Increased Risk of Adverse Neurocognitive Outcomes With Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors

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Background—There is encouraging evidence of the efficacy of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors; however, their long-term safety remains unclear. We performed a meta-analysis of studies to evaluate the long-term safety of PCSK9 inhibitors.

Methods and Results—Our search strategy yielded 11 studies (9 smaller early-phase and 2 larger outcome trials). The outcomes assessed were cumulative serious adverse events, musculoskeletal adverse events, neurocognitive adverse events, and stroke. Odds ratio (OR) was calculated using the Mantel–Haenszel method. Subgroup analysis was done to assess the difference in safety between the smaller early-phase studies and the larger outcome studies. Our meta-analysis suggested no difference in the incidence of serious adverse events (OR, 1.00; 95% confidence interval [CI], 0.88–1.15), musculoskeletal adverse events (OR, 1.01; 95% CI, 0.87–1.13), neurocognitive adverse events (OR, 1.29; 95% CI, 0.64–2.59), or stroke (OR, 1.44; 95% CI, 0.57–3.65) with the use of PCSK9 inhibitors. Subgroup analysis of the 2 large outcome studies did suggest an increased incidence of neurocognitive adverse events (OR, 2.85; 95% CI, 1.34–6.06) with the use of PCSK9 inhibitors. However, the overall incidence of neurocognitive adverse events and stroke was <1%, whereas the cumulative incidence of serious adverse events and musculoskeletal events was >10% in both the groups.

Conclusions—Our analysis suggests that PCSK9 inhibitors are not associated with an increased risk of cumulative severe adverse effects, musculoskeletal effects, or stroke. There is a signal toward adverse neurocognitive effects, seen in the outcome studies with a larger sample size and longer follow-up. There should be close monitoring, for the increased risk of neurocognitive events in the ongoing outcome studies and post-marketing surveillance. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003153. DOI: 10.1161/CIRCOUTCOMES.116.003153.)**

Key Words: cognitive impairment ■ meta-analysis ■ proprotein convertases ■ stroke ■ subtilisins

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have generated considerable interest because of their potential for cardiovascular risk reduction based on substantial lowering of low-density-lipoprotein (LDL) cholesterol. PCSK9 inhibitors have been recently approved by the United States Food and Drug administration for use in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease that requires additional lowering of LDL.

The evidence of LDL lowering has been used as a surrogate end point for cardiovascular outcomes in the studies with PCSK9 inhibitors. Several studies[1–24] and their meta-analysis[26] have demonstrated not only a marked decrease in LDL levels but also improvement in cardiovascular outcomes with PCSK9 inhibitors. There has been some suggestion of an increased risk of neurocognitive events with the use of PCSK9 inhibitors.[27] Statins had also been postulated to be associated with neurocognitive effects because of their lipid-lowering ability. There is a biological plausibility in support of the argument that lipid lowering may have an impact on cognitive function regardless of the capability of the drug to cross the blood–brain barrier.[28,29] However, high-quality evidence has not shown that lipid lowering achieved with statins leads to impaired cognitive function.[30–34] However, the mean reduction of LDL cholesterol was ≈22% as reported in a Cochrane review, which was achieved by a moderate intensity statin.[32] The effect on cognitive function of a much greater magnitude of lipid lowering achieved with PCSK9 inhibitors is still unclear. Given the clinical importance of these adverse events and their public health consequences, we performed a meta-analysis of randomized controlled trials to assess the safety of PCSK9 inhibitors.

Methods

Data Sources and Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to conduct and report the systematic review.[35] The search strategy was developed in PubMed and translated

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WHAT IS KNOWN

- PCSK9 inhibitors have demonstrated marked reduction in LDL cholesterol levels.
- Initial evidence of impact on cardiovascular outcomes is encouraging with a signal toward improved outcomes

WHAT THE STUDY ADDS

- The initial studies with PCSK9 inhibitors were of small sample size and designed to establish lipid-lowering ability, and only 2 trials were designed to assess clinical outcomes and long-term safety.
- The cumulative incidence of adverse events (musculoskeletal, stroke) was low with PCSK9 inhibitors supporting their safety; however, there was a 2-fold increase in neurocognitive events shown in studies with a larger sample size.
- The current ongoing larger outcome studies will provide more definitive results on the incidence and severity of neurocognitive events and may shed some light on subgroups particularly predisposed to these events

to match the subject headings and keywords for Embase, Cochrane Central Register of Controlled Trials, and ISI Web of Science from inception through January 2016. In addition, abstract presentations at scientific meetings were searched for articles pertaining to the search criteria. The following MeSH, Emtree, and keyword search terms were used in combination: proprotein convertase subtilisin-kexin type 9 inhibitor or PCSK9 antibody or evolocumab or AMG 145 or alirocumab or REGN727 or SAR236553 or bococizumab or RN316 and controlled trials or intervention study or randomized controlled trials and hypercholesterolemia. The search accounted for plurals and variations in spelling with the use of appropriate wildcards. There was no limitation of language. Further articles were selected by hand-searching relevant citations in review articles and commentaries. There were no language restrictions. All results were downloaded into EndNote (Thompson Reuters), and duplicate citations were identified and removed.

Study Selection and Data Extraction

Two investigators (A.R.K. and C.B.) independently assessed the eligibility of the studies identified. Randomized controlled trials were included if they evaluated the role of PCSK9 inhibitors, reported relevant safety outcomes with a follow-up >6 months.

From the included studies, 2 reviewers (S.K. and H.R.) independently extracted data on the population under study, patient characteristics, type of PCSK9 inhibitor used, and relevant outcomes. The relevant outcomes measured in our analysis were serious adverse events (SAE), neurocognitive events (NCE), stroke, and musculoskeletal events. The definition of the adverse events, neurocognitive events, musculoskeletal events, and ascertainment of stroke followed the respective definition delineated in the individual studies. We did not extract data on LDL or lowering of other lipid fractions and clinical outcomes as this issue has already been systematically studied in a previous review and meta-analysis[26]

Data Synthesis and Statistical Analysis

Data for relevant safety outcomes were pooled, and corresponding odds ratio (OR) were calculated. The Mantel–Haenszel (MH) method was used in a fixed-effects or a random-effects model to pool data depending on the associated heterogeneity. The I^2 statistic was used to assess heterogeneity among studies.[36] Publication bias was assessed by means of a funnel plot; the Egger test was used to assess funnel plot asymmetry and publication bias if needed.[37] The Trim and Fill method was used to adjust the effect estimate if publication bias was present.[38] A subgroup analysis was done to assess the difference in safety between the smaller early phase studies and the larger outcome studies.

Quality Assessment

The methodological quality of the included studies was evaluated using the Cochrane risk of bias tool by 2 reviewers (S.K. and T.F.). This tool is used to assess randomization, blinding both of participants and caregivers, outcome assessment, outcome reporting, and other potential bias.[39] Any disagreements between reviewers were either resolved by consensus or by a third reviewer (R.B.). All analyses were conducted using the statistical software Review Manager (v5.2).

