Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov

van Bruggen, F H; Nijhuis, G B J; Zuidema, S U; Luijendijk, H J

Published in:
Expert Review of Clinical Pharmacology

DOI:
10.1080/17512433.2020.1787832

Publication date:
2020

Taylor & Francis
Taylor & Francis Group

Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review

F. H. van Bruggen , G. B. J. Nijhuis , S. U. Zuidema & Hendrika Luijendijk

To cite this article: F. H. van Bruggen , G. B. J. Nijhuis , S. U. Zuidema & Hendrika Luijendijk (2020) Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review, Expert Review of Clinical Pharmacology, 13:7, 787-796, DOI: 10.1080/17512433.2020.1787832

To link to this article: https://doi.org/10.1080/17512433.2020.1787832

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2020, VOL. 13, NO. 7, 787–796
https://doi.org/10.1080/17512433.2020.1787832

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review

F. H. van Bruggen, G. B. J. Nijhuis, S. U. Zuidema and H. J. Luijendijk

University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly Care Medicine, Groningen, The Netherlands

ABSTRACT

Background: Previous reviews of PCSK9 inhibitor trials are limited by a focus on composite cardiovascular outcomes. ClinicalTrials.gov provides trial results for individual clinical outcomes. Aim of this systematic review was to assess the effect of PCSK9 inhibitors on the risk of myocardial infarction, stroke/TIA, heart failure, diabetes mellitus, neurocognitive events, all-cause serious adverse events (SAE), and all-cause deaths as registered on ClinicalTrials.gov.

Methods: PubMed, regulatory reports, ClinicalTrials.gov, and company websites were used to search studies. Randomized trials comparing PCSK9 inhibitor with placebo in participants with hypercholesterolemia were eligible. Study characteristics, risk of bias, and numbers of participants with the outcomes of interest were collected.

Results: We identified 33 lipid-lowering and 4 clinical outcomes trials with results on ClinicalTrials.gov (n = 16,958 and n = 73,836, respectively). Risk of bias was generally high. PCSK9 inhibitors did not affect the risk of any of the investigated outcomes in either type of trial. However, in clinical outcomes studies, alirocumab decreased the risk of all-cause SAE (OR 0.92; 95% CI 0.86–0.98), and evolocumab probably increased the risk of mortality (OR 1.12; 95% CI 1.00–1.25).

Conclusions: Our meta-analysis of clinical events registered on ClinicalTrials.gov did not show that PCSK9 inhibitors improve cardiovascular health. Evolocumab increased the risk of all-cause mortality.

ARTICLE HISTORY
Received 30 April 2020
Accepted 23 June 2020

KEYWORDS
Adverse events; all-cause mortality; ClinicalTrials.gov; PCSK9 inhibitors; review

1. Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective lipid-lowering drugs. Evolocumab and alirocumab, the two PCSK9 inhibitors that are currently on the market, reduce LDL cholesterol by 53–59%. This has been shown in at least 25 trials that investigated the lipid-lowering effects of PCSK9 inhibitors [1–6].

However, the effect of these drugs on clinical outcomes is unclear because prior reviews showed a number of limitations. First, reviews have focussed on the composite outcome 'major adverse cardiovascular events' (MACE) [7,8]. MACE includes a varying combination of cardiovascular diseases, revascularisation procedures, and hospitalizations. The substantial heterogeneity in this endpoint between trials makes it hard to interpret the results of reviews. Additionally, efficacy may be overestimated because patients with high blood cholesterol (in the placebo groups) might receive revascularisation procedures more often [9].

Second, prior systematic reviews about PCSK9 inhibitors included non-atherosclerotic types of myocardial infarction (MI) [10–12]. Besides spontaneous MI, clinical outcome trials have included MI due to supply-demand imbalance, cardiac death suggestive of MI without increased biomarkers, and MI related to revascularisation procedures [13,14]. These non-atherosclerotic subtypes may not be relevant outcomes of lipid-lowering treatment.

Third, unblinded (open-label) studies were included in previous reviews, whereas lipid-lowering trials were excluded [11,15]. Some lipid-lowering trials had not been published at the time, had a relatively small sample size and short follow-up, and did not report the investigated composite clinical outcomes. Nevertheless, these trials might represent a substantial number of patients and thus provide useful information.

