of Cao et al were consistent with our outcomes.[64] Both studies were published before ODYSSEY OUTCOMES and thus lacked this large data set.[10] To our knowledge, our current study is the largest updated meta-analysis that, in addition to systematically evaluating the association of LDL-C reduction with incident DM, has quantitatively compared the effects of statins and PCSK9 inhibitors to provide a more comprehensive overview of this issue.

The current study is subject to limitations. First, this study is a trial-level meta-analysis, and given lack of access to the individual patient data, we could not adjust our analysis for various comorbidities and baseline characteristics such as age, body mass index, baseline fasting blood glucose level, or HbA1c. Therefore, a patient-level meta-analysis could provide more valuable information to further evaluate such associations. Second, PCSK9 inhibitors were conducted in the background of statins. Third, it is important to note that the definition of incident DM was not uniform across the trials. Specifically, most trials reported nonadjudicated outcomes of incident DM; however, we tried to compensate for this by performing sensitivity analyses. Fourth, we could not detect publication bias; that said, because of exclusion of a notable number of trials that did not report incident

DM, a certain degree of publication bias could not be completely excluded. Finally, like any meta-analysis, this report is limited by heterogeneity in baseline characteristics, sample sizes, drugs, and durations of studies. Nevertheless, the results had low statistical heterogeneity, and we tried to compensate for variability in sample size and follow-up duration through sensitivity analysis.

In conclusion, the current study does not demonstrate an association between degree of LDL-C lowering by contemporary lipid-lowering therapies and risk of incident DM. Among intense lipid-lowering therapies, the risk of DM was higher with statins only, whereas PCSK9 inhibitors (in setting of background statin therapy) did not show a significant association with incident DM.

Disclosures

Blaha is on advisory boards for Amgen, Sanofi, Regeneron, Novartis, MedImmune, Medicure and receives grants from Amgen Foundation. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Search strategy.

Search String	("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields]) OR (("proprotein convertases"[MeSH Terms] OR ("proprotein"[All Fields] AND "convertases"[All Fields]) OR "proprotein convertases"[All Fields] OR ("proprotein"[All Fields] AND "convertase"[All Fields]) OR "proprotein convertase"[All Fields]) AND subtilisin/kexin[All Fields] AND type[All Fields] AND 9[All Fields] AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields])) OR (pcsk[All Fields] AND 9[All Fields] AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields])) OR ("ezetimibe"[MeSH Terms] OR "ezetimibe"[All Fields]) AND ("cholesterol, ldl"[MeSH Terms] OR ("cholesterol"[All Fields] AND "ldl"[All Fields]) OR "ldl cholesterol"[All Fields] OR ("low"[All Fields] AND "density"[All Fields] AND "lipoprotein"[All Fields] AND "cholesterol"[All Fields]) OR "low density lipoprotein cholesterol"[All Fields]) OR ldl-c[All Fields] AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields])

Table S2. Cochrane Quality risk assessment.

Studies	Randomization	Allocation concealment	Blinding (Physician/Patient)	Adjudication of outcomes	Selective outcome reporting	Incomplete data reporting addressed?	Free of other bias?
Statins							
PMSGCRP (1993)[1]	Low risk	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
4S (1994)[2]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
WOSCOP (1995)[3]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
LIPID (1998)[4]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
AFCAPS/TexCAPS (1998)[5]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
GISSI PREV (2000)[6]	Moderate risk	Moderate risk	High risk	Moderate risk	Low risk	Moderate risk	Moderate risk
ALLHAT-LLT (2002)[7]	Low risk	Low risk	High risk	Low risk	Low risk	Moderate risk	Moderate risk
GREACE (2002)[8]	Low risk	Moderate risk	High risk	Low risk	Low risk	Low risk	Low risk
PROSPER (2002)[9]	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
HPS (2003)[10]	Low risk	Moderate risk	Low risk	Low risk	High risk	Low risk	Moderate risk
ASCOT-LLA (2003)[11]	Low risk	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
A to Z (2004)[12]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
PROVE IT (2004)[13]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
IDEAL (2005)[14]	Moderate risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate risk

TNT (2005)[15]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
MEGA (2006)[16]	Low risk	Moderate risk	High risk	Low risk	High risk	Low risk	Low risk
CORONA (2007)[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
GISSI-HF (2008)[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
JUPITER (2008)[19]	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
ASTRONOMER (2010)[20]	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
SEARCH (2010)[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PCSK 9 inhibitors							
ODYSSEY OPTION I (2015)[22]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY FH I (2015)[23]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY FH II (2015)[23]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY LONG TERM (2015)[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
OSLER (2015)[25]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
GLAGOV (2016)[26]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY CHOICE I (2016)[27]	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
ODYSSEY JAPAN (2016)[28]	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
YUKAWA-2 (2016)[29]	Low risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY OPTION II (2016)[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

FOURIER (2017)[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ODYSSEY OUTCOMES (2018)[32]	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk

Table S3. Baseline characteristics of the entire study population for each trial.