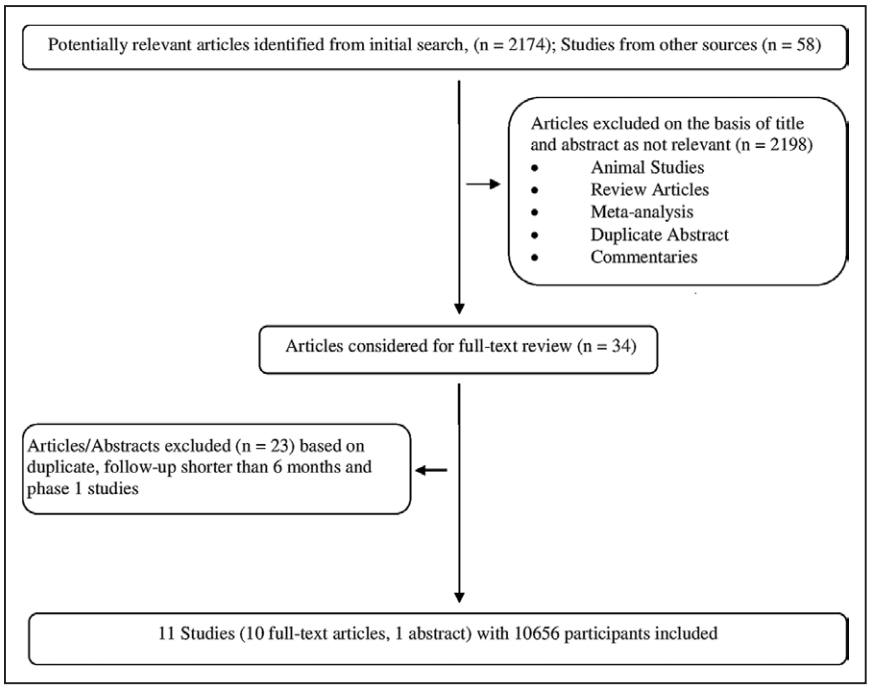

Figure 1. Flowchart of the eligible studies.

Table 1. Characteristics of Included Studies

Study	Center	Inclusion Criteria	Exclusion Criteria	Efficacy End Points	Clinical Outcomes	Follow-Up
Smaller early phase 2–3 studies						
DESCARTES,[15] 2014	88	Age 18–75 y, LDL ≥75 mg/dL, fasting TG ≤400 mg/dL,	Recent MI, uncontrolled HTN, HF, planned revascularization, moderate-severe renal failure, liver disease	Percent/absolute change in LDL other lipid fractions, patients with LDL<70 mg/dL	Adjudicated CV events, adverse events, MI, mortality	52 wk
ODYSSEY ALTERNATIVE,[16] 2014	67	Statin intolerant, LDL ≥70 mg/dL	NR	Percentage change in LDL	Safety analysis, adjudicated CV events, MI, mortality, neurocognitive disorders	24 wk
ODYSSEY COMBO I,[17] 2015	76	Age ≥18 y, LDL ≥70 and established CHD, LDL ≥100 and CHD risk equivalent, maximally tolerated statin dose ± other LLT	Hypersensitivity, BP >160/100 mm Hg, disease known to affect lipoprotein or lipid, TG >400 mg/dL, recent CV event	Percent or absolute change in LDL, patient proportion reaching LDL<70 mg/dL, change in lipid fractions	Safety analysis, adverse event reporting, adjudicated CV events	52 wk
ODYSSEY COMBO II,[18] 2015	126	CHD/CHD-R, max. tolerated statin, CVD and LDL ≥70, high-risk for CVD and LDL ≥100	<18 y, on statins other than simvastatin, atorvastatin or rosuvastatin, use of other LLT	Percent or absolute change in LDL, change in various lipid fractions	Safety analysis, adverse event including death, adjudicated CV events	104 wk
ODYSSEY FH I and II,[19] 2015	89 (I), 26 (II)	HeFH, LDL not controlled on maximal tolerated dose of statin	Homozygous FH, not on stable LLT, TG >400 mg/dL, use of fibrates other than fenofibrate	Percent/absolute change in LDL/other lipid fractions, patient reached target LDL	Safety analysis, adverse event, adjudicated CV events, and death	78 wk
ODYSSEY HIGH FH,[20] 2014	31	HeFH, LDL uncontrolled on maximal tolerated statin, LDL< 160 mg/dL, no other LLT	Not on stable LLT, HFH, fasting TG >400 mg/dL, use of fibrates other than fenofibrate	Percent change in LDL, achieved change in LDL over time	Safety analysis, adverse events, CV events, neurocognitive issues	52–78 wk
ODYSSEY MONO,[22] 2014	8	Age ≥ 18 y, 10-y risk of fatal CV events ≥1% and <5%, no statin/LLT for at least 4 wk	Established CHD, LDL<100 or >190 mg/dL, BP >160/100, planned revascularization	Percent change in LDL	Safety analysis, clinically significant adverse event	24 wk
ODYSSEY OPTIONS I,[23] 2015	85	Age ≥18 y, established CHD and LDL >70, CHD-R and LDL >100, on statin	NR	Percent or absolute change in LDL/other lipid fraction, proportion with LDL<70	Safety analysis, adverse events: CV, neurocognitive events	24 wk
ODYSSEY OPTIONS II,[24] 2015	79	Hypercholesterolemia, CHD and LDL>70, CHD-R and LDL>100, on statin	Statins other than rosuvastatin, no ezetimibe, LLT or statin for at least 4 wk	Percent change in LDL or other lipid fractions, patient with LDL<70 mg/dL	Safety analysis, clinically significant adverse event	24 wk
Larger Outcome Studies						
ODYSSEY LONG TERM,[21] 2015	320	Age ≥18 y, HeFH, established CHD or CHD-R, LDL> 70 mg/dL, on high dose or maximal tolerated dose of statin	Without HeFH, not on a stable dose of LLT, on statin other than simvastatin, atorvastatin or rosuvastatin, use of other LLT	Percent change in LDL, change in various lipoprotein variables	Safety analysis, adverse event, CV events, end point of CHD death, MI, stroke, unstable angina	78 wk
OSLER,[14] 2015	510	Completed the parent trial of OSLER, no adverse event with the PCSK9 inhibitor; no need to optimize other lipid-lowering therapy	Adverse event with evolocumab in parent trial, unstable medical condition (judged by the investigator)	Change in LDL and other lipid fractions	Adverse events, adjudicated cardiovascular events	48 wk

BP indicates blood pressure; CHD, coronary heart disease; CHD-R, coronary heart disease risk equivalent; CV, cardiovascular; DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; HeFH, familial hypercholesterolemia; HF, heart failure; HTN, hypertension; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; MI, myocardial Infarction; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; OSLER, Open label Study of 12 early phase 2–3 trials; OSLER-1, 5 phase 2 trials; OSLER-2, 7 phase 3 trials; PCSK9, proprotein convertase subtilisin-kexin type 9; and TG, triglycerides.