Trial results registered on ClinicalTrials.gov offer a unique opportunity to investigate outcomes of PSCK9 inhibitors independent of a study's publication status [16]. Since 2007, 'all anticipated and unanticipated' serious adverse events (SAE) that occurred in a trial of a registered drug need to be documented on ClinicalTrials.gov as mandated by the FDA (2016 22129 FDA ruling). An SAE is potentially fatal or causes permanent health damage. SAE are diagnosed and registered by the patients' clinicians as part of the trial in a standardized way according to FDA ruling [16]. All-cause mortality was added to the standard format of the website in 2017 [17]. No systematic review about clinical outcomes of PCSK9 inhibitors with ClinicalTrial.gov data has been published before. The aim of our

CONTACT H. J. Luijendijk h.j.luijendijk@umcg.nl University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly Care Medicine, Groningen 9700 AD, The Netherlands

This article has been republished with minor changes. These changes do not impact the academic content of the article.

Supplemental data for this article can be accessed here.

Article highlights

- This is the first systematic review of individual cardiovascular outcomes in placebo-controlled trials of PCSK9 inhibitors with ClinicalTrial.gov data.
- ClinicalTrials.gov provides the number of cardiovascular events diagnosed by the attending physicians of participants in trials.
- ClinicalTrials.gov enables the use of published and unpublished PCSK9 inhibitor trials in a meta-analysis.
- PCSK9 inhibitors did not reduce the risk of myocardial infarction or stroke/TIA compared to placebo as reported on ClinicalTrials.gov.
- Evolocumab probably increased the risk of all-cause mortality compared to placebo in a large clinical outcomes study.

review was to assess the risk of myocardial infarction, stroke/TIA, heart failure, diabetes mellitus, neurocognitive events, all-cause SAE and all-cause mortality for PCSK9 inhibitors compared to placebo using data registered on ClinicalTrial.gov.

2. Methods

We performed a systematic review of randomized trials among adult patients with hypercholesterolemia, a history of cardiovascular disease, and no contra-indications for PCSK9 inhibitor use (P). A PCSK9 inhibitor (I) needed to be tested against placebo (C). Our primary outcomes (O) were myocardial infarction, stroke/TIA, heart failure, diabetes mellitus, neurocognitive events, and all-cause SAE. Additional outcomes were any adverse events and all-cause mortality. The protocol has been registered on PROSPERO (CRD42018104676).

2.1. Search and selection

Two independent reviewers performed the search and selection of the trials. Five PCSK9 inhibitors have been tested in patients at risk of cardiovascular disease: evolocumab, alirocumab, bococizumab, LY3015014, and RG7652. We used three sources to find phase 2 and phase 3 randomized placebo-controlled trials of these drugs. First, we searched Pubmed with the terms 'evolocumab, alirocumab, bococizumab, LY3015014, RG7652' and 'placebo.' In addition, we hand-searched the references of the FDA reports and EMA reports about evolocumab and alirocumab, and two systematic reviews [3,15,18–20]. Finally, we looked for trials that were registered on clinicaltrials.gov and mentioned in online reports of the pharmaceutical companies. We reran our search in June 2019.

When title and abstract suggested a potentially eligible trial, we assessed the full-text publication or protocol. We selected trials that were randomized, placebo-controlled, and performed among adult patients at an increased risk of cardiovascular disease. Language and publication date were not exclusion criteria.

2.2. Risk of bias assessment

Two independent reviewers (HJL and FvB or GBJN) assessed the risk of bias. In line with the revised Cochrane risk of bias tool, we scored five domains of bias that can affect the measured effect of the intended treatment: randomization, blinding of outcome assessment, drop-out during follow-up /handling of missing data, selective reporting, and other sources of bias [21,22]. A domain was considered as a low risk of bias, if the related design, conduct, and results did not indicate that bias might have occurred, a high risk if there were indications for bias, and unclear risk if information was missing. Disagreements were resolved in consensus meetings.

2.3. Data extraction

Two independent reviewers (HJL and FvB or GBJN) extracted the data with a standardized data form. First, we abstracted general study characteristics: investigated drug, type of hypercholesterolemia (familial, non-familial), number of participants, background lipid-lowering therapy, and study duration [9,23]. We included all patients randomized except those in PCSK9 inhibiting groups that differed from the placebo group in another way than just the randomized treatment.

