Meta-analysis of Randomized Controlled Trials Assessing the Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies on Mortality and Cardiovascular Outcomes

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition by monoclonal antibodies has been shown to reduce low density lipoprotein (LDL-C) but its effects on cardiovascular (CV) outcomes have not been fully described. The aim of this study is to assess the impact of PCSK9 inhibition on mortality and CV outcomes by pooling data from all available randomized clinical trials (RCT) of PCSK9 inhibitors. We conducted a comprehensive search of electronic databases, up to December 1, 2018, for all RCTs comparing PCSK9 inhibition to placebo or ezetimibe in patients with hypercholesterolemia or coronary artery disease receiving maximally tolerated statin for primary or secondary prevention of mortality and cardiovascular outcomes. We used random-effects meta-analyses to summarize the studies. We retained 23 RCTs having included 88,041 patients in primary and secondary prevention. The follow-up ranged from 6 to 36 months. PCSK9 inhibition was not significantly associated with reductions in total mortality (odds ratio [OR] 0.91, 95% confidence interval [CI] 078 to 1.06; p = 0.22) and CV mortality (OR 0.95, 95% CI 0.84 to 1.07; p = 0.37). In contrast, PCSK9 inhibition was associated with reductions in myocardial infarction (OR 0.80, 95% CI 0.71 to 0.91; p <0.0001), stroke (OR 0.75, 95% CI 0.65 to 0.85; p <0.0001), and coronary revascularization (OR 0.82, 95% CI 0.77 to 0.88; p <0.0001). In conclusion, PCSK9 inhibition was associated with reductions in myocardial infarction, stroke, and coronary revascularization. Future analyses may identify high-risk patients who may benefit more from these agents and longer follow-up of current or new trials may show a mortality benefit. **(Am J Cardiol 2019;124:1869−1875)**

Statins are the foundation of lipid-lowering therapy for primary and secondary prevention of cardiovascular events.[1] The lower the low-density lipoprotein cholesterol (LDL-C) concentration, the greater the reduction in cardiovascular (CV) outcomes observed with high-intensity statins[1,2] and ezetimibe.[3] However, up to 40% of patients do not achieve sufficient LDL-C lowering even with high intensity statin plus ezetimibe[3] or due to intolerance to statins.[4] These patients are particularly at high risk for myocardial infarction (MI) and the need for coronary revascularization.[4,5] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition by monoclonal antibodies reduces LDL-C by at least 50%.[6] LDL-C levels as low as 10 to 20 mg/dl (0.26 to 0.52 mmol/L) have been achieved in patients treated with PCSK9 inhibitors; 10% of patients in the FOURIER trial achieved concentrations ≤20 mg/dl (0.52 mmol/L).[7] The effects of such intense LDL-C lowering with PCSK9 inhibitors on CV outcomes have not been fully elucidated. Navarese et al completed a pooled analysis of PCSK9 inhibitors on CV outcomes[6] but their meta-analysis was limited by a short follow-up with very few CV events. With the recent publications of the FOURIER and ODYSSEY outcomes trials,[8,9] more precise estimates of the impact of PCSK9 inhibitors on CV outcomes may be obtained. We aim to evaluate the impact of PCSK9 inhibition on mortality and CV outcomes by pooling data from all available randomized controlled trials (RCTs).

Methods

We searched the electronic databases MEDLINE, PubMed, Embase, ClinicalTrials.gov, and Web of Science up to December 1, 2018, using a combination of relevant keywords and medical subject heading terms: PCSK9; PCSK9 antibody/inhibitor, alirocumab, evolocumab, bococizumab, AMG145, REGN727, SAR236553, RN 316, and PF-04950615. Database searching was supplemented by manually screening references of relevant articles, proceedings of pertinent meetings, and contacting clinical experts

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See page 1874 for disclosure information.

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in the field. Our search had no restriction on publication type and language. We included all RCTs which compared PCSK9 inhibitors with control (either placebo or lipid lowering therapy), with at least 6 months of follow-up. We excluded observational studies, abstracts, reviews, commentaries, and letters. Disagreements about inclusion of studies were resolved by consensus.