Table 2. Characteristics of Included Patients

Study	PCSK9: Dose Control: Dose	n	Lipid-Lowering Therapy	Baseline LDL	Age, y	Race*, %	Male, %	DM, %	CAD, %	CAD-R, %
DESCARTES,[15] 2014	Evolocumab: 420 mg Q4W	599	(A) 10 mg/80 mg	104.2±22.1	55.9±10.8	79.5	48.4	10.4	15.7	NR
	Placebo	302	(A) 80 mg+(E) 10 mg	104.4±21.6	56.7±10.1	82.1	46.4	13.9	13.9	NR
ODYSSEY ALTERNATIVE,[16] 2014	Alirocumab: 75/150 mg Q2W	126	No statin, other LLT	191.1±72.7	64.1±9.0	92.9	55.6	28.6	50.8	NR
	Ezetimibe 10 mg	125		193.5±70.9	62.8±10.1	92.8	53.6	19.2	43.2	NR
	(A) Atorvastatin 20 mg	63		187.3±59.5	63.4±8.9	98.4	55.6	23.8	44.4	
ODYSSEY COMBO I,[17] 2015	Alirocumab: 75/150 mg Q2W	207	(A) 40–80 mg, (R) 20–40 mg, (S) 80 mg, other LLT	100.2±29.5	63.0±9.5	81.3	62.7	45	78.5	40.7
	Placebo	107		106±35.3	63.0±8.8	82.2	72	39.3	77.6	47.7
ODYSSEY COMBO II,[18] 2015	Alirocumab: 75/150 mg Q2W	479	(A) 40–80 mg, (R) 20–40 mg, (S) 80 mg	108.3±34.8	61.7±9.4	84.3	75.2	30.7	91.2	31.5
	Ezetimibe 10 mg	241		104.4±34.8	61.3±9.2	85.5	70.5	31.5	88	29.9
ODYSSEY FH I,[19] 2015	Alirocumab: 75/150 mg Q2W	322	(A) 40–80 mg, (R) 20–40 mg, (S) any dose	144.7±2.9	52.1±12.9	92.9	55.7	9.9	45.5	16.7
	Placebo	163		144.4±3.7	51.7±12.3	88.3	57.7	15.3	47.9	15.3
ODYSSEY FH II,[19] 2015	Alirocumab: 75/150 mg Q2W	166	(A) 40–80 mg, (R) 20–40 mg, (S) any dose	134.6±3.2	53.2±12.9	98.2	51.5	4.2	34.7	9
	Placebo	81		134±4.6	53.2±12.5	97.6	54.9	3.7	37.8	4.9
ODYSSEY HIGH FH,[20] 2014	Alirocumab: 150 mg Q2W	72	(A) 40–80 mg, (R) 20–40 mg, (S) 80 mg	196.3±57.9	49.8±14.2	88.9	486	12.5	43.1	NR
	Placebo	35		201.0±43.4	52.1±11.2	85.7	62.9	17.1	62.9	NR
ODYSSEY LONG TERM,[21] 2015	Alirocumab: 150 mg Q2W	1553	(A) 40–80 mg, (R) 20–40 mg, (S) 80 mg, (E) 10 mg	122.7±42.6	60.4±10.4	92.8	63.3	34.9	67.9	41.1
	Placebo	788		121.9±41.4	60.6±10.4	92.6	60.2	33.9	70.1	41
ODYSSEY MONO,[22] 2014	Alirocumab: 75 mg Q2W	52	None	141.1±27.1	60.8±4.6	88.5	53.8	5.8	NA	NA
	Ezetimibe 10 mg	51		138.3±24.5	59.6±5.3	92.2	52.9	2	NA	NA
ODYSSEY OPTIONS I,[23] 2015	Alirocumab: 75/150 mg Q2W AND (A) 20/40 mg	57	(A) 20 mg or 40 mg	103.9±34.9	62.2±10	84.2	57.9	57.9	38.6	28.1
		47		100.4±29.5	64.2±10.4	91.5	66	53.2	70.2	21.3
	Ezetimibe 10 mg+(A) 20 mg	55		100.4±29.5	65.7±9.0	87.3	56.4	52.7	50.9	29.1
	(A) 40 mg	57		100.3±29.8	63.0±9.9	87.7	61.4	54.4	50.9	33.3
	Ezetimibe 10 mg+(A) 40 mg	47		98.9±29.2	63.9±10.3	91.5	76.6	34	74.5	21.3
	(A) 80 mg, (R) Rosuvastatin 40	47		108.6±37.5	63.2±10.9	87.2	70.2	53.2	66	34
		45		109.8±39.0	57.5±10.0	73.3	71.1	40	48.9	17.8
ODYSSEY OPTIONS II,[24] 2015	Alirocumab: 75/150 mg Q2W AND (R) 10/20 mg	49	(R) 20–40 mg, other	107.3±26.4	62.2±11.1	91.8	63.3	38.8	46.9	32.7
		54	LLT except (E)	118.3±32.2	57.9±8.9	77.8	51.9	33.3	59.3	20.4
	Ezetimibe 10 mg+(R) 10 mg	48		102.4±41.9	60.4±10.4	87.5	54.2	47.9	60.4	25
	(R) 20 mg	48		105.9±36.0	61.5±11.1	77.1	68.8	58.3	52.1	31.3
	Ezetimibe 10 mg+(R) 20 mg	53		119.0±48.0	63.1±10.2	86.8	58.5	39.6	60.4	20.8

(*Continued*)

Table 2. Continued

Study	PCSK9: Dose Control: Dose	n	Lipid-Lowering Therapy	Baseline LDL	Age, y	Race*, %	Male, %	DM, %	CAD, %	CAD-R, %
	(R) 40 mg	53		112.9±43.3	60.6±10.1	83	71.7	32.1	67.9	26.4
OSLER,[14] 2015†	Evolocumab 420 mg QM or 140 mg Q2W	2976		120 (51)‡	57.8±11	50.1	86	12.8	19.8	
	Statin±ezetimibe	1489		121 (54)	58.2±10.9	51.4	85.1	14.6	20.6	

*White race.

†Open-label trial of 12 earlier phase 2–3 trials.

‡Median (interquartile range).

(A) indicates atorvastatin; CAD, coronary artery disease; CAD-R, coronary artery disease risk equivalent; DM, diabetes mellitus; (E), Ezetemibe; LDL, low-density-lipoprotein; other LTT (lipid-lowering therapy), bile acid sequestrant, ezetimibe, niacin, omega-3 or fenofibrate; PCSK9, proprotein convertase subtilisin-kexin type 9; Q2W, every 2 weeks; QM, every month; (R), rosuvastatin; and (S), simvastatin.

Results

Identification of Studies

After removal of duplicates, the literature search identified 2174 publications, of which 11 studies were eligible for our analysis[10,14–21,23,24] (Figure 1). As we investigated long-term safety, studies with <6-month follow-up were excluded.[1–13,22] However, these early studies were included in an open-label extension study to assess long-term outcomes of PCSK9 inhibitors (OSLER [Open-Label Study of 12 Early Phase 2–3

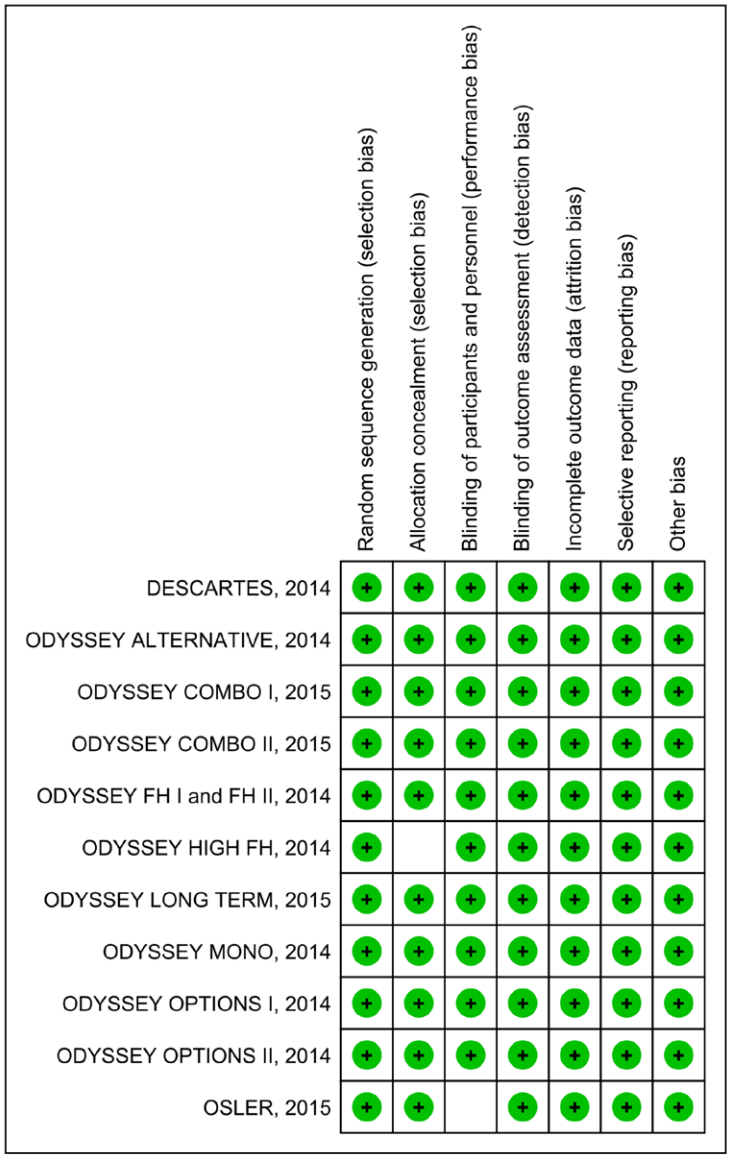

Figure 2. Quality assessment (risk of bias) of the included studies.[14–24] DESCARTES indicates Durable Effect of PCSK9 Antibody Compared With Placebo Study; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY MONO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; 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 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 Trial.