Next, we extracted the number of participants with arteriosclerotic myocardial infarction, stroke, TIA, and heart failure (see Supplementary Table 1 for the definitions). The rationale for investigating heart failure lies in its pathophysiology. It is often caused by ischemic cardiomyopathy after a (silent) myocardial infarction [24–27]. Furthermore, heart failure is considered to be a cardiovascular disease in itself and sometimes included in MACE too [28]. Moreover, it had been adopted as a cause of cardiovascular death in the PCSK9 inhibitor trials.

We also recorded the number of participants with diabetes mellitus and neurocognitive disorders – unintended SAE that regulatory agencies were especially interested in [18–20,29] – as well as all-cause SAE and all-cause deaths. Our source of information for these outcomes was ClinicalTrials.gov. If SAE were reported on this website but a disease of our interest was not, we assumed that it had not occurred. Additionally, we planned to extract the outcome 'any adverse event.' However, we found that this outcome is not registered on ClinicalTrials.gov.

If multiple drug groups were present in a trial because multiple dosages were tested, the number of participants and events was combined. The same applied to multiple placebo groups. Disagreements about abstracted data were also resolved in consensus meetings. We checked the website for new trial results until June 2019.

2.4. Statistical analysis

We calculated the pooled odds ratios (OR) for myocardial infarction, stroke/TIA, heart failure, diabetes mellitus, neurocognitive events, all-cause SAE, and all-cause mortality for PCSK9 inhibitors compared to placebo use. If the event rates were higher than 30% in one or both groups, we calculated the risk ratio (RR) [21].

As the number of participants with individual SAE and deaths was often zero or very low, we used the Mantel–Haenszel weighted fixed effects model with continuity correction [30,31]. As many trials reported no events in both

arms, we used the reciprocal of the opposite group arm size to obtain the continuity correction [32]. We used a fixed effects model to start with. If heterogeneity was found to be moderate to large based on Chi^2 (p-value of <0.05) or I^2 (>40%), we used a random effects model [21].

We generated pooled risks for all PCSK9 inhibitors, and after receiving reviewer comments, for the registered drugs evolocumab and alirocumab separately as well. We did not combine the results of the smaller lipid-lowering (efficacy) studies that focus on LDL-cholesterol reduction with those of the 'supersized' clinical outcomes studies. The latter would have a very high weight in the overall estimate due to the sheer number of patients and events.

We pooled the results of lipid-lowering studies (8–78 weeks) and clinical outcomes studies (40–146 weeks) independent of study duration. The cumulative incidence curves in the regulatory reports and published articles show a linear risk of major adverse events and death for the active drug and placebo groups over time [7,19,29,33]. A previous meta-analysis about PCSK9 inhibitors did not detect substantial differences with or without adjustment for person-years either [34]. We also aggregated results across doses, because phase 2 and 3 studies have not shown dose-related effects on adverse events and deaths in a previous FDA evaluation [19].

A post hoc decision was to test whether the pooled risks differed significantly between the lipid-lowering and clinical outcomes studies. We calculated standard errors from the confidence intervals of the coefficients, and entered them in the z-formula to obtain z-scores, and from them p-values.

3. Results

Our search yielded 53 potentially eligible trials (Figure 1). After application of exclusion criteria, we included 38 completed trials that tested one of five PCSK9 inhibitors versus placebo [3,30,34–66]. For all trials except EQUATOR, outcome data have been reported on ClinicalTrials.gov. Hence, we performed analyses with the data of 33 lipid-lowering studies (total n = 16,958) and four clinical outcomes studies (n = 73,836).

3.1. Study characteristics

The trials were conducted in patients with primary, polygenic or heterozygous familial hypercholesterolemia, and hyper- or mixed lipidemia (Table 1). Most patients already used a statin, or were prescribed statins before randomization. The average study duration weighted for the number of participants was 43 weeks for the lipid-lowering trials (range 8–78 weeks), and 95 weeks for the clinical outcomes trials (range 30–146 weeks). The lipid-lowering studies included patients with a heterogeneous baseline risk for cardiovascular disease, while most of the participants in the clinical outcome studies had already experienced a cardiovascular event (see yearly risk of cardiovascular events in supplementary Table 2). All except two studies scored a high risk of bias on at least one domain other than commercial funding (supplementary Table 3).