Three investigators (AAT, MM, and AD) independently extracted information on study characteristics (author, study type, and publication year), duration of follow-up (mean, median, or maximum number of follow-up), sample size, sex, mean age, diabetes mellitus, hypertension, and coronary artery disease. Disagreements on interpretation of data were resolved by consensus. The primary efficacy outcomes were all-cause mortality and major adverse cardiovascular events (MACE), which was defined as CV death, nonfatal MI, and nonfatal stroke. The secondary outcomes of interest were CV death, MI, stroke, and coronary revascularization, separately.

We evaluated the quality of included RCTs by using the Risk of Bias Tool developed by the Cochrane Collaboration. For each RCT, 3 reviewers (AAT, MM, and AD) independently assigned a score of high, low, or unclear to each of the following domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data and selective outcome reporting. Disagreements were resolved by consensus. We included all eligible RCTs regardless of their assessed quality.

We used random effects models to pool the outcomes of the retained RCTs. The results are presented as odds ratios (OR) with 95% confidence intervals (CIs). Two-tailed probability values of <0.05 were considered significant.

We completed subgroup analyses for evolocumab and alirocumab separately, trials with at least 1-year of follow-up and RCTs which compared PCSK9 to ezetimibe. We did not perform a separate analysis for bococizumab since there were only 2 trials that were both prematurely terminated. We also examined the potential impacts of age, sex, and mean LDL-C on the effects of PCSK9 inhibition on CV outcomes by metaregression. Furthermore, repeat analysis with fixed-effects models was performed. All statistical analyses were performed with the use of Comprehensive Meta-Analysis Software version 3.4 (Biostat, Inc).

Results

Our systematic search of the literature identified 3,295 records. Supplementary Figure 1 shows the PRISMA flow chart of study selection. After title and abstract review, 61 full text articles were evaluated.

The final number of RCTs retained were 23 trials with 88,041 patients randomized to PCSK9 inhibition (n = 46,157) or control (n = 41,884).[8–24] All included studies had a low risk of bias as assessed by the Cochrane Collaboration bias detection tool[8–24] (Supplementary Table 1). There were 16, 5, and 2 studies evaluating the effects of alirocumab,

Table 1
Study characteristics

Study	Enrollment period	N	PCSK9 inhibitor	Comparator	CAD	Statin use	Ezetimibe (PCSK9 group/ comparator group	Mean or median follow-up (months)
DESCARTES	2012-2013	901	Evolocumab	Placebo	+ 16%	Atorvastatin 88%	21%/21%	12
FOURIER	2013- 2015	27564	Evolocumab	Placebo	+ 80%	Atorvastatin 69%	5%/5%	26
GAUSS-3	2013-2014	218	Evolocumab	Ezetemibe	+ 32%	0%	0%/100%	6
GLAGOV	2013-2015	968	Evolocumab	Placebo	+	Any statin 100%	2%/2%	18
ODYSSEY ALTERNATIVE	2012 −2013	251	Alirocumab	Ezetemibe	+ 47%	0%	0%/100%	6
ODYSSEY CHOICE I	2013-2014	803	Alirocumab	Placebo	+ 52%	Any statin 68%	14%/14%	7
ODYSSEY CHOICE II	2014	233	Alirocumab	Placebo	+ 57%	0%	60%/60%	4
ODYSSEY COMBO I	2012-2014	316	Alirocumab	Placebo	+ 78%	Any statin 100%	7%/10%	6
ODYSSEY COMBO II	2012-2013	720	Alirocumab	Ezetemibe	+ 90%	Any statin 100%	0%/100%	12
ODYSSEY DM-DYSLIPIDEMIA	2016- 2016	413	Alirocumab	Usual Care*	+ 34%	Any statin 81%	38%/38%	6
ODYSSEY DM-INSULIN		517	Alirocumab	Placebo	+ 35%	Any statin 74%	14%/8%	6
ODYSSEY FH I		486	Alirocumab	Placebo	+ 46%	Any statin 100%	56%/60%	6
ODYSSEY FH II		248	Alirocumab	Placebo	+ 36%	Any statin 100%	67%/65%	6
ODYSSEY HIGH FH	2012-2015	104	Alirocumab	Placebo	0%	Any statin 100%	14%/12%	18
ODYSSEY JAPAN	2014-2015	215	Alirocumab	Placebo	0%	Any statin 100%	-	12
ODYSSEY KT		199	Alirocumab	Placebo,	+ 97%	Any statin 100%	14%/12%	6
ODYSSEY LONG TERM		2338	Alirocumab	Placebo	+	Any statin 100%	14%/15%	20
ODYSSEY OPTIONS I	2012-2014	205	Alirocumab	Ezetimibe	+	Any statin 100%	0%/100%	6
ODYSSEY OPTIONS II	2012-2014	204	Alirocumab	Ezetimibe	+	Any statin 100%	0%/100%	6
ODYSSEY OUTCOMES	2012-2015	18924	Alirocumab	Placebo	+	Any statin 100%	3%/3%	36
OSLER	2011-2014	4465	Evolocumab	Placebo	+ 10%	Any statin 70%	13%/15%	12
SPIRE I	2013-2016	16817	Bococizumab	Placebo	+	Any statin 100%	8%/8%	10
SPIRE II	2013-2016	10621	Bococizumab	Placebo	+	Any statin 83%	13%/14%	10