Trials]), which was included in our analysis.[14] All included studies were published articles except one, which was presented at a scientific meeting as an abstract.[20]

Study Characteristics

A total of 11 studies[14–24] comprising 10 656 (ranging from 103 to 2341 in individual trials) were included in the analysis. The studies were divided into 2 subgroups: early phase 2 to 3 studies with a small sample size[15–20,22–24] mainly designed to assess safety and efficacy of LDL lowering and outcome trials (ODYSSEY [Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy][21] and OSLER[14]) with a larger sample size designed to assess long-term cardiovascular events. ODYSSEY LONG TERM[21] assessed the effect of alirocumab on long-term cardiovascular events, and OSLER[14] was an extension study in which patients from the previous 12 phase 2/3 studies[1–4,6,8,9,12,13] of evolocumab were randomized into 2 open-label trials. The 2 larger outcome studies constituted almost two thirds of the patients in the analysis. Seven trials included patients with unspecified hypercholesterolemia,[15–18,22–24] 2 trials had patients with heterozygous familial hypercholesterolemia,[19,20] and 1 trial included patients with both hypercholesterolemia and heterozygous familial hypercholesterolemia.[21] All patients had either coronary artery disease or coronary artery disease risk equivalent or were at high risk for coronary artery disease along with hypercholesterolemia. All trials except 2[16,22] studied patients on a background of lipid-lowering therapy. Tables 1 and 2 highlight the characteristics of the included studies and the patient populations in these studies.

The risk of bias in all included studies was determined to be low. All studies were of sound methodological quality, with adequate randomization reported in all trials. There was no allocation bias in any trial except 2; in one[20] in which the risk was unclear and another one[14] in which the risk was high because of the open-label nature of the trial. All assessments of outcomes measured were blinded, with a low risk of documented bias both for selection and for reported outcomes in

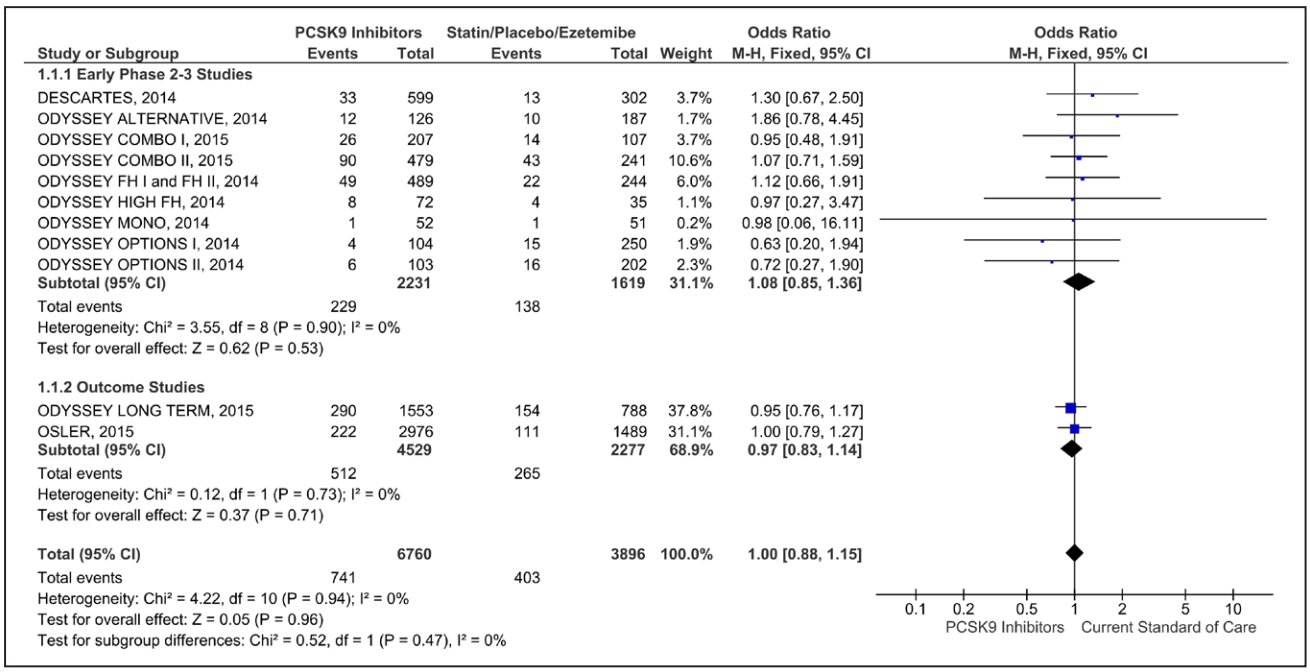

Figure 3. Forest plot comparing incidence of cumulative serious adverse events in patients who received proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors compared with the current standard of care.[14–24] Squares represent the odds ratio of the individual studies. Horizontal lines represent the 95% confidence intervals (CIs) of the odds ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. Diamond represents the pooled odds ratio or the overall effect. DESCARTES, Durable Effect of PCSK9 Antibody Compared with Placebo Study; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY MONO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; 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 LONG TERM, Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy; OSLER, Open Label Study of Long Term Evaluation Against LDL-C Trial; and OM–H, Mantel–Haenszel.

all trials except one,[14] in which the allocation and outcome were not blinded. The randomized controlled trials included in the analysis had a low risk of bias because of attrition during follow-up (Figure 2).

There was excellent agreement between the reviewers with respect to inclusion of the studies, data abstraction, and quality assessment (κ>0.85).

Meta-Analysis

Serious Adverse Events

The incidence of SAE was 741 of 6760 (11.0%) among patients on PCSK9 inhibitors and 403 of 3896 (10.3%) among patients without PCSK9 inhibitors. The meta-analysis suggested no difference in the incidence of SAE with the use of PCSK9 inhibitors (OR, 1.00; 95% confidence interval [CI], 0.88–1.15; *P*=0.96). There was no between-study heterogeneity (*P*=0.94; I^2=0%; *P*=0.2; Figure 3). There was no funnel plot asymmetry, and the Egger test also did not show any presence of publication bias (*P*=0.2; Figure I in the Data Supplement).

Subgroup analysis showed no difference in the risk of SAE between the early-phase studies (OR, 1.08; 95% CI, 0.85–1.36; *P*=0.53; I^2=0%) and the outcome studies (OR, 0.97; 95% CI, 0.83–1.14; *P*=0.71; I^2=0%; *P*=0.2; Figure 3).