3.2. Individual serious adverse events

The risk of myocardial infarction was not lower between the PCSK9 inhibitor and the placebo groups in the lipid-lowering trials (OR 0.92; 95% CI: 0.64–1.30) and clinical outcomes trials

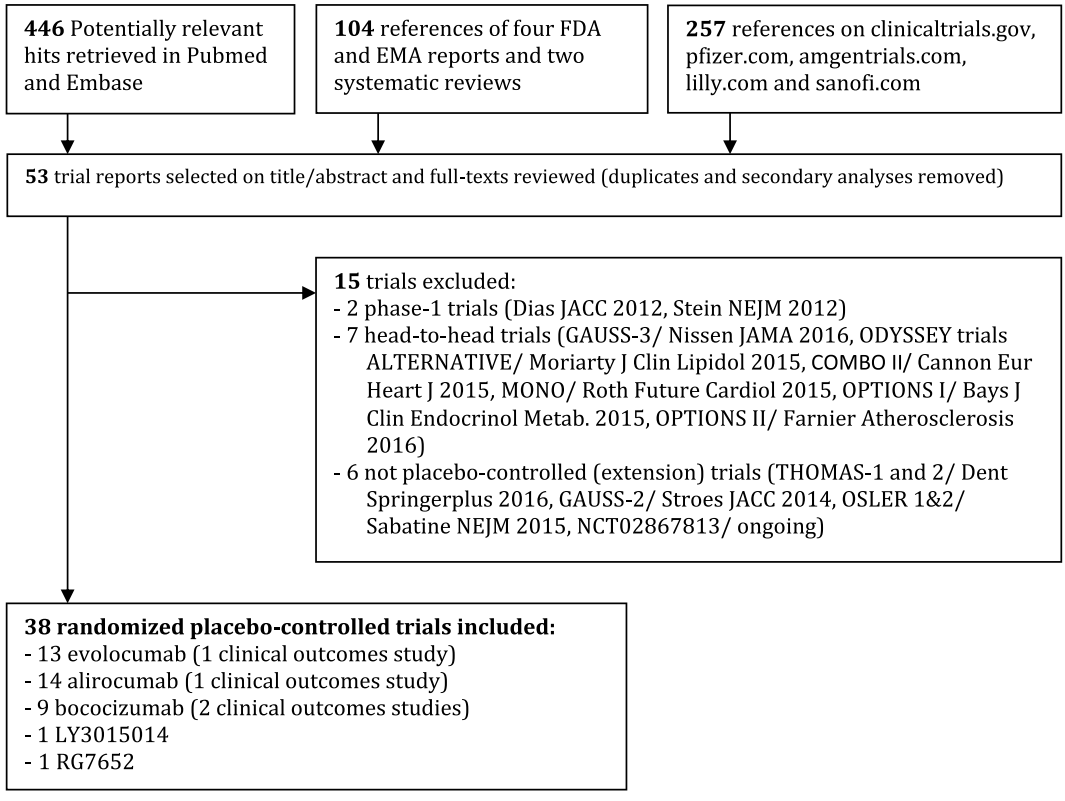

Figure 1. Flow diagram of literature search and study selection.

Table 1. Characteristics of included placebo-controlled PCSK9 inhibitor trials.