Studies (Year)	N	Groups	Age (years)	Men (%)	Coronary heart disease (%)	Hypertension (%)	Smoking (%)
PMSGCRP (1993)[1]	1,062	Pravastatin 20 mg	55	77	32	47	28
		Placebo	55	76	36	48	30
4S (1994)[2]	4,444	Simvastatin 20-40 mg	58.6	82	100	26	24
		Placebo	58.6	81	100	26	27
WOSCOPS (1995)[3]	6,595	Pravastatin 40 mg	55.3	100	0.0	16	44
		Placebo	55.1	100	0.0	15	44
LIPID (1998)[4]	9,014	Pravastatin 40 mg	62	83	100	41	9
		Placebo	62	83	100	42	10
AFCAPS/TexCAPS (1998)[5]	6,605	Lovastatin 20-40 mg	58	85	0.0	22	13
		Placebo	58	85	0.0	22	12
GISSI PREV (2000)[6]	3, 460	Pravastatin 20 mg	59.3	86.3	–	36.5	11.8
		Usual care					
ALLHAT-LLT (2002)[7]	10,355	Pravastatin 40 mg	66.4	51.4	13.4	89.8	23.1
		Usual care	66.3	51.0	15.0	89.9	23.3
GREACE (2002)[8]	1,600	Atorvastatin 80 mg	58	78	100	42	NR

		Usual care	59	79	100	44	NR
PROSPER (2002)[9]	5,804	Pravastatin 40 mg	75.4	48.3	45.2	62.2	26.0
		Placebo	75.3	48.3	43.2	61.6	27.6
HPS (2003)[10]	20,536	Simvastatin 40 mg	87	86	87	—	—
		Placebo	23	18	22	—	—
ASCOT-LLA (2003)[11]	10,342	Atorvastatin 10 mg	63.1	81.1	0.0	—	33.2
		Placebo	63.2	81.3	0.0	—	32.2
A to Z (2004)[12]	4,497	Simvastatin 20mg	61	75	16	50	41
		Simvastatin 40/80 mg	61	76	18	50	41
PROVE IT (2004)[13]	4,162	Pravastatin 40 mg	58.3	78.4	100	49.2	37.1
		Atorvastatin 80 mg	58.1	77.8	100	51.3	36.4
IDEAL (2005)[14]	8,888	Simvastatin 20 mg	61.6	80.8	100	33.0	21.2
		Atorvastatin 80 mg	61.8	80.9	100	32.9	20.1
TNT (2005)[15]	10,001	Atorvastatin 80 mg	61.2	81.2	100	53.9	13.4
		Atorvastatin 10 mg	60.9	80.8	100	54.4	13.4
MEGA (2006)[16]	7,832	Pravastatin 10-20 mg	58.2	32	0.0	42	21
		Usual care	58.4	31	0.0	42	20

CORONA (2007)[17]	5,011	Rosuvastatin 10 mg	73	76	100	63	9
		Placebo	73	76	100	63	8
GISSI-HF (2008)[18]	4,631	Rosuvastatin 10 mg	68	76.2	31.8	55.1	14.1
		Placebo	68	78.6	33.8	53.5	14.0
JUPITER (2008)[19]	17,802	Rosuvastatin 20 mg	66	5474	0.0	—	—
		Placebo	66	5527	0.0	—	—
ASTRONOMER (2010)[20]	269	Rosuvastatin 40 mg	58.0	60.5	0.0	—	11.2
		Placebo	57.9	63.0	0.0	—	10.4
SEARCH (2010)[21]	12,064	Simvastatin 80 mg	64 (9)	83	100	42	30
		Simvastatin 20 mg					
ODYSSEY OPTIONS I (2015)[22]	355	Alirocumab 75/150 mg every 2 weeks	63.1	61.5	52.9	76.9	—
		Ezetimibe	62.8	66.5	57.8	78.9	—
ODYSSEY FH I (2015)[23]	486	Alirocumab 75 mg every 2 weeks	52.1	180	147	139	39
		Placebo	51.7	94	78	71	30
ODYSSEY FH II (2015)[23]	249	Alirocumab 75 mg every 2 weeks	53.2	86	58	57	36