Musculoskeletal Events

The incidence of musculoskeletal adverse events was reported in 8 studies. There were 957 of 6760 (14.2%) events among patients on PCSK9 inhibitors and 494 of 3896 (12.7%) events among patients without PCSK9 inhibitors. The meta-analysis suggested no difference in the incidence of musculoskeletal adverse events with the use of PCSK9 inhibitors (OR, 1.01; 95% CI, 0.87–1.13; *P*=0.90). There was mild between-study heterogeneity (*P*=0.33; I^2=13%; *P*=0.2; Figure 4). There was some suggestion of funnel plot asymmetry, but the Egger test also did not show any presence of publication bias (*P*=0.6; Figure II in the Data Supplement).

Subgroup analysis showed no difference in the risk of musculoskeletal adverse events between the early-phase studies (OR, 0.90; 95% CI, 0.71–1.14; *P*=0.37; I^2=0%) and

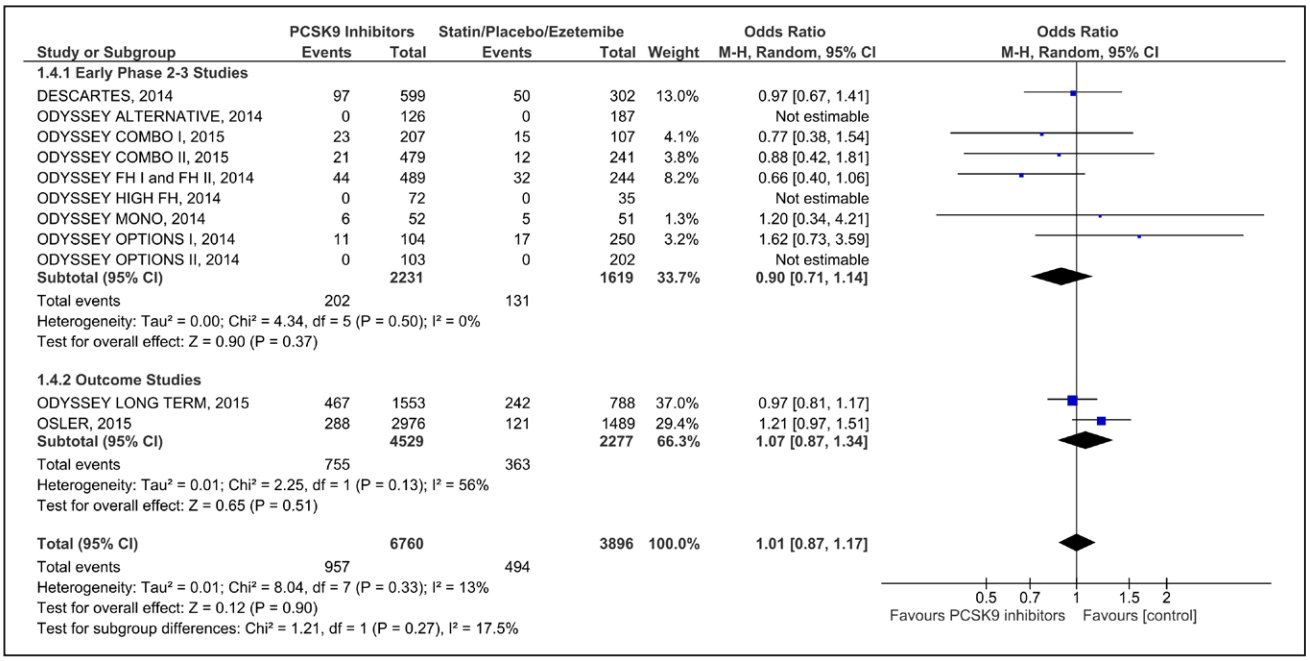

Figure 4. Forest plot comparing incidence of musculoskeletal adverse events in patients who received proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors compared with the current standard of care.[14–24] Squares represent the odds ratio of the individual studies Horizontal lines represent the 95% confidence intervals (CIs) of the odds ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. Diamond represents the pooled odds ratio or the overall effect. DESCARTES, Durable Effect of PCSK9 Antibody Compared With Placebo Study; M–H, Mantel–Haenszel; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY MONO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; 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 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 Trial.

the outcome studies (OR, 1.07; 95% CI, 0.87–1.34; *P*=0.51; I^2=56%; Figure 4).

Neurocognitive Events

Neurocognitive events were reported in 8 studies. These events included delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders. The incidence of all reported neurocognitive events was 56 of 6760 (0.8%) among patients on PCSK9 inhibitors and 20 of 3896 (0.5%) among patients not on PCSK9 inhibitors. The meta-analysis suggested no difference in the incidence of neurocognitive events with the use of PCSK9 inhibitors (OR, 1.29; 95% CI, 0.64–2.59; *P*=0.47; I^2=27%). There was a slight between-study heterogeneity (*P*=0.22; I^2=27%; Figure 5). There was some funnel plot asymmetry and Egger test demonstrated the presence of publication bias (*P*=0.02; Figure III in the Data Supplement). There was no change in the adjusted odds ratio by the Trim and Fill method.

Subgroup analysis done to assess the effect of individual studies demonstrated that although there was no difference in the incidence of neurocognitive events with the early studies (OR, 0.69; 95% CI, 0.30–1.58; *P*=0.38; I^2=0%), the outcome studies showed >2-fold increased incidence of neurocognitive adverse events (OR, 2.81; 95% CI, 1.32–5.99; *P*=0.007; I^2=0%; Figure 5).

Stroke

The incidence of stroke was 16 of 6760 (0.2%) among patients on PCSK9 inhibitors and 05 of 3896 (0.1%) among patients not on PCSK9 inhibitors. The meta-analysis suggested no difference in stoke risk between the 2 groups (OR, 1.44; 95% CI, 0.57–3.65; *P*=0.45; I^2=0%). There was no between-study heterogeneity (*P*=0.82; I^2=0%; Figure 6). There was no funnel plot asymmetry, and the Egger test also did not show any presence of publication bias (*P*=0.38; Figure IV in the Data Supplement).

Subgroup analysis revealed a numerically higher stroke events (13/3784 [0.3%]) among patients with PCSK9 inhibitors than among patients without PCSK9 inhibitors (03/2407 [0.1%]) in the outcome studies; however, it did not reach statistical significance (OR, 1.52; 95% CI, 0.49–4.71; *P*=0.47; I^2=0%; Figure 6).