N = number; PCSK9 = Proprotein convertase subtilisin/kexin type 9; CAD = coronary heart disease; FH = familial hypercholesterolemia; NR = not reported.

* Including ezetimibe, fenofibrate and omega-3 fatty acids.

evolocumab, and bococizumab, respectively. The comparator arm was placebo in 18 studies and ezetimibe in 5 studies. Fourteen studies involved secondary prevention of coronary heart disease (CAD) predominantly; 5 RCTs were for primary prevention in patients without established CAD and 4 other RCTs were for primary prevention in patients with familial hypercholesterolemia. Study characteristics are summarized in (Table 1). The baseline characteristics were similar in patients randomized to PCSK9 inhibitors and the control groups (Table 2). The mean age of patients ranged from 50 to 64 years in the PCSK9 group compared with 52 to 63 years in the control group. The proportion of included females was 38% and 37% for patients randomized to PCSK9 inhibitions and controls, respectively. The baseline LDL-C ranged from 92 to 218 mg/dl (2.38 to 5.64 mmol/L) in the PCSK9 groups and from 91 to 221 mg/dl

Table 2
Baseline patient characteristics

Study	PCSK9 inhibitor						Control					
	Age (mean) (years)	Men	HTN	DM	CAD	Mean LDL, (mg/dl)	Age (mean) (years)	Men	HTN	DM	CAD	Mean LDL, (mg/dl)
DESCARTES	56	48%	48%	10%	16%	104	57	46%	49%	14%	14%	104
FOURIER	63	75%	80%	37%	81%	92	63	76%	80%	37%	81%	92
GAUSS-3	59	54%	48%	11%	33%	218	59	47%	59%	14%	29%	221
GLAGOV	60	72%	82%	20%	100%	93	60	72%	84%	22%	100%	92
ODYSSEY ALTERNATIVE	64	56%	68%	29%	51%	179	63	54%	62%	19%	43%	188
ODYSSEY CHOICE I	61	56%		26%		127	61	61%		29%		122
ODYSSEY CHOICE II	63	57%	69%	17%	32%	158	63	53%	64%	16%	47%	159
ODYSSEY COMBO I	63	63%		45%	79%	95	63	72%		39%	78%	100
ODYSSEY COMBO II	62	75%		31%	91%	108	61	71%		32%	88%	104
ODYSSEY DM-DYSLIPIDEMIA	63	53%	87%	51%		155	63	50%	90%	58%		162
ODYSSEY DM-INSULIN	62	55%		100%	32%	114	63	55%		100%	31%	126
ODYSSEY FH I	52	56%	43%	10%	46%	143	52	58%	44%	15%	48%	143
ODYSSEY FH II	53	52%	34%	4%	35%	135	53	55%	29%	4%	38%	135
ODYSSEY HIGH FH	50	49%	56%	13%	43%	196	52	63%	60%	17%	63%	201
ODYSSEY JAPAN	60	58%		73%	32%	143	62	65%		60%	38%	143
ODYSSEY KT	60	69%		42%	54%	143	60	74%		40%	69%	140
ODYSSEY LONG TERM	60	63%		35%	68%	122	61	60%		34%	70%	121
ODYSSEY OPTIONS I	63	60%					63	60%				
ODYSSEY OPTIONS II		60%						60%				
ODYSSEY OUTCOMES	59	75%	65%	29%	100%	92	59	75%	36%	71%	100%	92
OSLER	58	50%	52%	13%	20%	120	58	51%	52%	15%	21%	121
SPIRE I	63	78%	81%	48%		94	63	78%	81%	47%		94
SPIRE II	62	66%	80%	48%		134	63	65%	81%	46%		133