		Placebo	53.2	45	31	24	13
ODYSSEY LONG TERM (2015)[24]	2,341	Alirocumab 150 mg every 2 weeks	60.4	983	1055	—	325
		Placebo	60.6	474	552	—	159
OSLER (2015)[25]	4,465	Evolocumab 140 mg every 2 weeks or 420 mg monthly	57.8	1490	589	1545	465
		Placebo	58.2	765	307	777	222
GLAGOV (2016)[26]	968	Evolocumab 420 mg monthly	59.8	349	484	398	124
		Placebo	59.8	350	484	405	113
ODYSSEY CHOICE I (2016)[27]	803	Alirocumab 300 mg monthly or 75 mg every 2 weeks	59.2	80	40	—	—
		Placebo	59.4	40	20	—	—
ODYSSEY JAPAN (2016)[28]	206	Alirocumab 150 mg every 2 weeks	60.3	84	18	—	—
		Placebo	61.8	47	8	—	—
YUKAWA-2 (2016)[29]	404	Evolocumab 140 mg every 2 weeks or 420 mg monthly	62.0	60	15	75	23
		Placebo	61.0	61	11	72	26

ODYSSEY OPTIONS II (2016)[30]	305	Alirocumab 75 mg every 2 weeks	59.9	57	53	74	—
		Usual care	61.3	63	60	72	—
FOURIER (2017)[31]	27,564	Evolocumab 140 mg every 2 weeks or 420 mg monthly	62.5	75.4	80.9	80.1	28.0
		Placebo	62.5	75.5	81.3	80.1	28.5
ODYSSEY OUTCOMES (2018)[32]	18,924	Alirocumab 75-150 mg every 2 weeks	58.5	74.7	100	65.6	24.1
		Placebo	58.6	74.9	100	63.9	24.1

Table S4. Analyses According to Fixed Effects Model.

Analysis	Studies	Patients	RR [95% CI]	P-interaction
Risk of Incident DM in Total Population				
More intensive lipid lowering therapy	33	163,688	1.07 [1.03, 1.11]	
Statins	21	124,755	1.10 [1.05, 1.15]	0.02
PCSK9 Inhibitors	12	38,933	1.00 [0.93, 1.07]	
Subgroup Analysis According to Weighted Between-Group Difference in LDL-C Achieved				
0.51 mmol/L	5	32,752	1.11 [1.03, 1.19]	
1.15 mmol/L	16	92,003	1.09 [1.03, 1.16]	0.08
1.58 mmol/L	12	38,933	1.00 [0.93, 1.07]	
Sensitivity Analysis According to Statins Subgroups				
High intensity statin versus low intensity statin	5	32,752	1.11 [1.03, 1.19]	0.72
Statin vs no statin	16	92,003	1.09 [1.03, 1.16]	
Trials with sample size of ≥ 500 patients which reported outcome at follow-up ≥ 1 year				
More intensive lipid lowering therapy	25	161,531	1.07 [1.03, 1.11]	
Statins	20	124,486	1.10 [1.05, 1.15]	0.03
PCSK9 Inhibitors	5	37,045	1.00 [0.93, 1.08]	