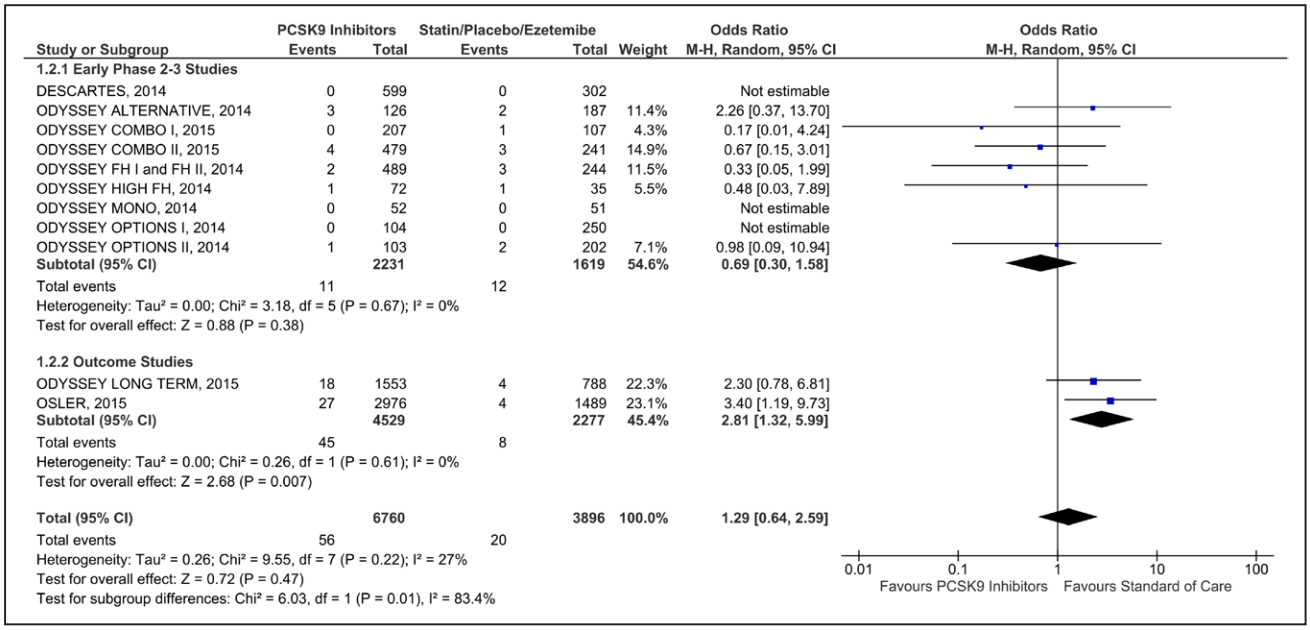

Figure 5. Forest plot comparing incidence of neurocognitive events in patients who received proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors compared with the current standard of care.[14–24] Squares represent the odds ratio of the individual studies. Horizontal lines represent the 95% confidence intervals (CIs) of the odds ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. Diamond represents the pooled odds ratio or the overall effect. DESCARTES indicates Durable Effect of PCSK9 Antibody Compared With Placebo Study; M–H, Mantel–Haenszel; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY MONO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; 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 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 Trial.

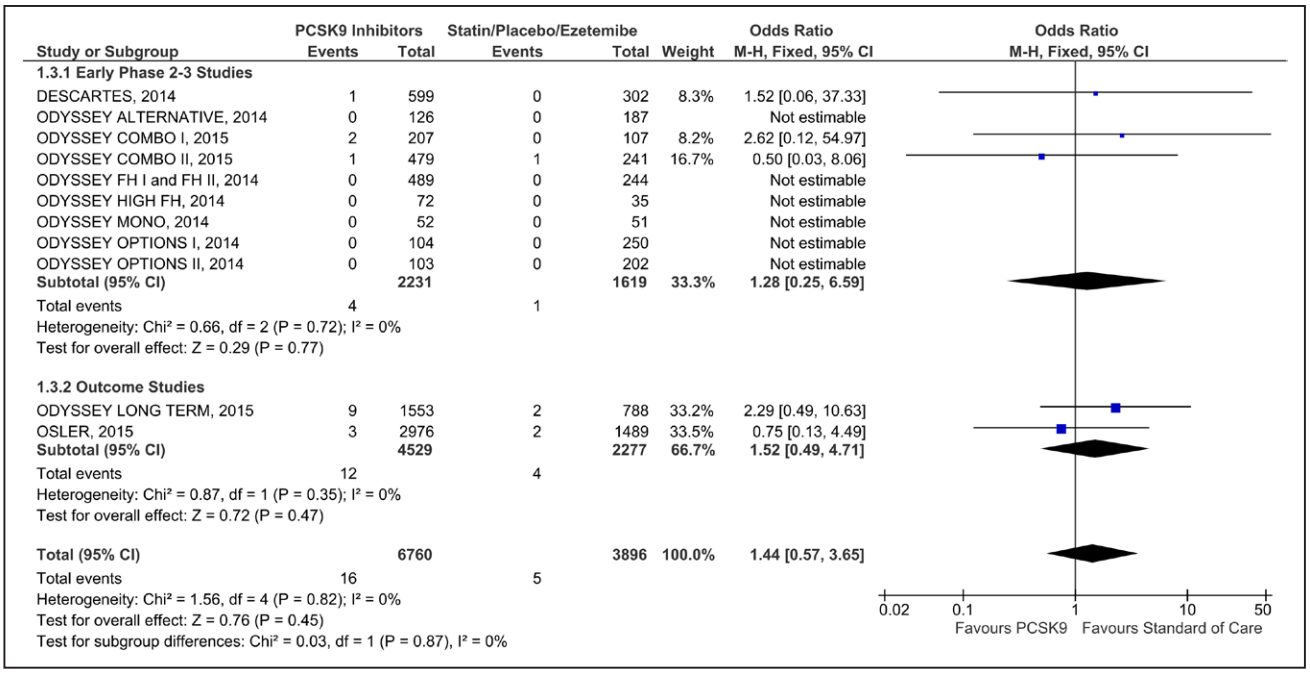

Figure 6. Forest plot comparing incidence of stroke in patients who received proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors compared with the current standard of care.[14–24] Squares represent the odds ratio of the individual studies. Horizontal lines represent the 95% confidence intervals (CIs) of the odds ratio. The size of the square reflects the weight that the corresponding study exerts in the meta-analysis. Diamond represents the pooled odds ratio or the overall effect. DESCARTES indicates Durable Effect of PCSK9 Antibody Compared With Placebo Study; M–H, Mantel–Haenszel; ODYSSEY ALTERNATIVE, A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients With Primary Hypercholesterolemia Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With 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 HIGH FH, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY MONO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia; 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 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 Trial.

Discussion

Our meta-analysis suggests that the administration of PCSK9 inhibitors is not associated with an increased risk of cumulative SAEs, musculoskeletal adverse events, or stroke when compared with the current standard of care. However, we did find >2-fold increase in the incidence of neurocognitive events with PCSK9 inhibitors in a subgroup analysis of the larger outcome studies; ODYSSEY LONG TERM[21] and OSLER.[14] However, these were the only studies designed to assess clinical outcomes and long-term safety with a large sample size and longer duration of follow-up. If the outcome studies are reflective of improved cardiovascular outcomes with PCSK9 inhibitors,[25] then their signal toward an increased risk of NCE is a cause for concern. Even though there is an overall low incidence of NCE (<1% in both the groups), these adverse events may have important public health implications with the expected increase in use of PCSK9 inhibitors and possible expansion of their indication. In a recent systematic review,[25] Navarese et al[25] found PCSK9 inhibitors to be effective with a reduction in all-cause mortality and cardiovascular outcomes; however, they did not evaluate safety parameters such as neurocognitive or stroke events. Our analysis expands on the previous review, by inclusion of relevant safety parameters such as neurocognitive or stroke events to help assess the safety of PCSK9 inhibitors.

Although our analysis shows a possibility of neurocognitive impairment with the use of PCSK9 inhibitors, there are some limitations to our analysis that negatively affect the evidence. First, the NCE were self-reported with no objective assessment of cognitive ability performed. Second, there was no information of the baseline cognition of the patients in the individual studies. In addition, there were differences in the population studied with regards to the magnitude of LDL lowering, which may have an effect on neurocognition. The evaluation of all these factors will only be possible in an individual patient data meta-analysis or by the ongoing large outcome studies. The United States Food and Drug administration is aware of the neurocognitive adverse events of these inhibitors and have advised the drug developers to gather data on these events.[26]

There are some other questions that also need to be answered before the widespread use of these monoclonal antibodies. With the extent of LDL lowering demonstrated by PCSK9 inhibitors, it needs to be established the lower limit to which LDL can be decreased without any impact on cognition. With the LDL levels reaching lower than 25 mg/dL, which is far lower than found in healthy neonates and native hunter-gatherers;[39] the long-term effect on NCE is not known. However, one of the studies included in the analysis did not find an association of NCE with LDL levels even as low as 25 mg/dL.[14] There is a possibility that not all patients develop NCE with PCSK9 inhibitors and high-risks subgroups need to be identified. Also the type of NCE occurring would be important, whether the events are relatively minor and reversible (such as confusion or temporary delirium) or relatively severe and persistent (such as dementia). With the current evidence, because of the relatively low incidence of NCE, we were unable to assess either the different types of NCE that occurred or subgroups that are at a higher risk for these events.