PCSK9 = Proprotein convertase subtilisin/kexin type 9; HTN = hypertension; DM = diabetes mellitus; CAD = coronary heart disease; LDL = low-density lipoprotein.

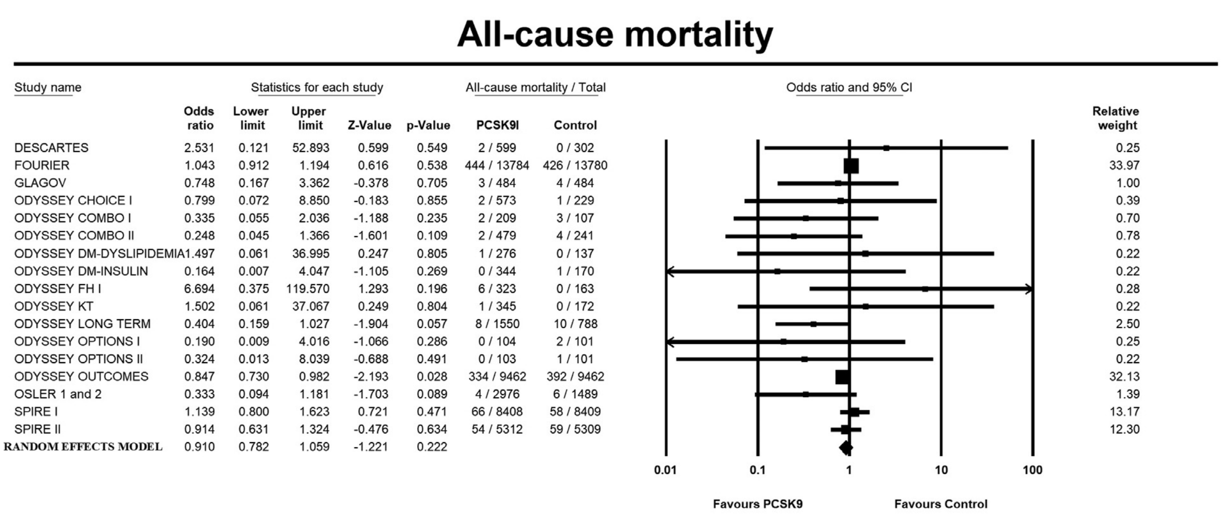

Figure 1. Forest plot showing the risk of mortality associated with PCSK9 inhibition.

(2.35 to 5.72 mmol/L) in the controls. The mean follow-up ranged from 6 to 36 months (weighted mean 18 months).