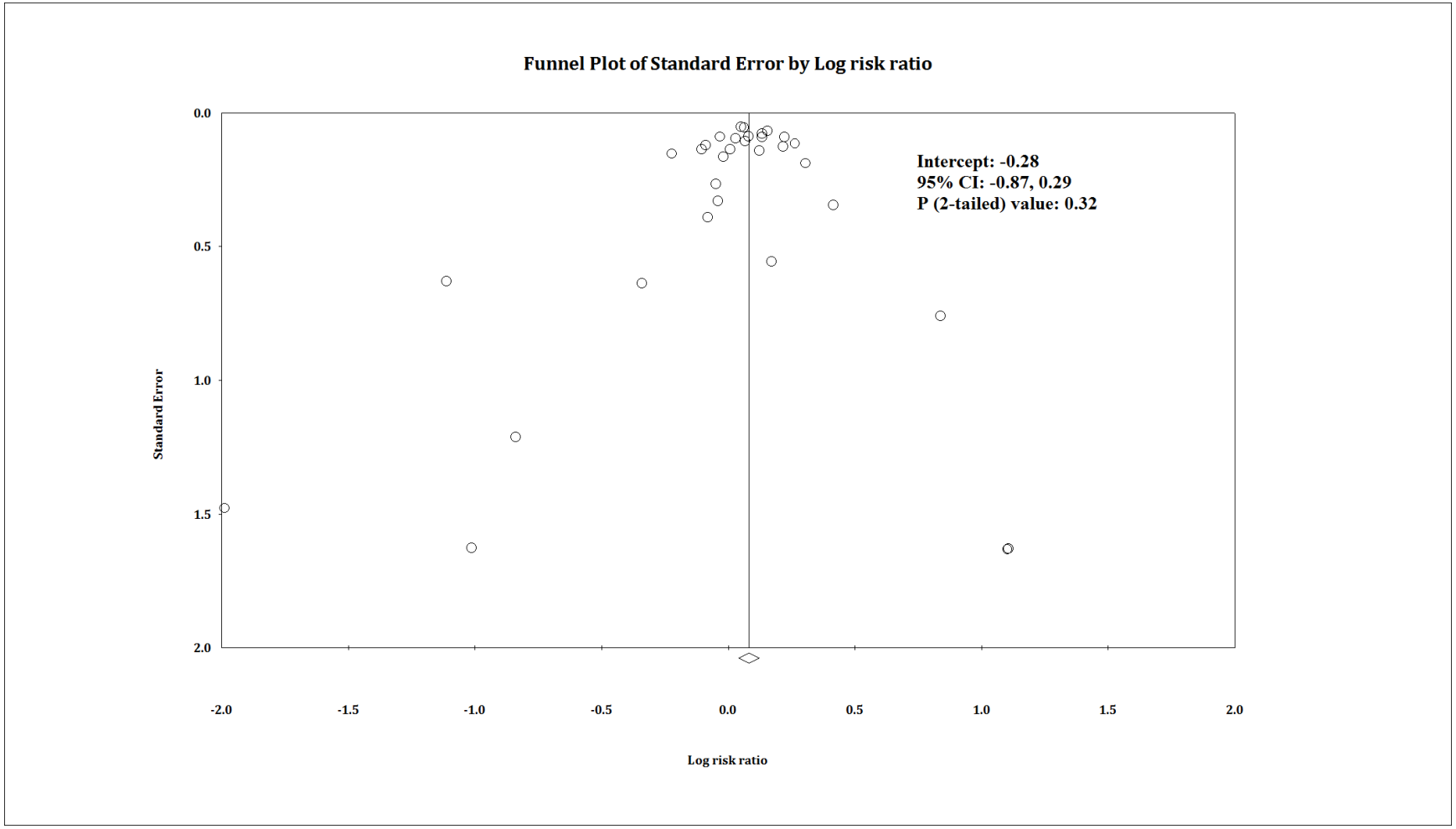
*P-interaction corresponds to statin and PCSK9 inhibitor subgroup interaction

Table S5. Sensitivity Analyses According to Year of Publication and Definition of Diabetes Mellitus.

			Risk Ratio [95% CI]			
	Studies	**Patients**	**More intensive lipid lowering therapy**	**Statin**	**PCSK9 Inhibitor**	***P interaction**
Cumulative Meta-Analysis Accounting for the Year of the Trial Publication						
Original meta-analysis	33	163,688	1.07 [1.03, 1.11]	1.10 [1.05, 1.15]	1.00 [0.93, 1.07]	0.02
4S and WOSCOPS excluded	31	153,472	1.08 [1.04, 1.12]	1.11 [1.06, 1.17]	1.00 [0.93, 1.07]	0.01
Year before 2000 excluded	28	139,202	1.08 [1.04, 1.13]	1.13 [1.07, 1.18]	1.00 [0.93, 1.07]	0.006
Year before 2010 excluded	14	49,999	1.02 [0.96, 1.08]	1.07 [0.96, 1.19]	1.00 [0.93, 1.07]	0.31
Meta-Analysis Stratified According to Definition of Diabetes Mellitus						
Two FBG levels ≥ 126 mg/dL	11	89,303	1.10 [1.04, 1.16]	1.11 [1.05, 1.18]	1.05 [0.95, 1.17]	0.37
Medication/Adverse events	14	45,625	1.07 [0.97, 1.18]	1.08 [0.98, 1.19]	0.96 [0.61, 1.51]	0.62
Adverse events only	8	28,760	1.00 [0.92, 1.08]	1.08 [0.95, 1.23]	0.95 [0.86, 1.05]	0.12

*P-interaction corresponds to statin and PCSK9 inhibitor subgroup interaction. FBG (Fasting Blood Glucose)

Figure S1. Funnel plot for publication bias assessment.



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