These unresolved questions and safety concerns will be addressed by the ongoing large outcome studies, ODYSSEY OUTCOMES[40,41] and FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk),[42] which are looking at long-term safety and efficacy of PCSK9 inhibitors. Moreover, an ongoing substudy of 4000 patients from the FOURIER[42] would shed more light with objective assessment of NCE in patients without baseline dementia or mild cognitive impairment. These studies may be able to conclusively resolve the concerns on the safety of PCSK9 inhibitors.

Conclusions

PCSK9 inhibitors have considerable therapeutic potential, as shown by the marked LDL lowering and initial encouraging clinical outcomes. Our analysis suggests that PCSK9 inhibitors are not associated with an increased risk of cumulative severe adverse effects, musculoskeletal effects, or stroke. There is a signal toward adverse neurocognitive effects, seen in studies with a larger sample size and longer follow-up. There should be close monitoring, for the increased risk of neurocognitive events in the ongoing outcome studies and post-marketing surveillance.

Disclosures

None.

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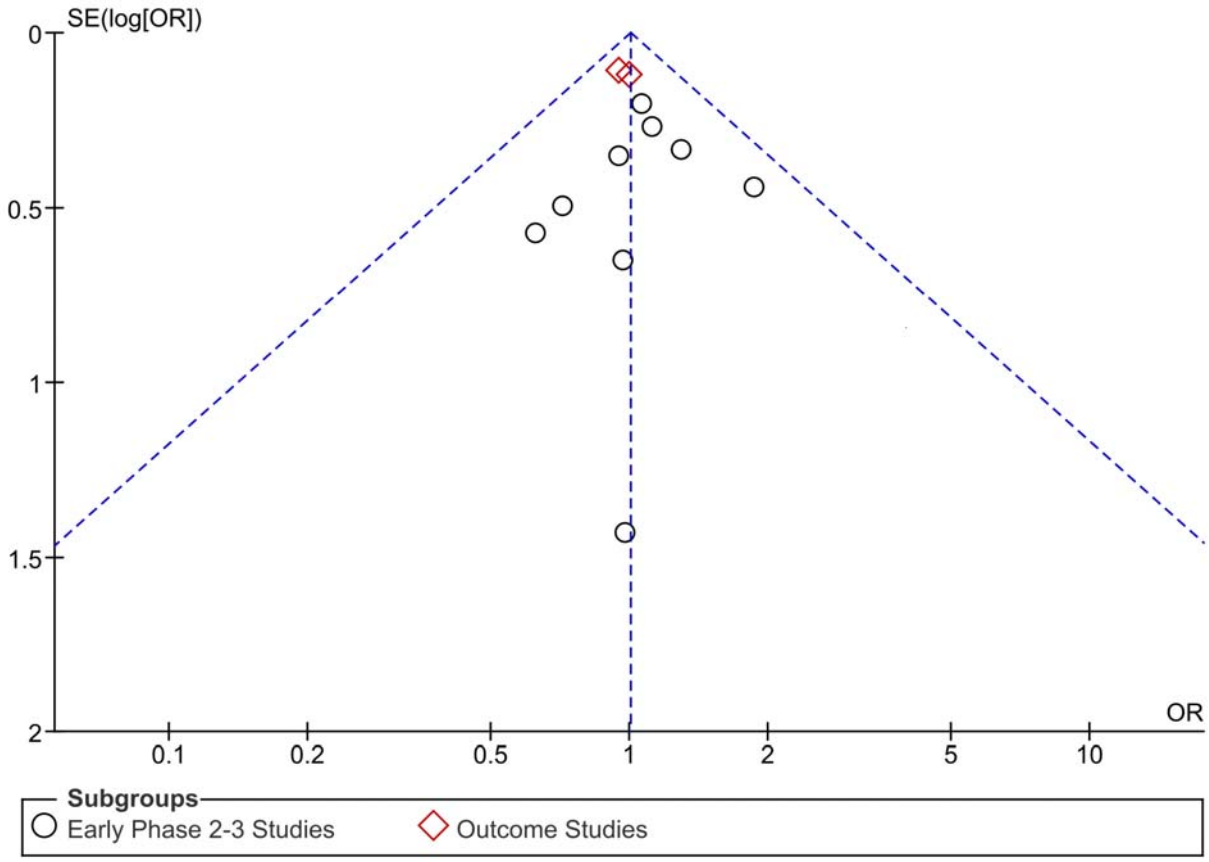
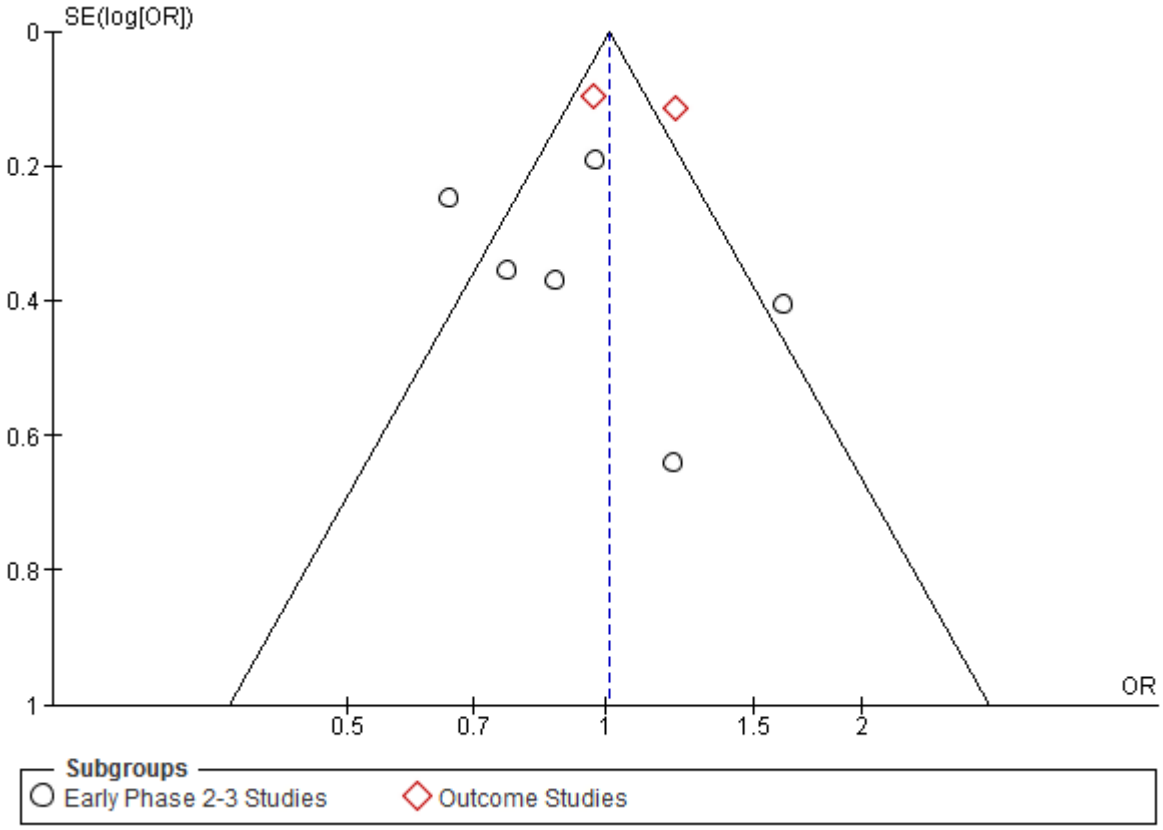
SUPPLEMENTAL MATERIAL