PCSK9 inhibition was not associated with reduction in either all-cause mortality (OR 0.91, 95% CI 078 to 1.06; $p = 0.22$; $I^2 = 21\%$) (Figure 1) nor in CV deaths (OR 0.95, 95% CI 0.84 to 1.07; $p = 0.37$; $I^2 = 0\%$) compared with controls (Supplementary Figure 2). In contrast, PCSK9 inhibition was associated with a 18% reduction in MACE (OR 0.82, 95% CI 0.77 to 0.87; $p < 0.0001$; $I^2 = 0\%$) (Figure 2) and MI (OR 0.80, 95% CI 0.71 to 0.91; $p < 0.0001$; $I^2 = 20\%$) (Figure 3). These agents were also associated with 25% reduction in stroke (OR 0.75, 95% CI 0.65 to 0.85; $p < 0.0001$; $I^2 = 0\%$) (Figure 4) and 18% reduction in coronary revascularization (OR 0.82, 95% CI 0.77 to 0.88; $p < 0.0001$; $I^2 = 0\%$) (Supplementary Figure 3). The results remained similar in sensitivity analyses with evaluation of either evolocumab or alirocumab separately (Supplementary Figures 4−9), in RCTs with at least 1-year follow-up (Supplementary Table 2). In an analysis of 5 RCTs with 1,500 patients and 6 months of follow-up that compared PCSK9 inhibition with ezetimibe, there was a reduction in all-cause mortality with PCSK9 inhibition, although there was no difference in other CV outcomes (Supplementary Table 3).

Metaregression was performed using age, sex, duration of follow-up, and mean LDL-C. This analysis did not

Major adverse cardiovascular events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	MACE / Total PCSK9I	MACE / Total Control	Relative weight
DESCARTES	3.550	0.183	68.946	0.837	0.403	3 / 599	0 / 302	0.04
FOURIER	0.798	0.729	0.873	-4.916	0.000	926 / 13784	1141 / 13780	41.58
GAUSS-3	0.500	0.031	8.110	-0.488	0.626	1 / 145	1 / 73	0.04
GLAGOV	0.705	0.359	1.385	-1.015	0.310	15 / 484	21 / 484	0.74
ODYSSEY ALTERNATIVE	2.976	0.120	73.759	0.666	0.505	1 / 126	0 / 124	0.03
ODYSSEY CHOICE I	0.132	0.014	1.273	-1.752	0.080	1 / 573	3 / 229	0.07
ODYSSEY CHOICE II	1.017	0.041	25.319	0.011	0.992	1 / 173	0 / 58	0.03
ODYSSEY COMBO I	1.024	0.185	5.684	0.028	0.978	4 / 209	2 / 107	0.11
ODYSSEY COMBO II	1.266	0.485	3.306	0.482	0.630	15 / 479	6 / 241	0.37
ODYSSEY DM-INSULIN	0.164	0.007	4.047	-1.105	0.269	0 / 344	1 / 170	0.03
ODYSSEY FH I	2.547	0.295	21.984	0.850	0.395	5 / 323	1 / 163	0.07
ODYSSEY FH II	0.160	0.006	3.976	-1.118	0.264	0 / 167	1 / 81	0.03
ODYSSEY HIGH FH	4.270	0.223	81.699	0.964	0.335	4 / 72	0 / 32	0.04
ODYSSEY JAPAN	0.500	0.031	8.111	-0.488	0.626	1 / 143	1 / 72	0.04
ODYSSEY KT	0.099	0.005	2.067	-1.492	0.136	0 / 345	2 / 172	0.04
ODYSSEY LONG TERM	0.500	0.291	0.858	-2.516	0.012	27 / 1550	27 / 788	1.16
ODYSSEY OPTIONS I	0.321	0.013	7.962	-0.694	0.488	0 / 104	1 / 101	0.03
ODYSSEY OPTIONS II	0.136	0.007	2.666	-1.314	0.189	0 / 103	3 / 101	0.04
ODYSSEY OUTCOMES	0.836	0.764	0.916	-3.867	0.000	977 / 9462	1145 / 9462	41.16
OSLER 1 and 2	0.799	0.362	1.766	-0.554	0.580	16 / 2976	10 / 1489	0.54
SPIRE I	1.000	0.798	1.253	0.001	0.999	154 / 8408	154 / 8409	6.64
SPIRE II	0.752	0.605	0.934	-2.577	0.010	148 / 5312	195 / 5309	7.16
RANDOM EFFECTS MODEL	0.817	0.771	0.866	-6.810	0.000			