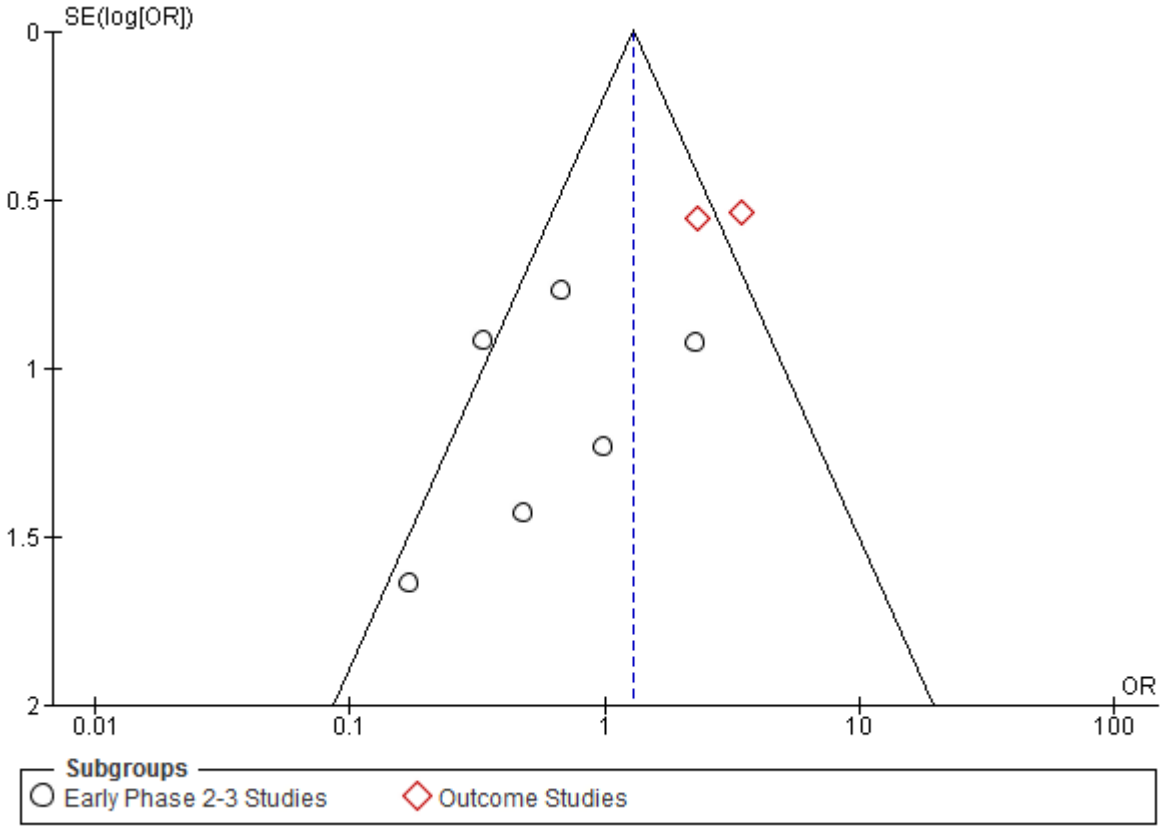
Supplementary Figure 1.	**Funnel plot comparing incidence of cumulative serious adverse events in patients who received PCSK9 inhibitors compared to current standard of care.**
Supplementary Figure 2.	**Funnel plot comparing incidence of musculoskeletal events in patients who received PCSK9 inhibitors compared to current standard of care.**
Supplementary Figure 3.	**Funnel plot comparing incidence of neurocognitive events in patients who received PCSK9 inhibitors compared to current standard of care.**
Supplementary Figure 4.	**Funnel plot comparing incidence of stroke in patients who received PCSK9 inhibitors compared to current standard of care.**



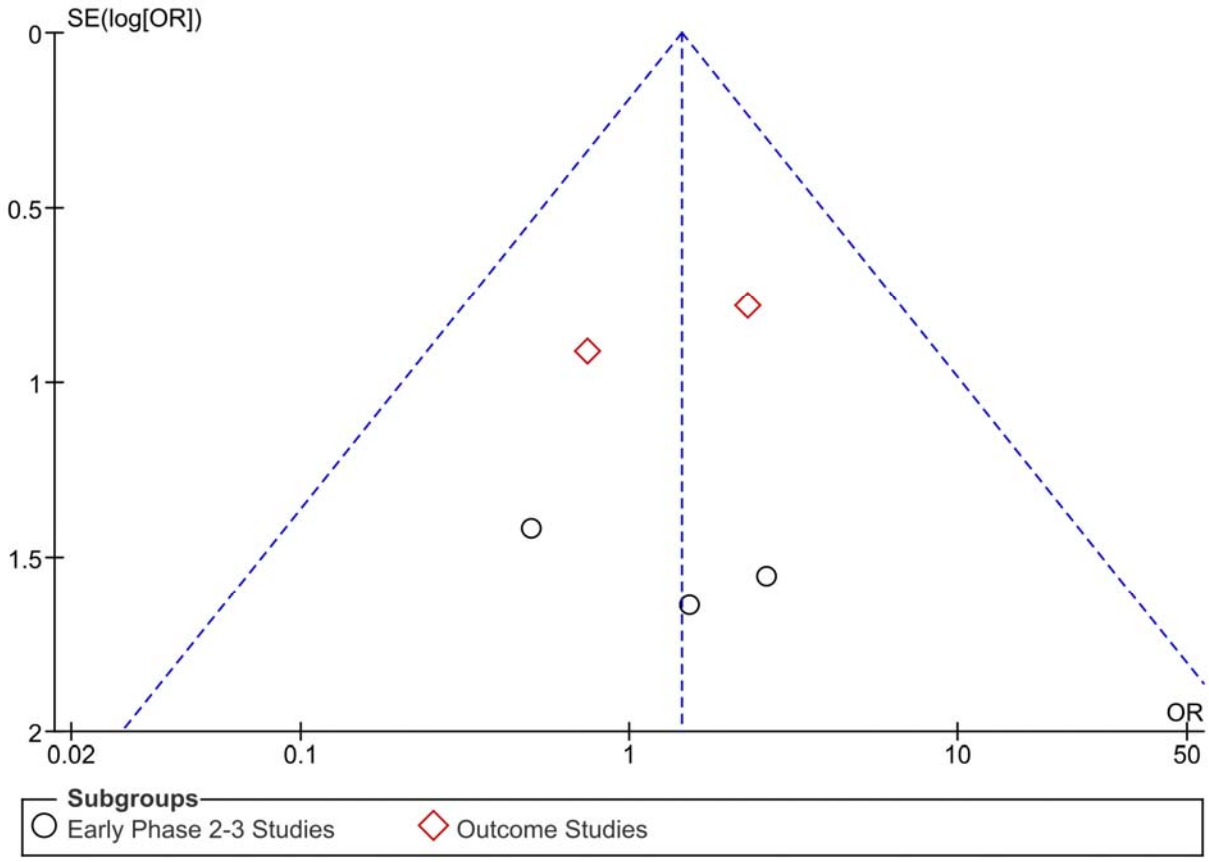
Supplementary Figure 1. Funnel plot comparing incidence of cumulative serious adverse events in patients who received PCSK9 inhibitors compared to current standard of care.



Supplementary Figure 2. Funnel plot comparing incidence of musculoskeletal events in patients who received PCSK9 inhibitors compared to current standard of care.



Supplementary Figure 3. Funnel plot comparing incidence of neurocognitive events in patients who received PCSK9 inhibitors compared to current standard of care.



Supplementary Figure 4. Funnel plot comparing incidence of stroke in patients who received PCSK9 inhibitors compared to current standard of care.