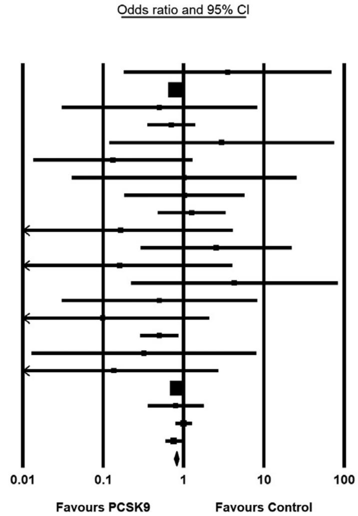

Figure 2. Forest plot showing the risk of major adverse cardiovascular events associated with PCSK9 inhibition.

Myocardial infarction

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	MI / Total PCSK9I	MI / Total Control	Relative weight
DESCARTES	1.516	0.062	37.332	0.255	0.799	1 / 599	0 / 302	0.14
FOURIER	0.723	0.640	0.816	-5.230	0.000	468 / 13784	639 / 13780	31.52
GAUSS-3	0.500	0.031	8.110	-0.488	0.626	1 / 145	1 / 73	0.18
GLAGOV	0.708	0.311	1.610	-0.823	0.410	10 / 484	14 / 484	2.03
ODYSSEY ALTERNATIVE	2.976	0.120	73.759	0.666	0.505	1 / 126	0 / 124	0.14
ODYSSEY CHOICE I	0.132	0.014	1.273	-1.752	0.080	1 / 573	3 / 229	0.28
ODYSSEY CHOICE II	1.017	0.041	25.319	0.011	0.992	1 / 173	0 / 58	0.14
ODYSSEY COMBO I	0.510	0.032	8.228	-0.475	0.635	1 / 209	1 / 107	0.18
ODYSSEY COMBO II	2.039	0.570	7.293	1.095	0.273	12 / 479	3 / 241	0.86
ODYSSEY DM-INSULIN	0.164	0.007	4.047	-1.105	0.269	0 / 344	1 / 170	0.14
ODYSSEY FH I	0.503	0.031	8.095	-0.485	0.628	1 / 323	1 / 163	0.18
ODYSSEY FH II	0.160	0.006	3.976	-1.118	0.264	0 / 167	1 / 81	0.14
ODYSSEY HIGH FH	4.270	0.223	81.699	0.964	0.335	4 / 72	0 / 32	0.16
ODYSSEY JAPAN	0.500	0.031	8.111	-0.488	0.626	1 / 143	1 / 72	0.18
ODYSSEY KT	0.165	0.007	4.083	-1.100	0.271	0 / 345	1 / 172	0.14
ODYSSEY LONG TERM	0.390	0.193	0.788	-2.623	0.009	14 / 1550	18 / 788	2.72
ODYSSEY OPTIONS II	0.324	0.013	8.039	-0.688	0.491	0 / 103	1 / 101	0.14
ODYSSEY OUTCOMES	0.858	0.767	0.958	-2.711	0.007	626 / 9462	722 / 9462	33.33
OSLER 1 and 2	0.900	0.301	2.691	-0.188	0.851	9 / 2976	5 / 1489	1.16
SPIRE I	1.115	0.835	1.489	0.738	0.461	98 / 8408	88 / 8409	12.51
SPIRE II	0.766	0.584	1.005	-1.924	0.054	94 / 5312	122 / 5309	13.71
RANDOM EFFECTS MODEL	0.803	0.712	0.905	-3.595	0.000			

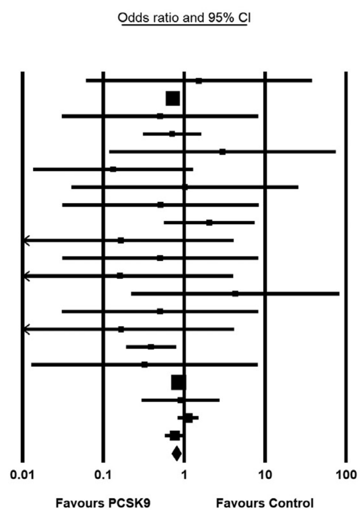

Figure 3. Forest plot showing the risk of myocardial infarction associated with PCSK9 inhibition.

Stroke

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PCSK9I	Control	Relative weight
	Statistics for each study					Stroke / Total		
FOURIER	0.787	0.655	0.945	-2.559	0.011	207 / 13784	262 / 13780	53.90
GLAGOV	0.665	0.111	3.999	-0.445	0.656	2 / 484	3 / 484	0.57
ODYSSEY COMBO I	2.590	0.123	54.439	0.613	0.540	2 / 209	0 / 107	0.20
ODYSSEY COMBO II	0.502	0.031	8.062	-0.486	0.627	1 / 479	1 / 241	0.24
ODYSSEY FH I	1.521	0.062	37.542	0.256	0.798	1 / 323	0 / 163	0.18
ODYSSEY KT	0.165	0.007	4.083	-1.100	0.271	0 / 345	1 / 172	0.18
ODYSSEY LONG TERM	2.295	0.495	10.649	1.061	0.289	9 / 1550	2 / 788	0.77
ODYSSEY OPTIONS II	0.324	0.013	8.039	-0.688	0.491	0 / 103	1 / 101	0.18
ODYSSEY OUTCOMES	0.727	0.568	0.930	-2.536	0.011	111 / 9462	152 / 9462	30.00
OSLER 1 and 2	0.750	0.125	4.495	-0.315	0.753	3 / 2976	2 / 1489	0.57
SPIRE I	0.527	0.302	0.919	-2.257	0.024	19 / 8408	36 / 8409	5.88
SPIRE II	0.665	0.404	1.093	-1.609	0.108	26 / 5312	39 / 5309	7.35
RANDOM EFFECTS MODEL	0.745	0.651	0.853	-4.276	0.000			

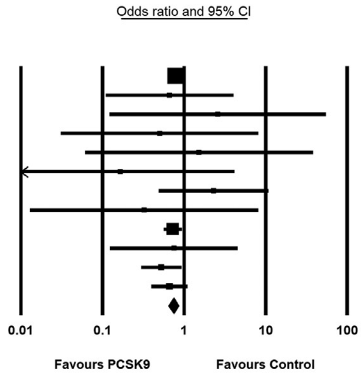

Figure 4. Forest plot showing the risk of stroke associated with PCSK9 inhibition.

predict the observed benefit in MACE, MI, stroke, and coronary revascularization associated with PCSK9 inhibition (Supplementary Figures 10−15). Analyses using fixed-effects models did not change our results.

Discussion

Our study is the most comprehensive analysis of all reported trials of PCSK9 inhibition to date. We showed that PCSK9 inhibitors were associated with approximately 20% reduction in MI, stroke, and coronary revascularization without significant impact on total and CV mortality. The benefits of PCSK9 inhibition was consistent with alirocumab and evolocumab separately and in studies with at least 1 year of follow-up.

PCSK9 inhibition was not associated with any reduction in all-cause mortality or CV death. Our result is in contrast to the observed reduction in all-cause mortality observed in the ODYSSEY OUTCOMES trial.[9] It is of note that ODYSSEY OUTCOMES was the only RCT which enrolled patients after acute coronary syndromes who would be at higher risk of mortality than patients with stable CAD and without established CAD. Furthermore, follow-up duration in ODYSSEY OUTCOMES was the longest of all RCTs evaluating PCSK9 inhibition. The longer follow-up of ODYSSEY OUTCOMES may have provided more time to observe long-term mortality benefit of PCSK9 inhibitors. Nevertheless, it remains possible that the all-cause mortality reduction observed in ODYSSEY OUTCOMES was entirely due to chance since it was observed after termination of formal hierarchical statistical testing.

The observed reductions of MACE, MI, and coronary revascularization were notable despite relatively short follow-up (median <3 years) for the studies of PCSK9 inhibitors included in this meta-analysis, compared with a median of 6 years of follow-up in the IMPROVE-IT trial involving ezetimibe.[3] Moreover, the reductions in adverse CV events appeared to be of larger magnitude than those observed in the IMPROVE-IT trial, the latter showing only a relative risk reduction of 6% in its primary end point after a much longer follow-up. Cost appraisal may provide valuable insight into the cost-benefit of PCSK9 inhibitors compared with ezetimibe.

The 25% reduction in stroke with PCSK9 inhibition observed in our meta-analysis is noteworthy. Cannon et al showed 20% reduction in risk of ischemic stroke associated with addition of ezetimibe to high-intensity statin therapy following acute coronary syndromes.[4] Future studies may help to elucidate the potential benefits of PCSK9 inhibitors for primary and secondary stroke prevention.

Only a very small minority of patients enrolled in the FOURIER and ODYSSEY trials were on ezetimibe (5% and 3%, respectively), and only 5 RCTs compared PCSK9 inhibition to ezetimibe. We observed a survival benefit with PCSK9 inhibition, without significant reduction in total CV adverse outcomes, in our subgroup analysis of studies comparing PCSK9 inhibition with ezetimibe (Supplementary Table 3). In each of these 5 RCTs, there was a greater LDL-C reduction with PCSK9 inhibition than with ezetimibe. This analysis was limited by the small number of studies and relatively short follow-up. The benefits of PCSK9 inhibition compared with ezetimibe may be magnified with longer follow-up.

Our metaregression showed that the benefit of PCSK9 inhibitors was not modified by covariates such as LDL-C concentration, age, and duration of follow-up. The reductions in MACE were similar with both alirocumab and evolocumab. Our findings suggest that these benefits represent a class effect. Though there was a trend toward a reduction in MACE with bococizumab this did not reach statistical significance likely owing to the short follow-up as the trials were stopped prematurely; however, a significant reduction in stroke was still observed with bococizumab.

This meta-analysis has a few noteworthy limitations. Firstly, the pooled RCTs include heterogeneous populations such as subjects with established CV disease and those at risk but without known CV disease. Due to the absence of patient-level data, we could not evaluate the impact of PCKS9 inhibition on different patient risk profiles. Second, there were marked variations in the duration of follow-up. Nevertheless, we observed similar results in analyses limited to RCTs with at least 1 year of follow-up. Long-term follow-up (>3 years) may be needed to observe a reduction in mortality with PCSK-9 inhibition.

In conclusion, PCSK9 inhibition was associated with reductions in MACE including MI, stroke, and coronary revascularization. There was no observed mortality benefit associated with these medications in primary and secondary prevention in patients with and without established CAD. Future analyses may identify high-risk patients who may benefit more from these agents and longer follow-up of current or new trials may show a mortality benefit.

Disclosures

Dr. Dube received research support from AstraZeneca and DalCor and has a minor equity interest in DalCor. Dr. Sherman has received speaker or advisory board fees from Sanofi, NovoNordisk, AKCEA, Janssen and AstraZeneca. Dr. Gregoire has received speaker fees from Amgen, AZ, Bayer, Boehinger-Ingelheim, BMS, Merck. Novartis, Pfizer, Servier, Sanofi, Sunovion, Amgen, AZ, Bayer, Boehinger-Ingelheim, BMS, Eli-Lilly, HSL Therapeutics, Janssen, Merck. Novartis, NovoNordisk, Pfizer, Servier, Sanofi and is former co-chair of the Canadian Dyslipidemia Guideline (2012-2016), member of Hypertension Canada Guideline. Dr. Thanassoulis has participated in advisory boards for Amgen, Sanofi/Regeneron, and Ionis, has participated in speaker bureaus for Amgen, Sanofi, Boehringer, and Servier, and has received grant support from Ionis and Servier. Dr. Tardif has received research grants from Amarin, AstraZeneca, DalCor, Esperion, Ionis, Sanofi and Servier; honoraria from DalCor, Pfizer, Sanofi and Servier; and minor equity interest in DalCor. Dr. Huynh has received research grants and consulting honoraria from Amgen, Sanofi, Regeneron and Pfizer. The remaining authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.09.011.

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