Study	Acronym	Patient population	Background therapy	Duration, weeks	Patients randomized, n^
Alirocumab					
McKenney 2012	DFI11565	HC	Statin	12	183
Roth 2012	DFI11566	HC	Statin*, diet	8	61
Stein 2012	CL-1003	HeFH	Diet	12	77
Kastelein 2015	ODYSSEY FH I	HeFH with/without CVD	Statin, diet	78	486
Kastelein 2015	ODYSSEY FH II	HeFH with/without CVD	Statin, diet	78	249
Kereiakes 2015	ODYSSEY COMBO I	HC with high CVD risk	Statin	52	316
Robinson 2015	ODYSSEY LONG TERM	HeFH with (high risk of) CVD	Statin, diet	78	2338
Ginsberg 2016	ODYSSEY HIGH FH	HeFH with very high LDL-D	Statin, diet	78	107
Roth 2016	ODYSSEY CHOICE I	HC	Statin, FF or diet	48	803
Stroes 2016	ODYSSEY CHOICE II	HC, statin intolerant, moderate to very high CVD risk	EZ, FF or diet	24	228
Teramoto 2016a	DFI12361	HC	Statin	12	100
Teramoto 2016b	ODYSSEY JAPAN	HeFH or HC with (high risk of) CVD	Statin	52	216
Teramoto 2017	ODYSSEY NIPPON	HeFH or HC with coronary heart disease	Statin, other lipid drug or diet	12	163
Schwartz 2014	ODYSSEY OUTCOMES	Prior ACS patients with HC	Statin	146#	19,924
Bococizumab					
Ballantyne 2015	NCT01592240	HC	Statin	24	354
Ridker 2017a	SPIRE-AI	HC	Statin	12	299
Ridker 2017a	SPIRE-FH	Heterozygous Familial Hypercholesterolemia	Statin	52	370
Ridker 2017a	SPIRE-HR	Hyperlipidemia at high risk for CVD	Statin	52	711
Ridker 2017a	SPIRE-LDL	Hyperlipidemia patients with risk for CVD	Statin	52	2140
Ridker 2017a	SPIRE-LL	LDLC levels ≥100 mg/dL	Statin	52	750
Ridker 2017a	SPIRE-SI	Hyperlipidemia and statin intolerance	None	26	184
Ridker 2017b	SPIRE-1	HC with CVD, DM, or CKD, or PVD & CVD risk, or HeFH	Statin	30$	16,817
Ridker 2017b	SPIRE-2	See SPIRE-1, but statin intolerance allowed	Statin*	52$	10,621
Evolocumab					
Giugliano 2012	LAPLACE-TIMI 57	HC	Statin	12	631
Koren 2012	MENDEL-1	HC and CVD risk up to 10% per 10 yrs	Statin use not required	12	365
Raal 2012	RUTHERFORD-1	HeFH	Statin	12	168
Sullivan 2012	GAUSS-1	HC and statin intolerant	Lipid drugs not allowed	12	64
Blom 2014	DESCARTES	Hyperlipidemia	Statin*, diet	52	905
Hirayama 2014	YUKAWA-1	HC, and high CVD risk	Statin	12	310
Koren 2014	MENDEL-2	HC and CVD risk up to 10% per 10 yrs	Lipid drugs not allowed	12	461
Robinson 2014	LAPLACE-2	HC or mixed dyslipidemia	Statin*	12	1678
Kiyosue 2015	YUKAWA-2	HC, mixed dyslipidemia or HeFH, high CVD risk	Statin	12	404
Raal 2015	RUTHERFORD-2	HeFH	Statin	12	331
Amgen 2016	FLOREY	HC and mixed dyslipidemia	Statin	10	45
Nicholls 2016	GLAGOV	HC and angiographic coronary disease	Statin	76	968
Sabatine 2017	FOURIER	HC, with CVD	Statin	114$#	27,564
Other PCSK9 inhibitors					
Kastelein 2016	NCT01890967**	HC, or HeFH	Statin*, diet	16	527
Baruch 2017	EQUATOR^^	HC and (high risk for) CHD	Statin*	24	248

*Part of the study population used a statin; ^ only the groups included in our review; $ early terminated; # median follow-up; ** drug: LY3015014; ^^ drug: RG7652
ACS stands for acute coronary syndrome; CKD for chronic kidney disease; CVD for cardiovascular disease; DM for diabetes mellitus, EZ for ezetimibe; FF for fenofibrate; HC for hypercholesterolemia; HeFH for heterozygous familiar hypercholesterolemia; PVD for peripheral vascular disease.

(OR 0.88; 95% CI: 0.64–1.22) (Table 2 and Figure 2). The point estimate for stroke/TIA indicated an increased risk for PCSK9 inhibitors in the lipid-lowering trials (OR 1.32; 95% CI: 0.83–-2.09), but not in the clinical outcome trials (OR 0.97; 95% CI: 0.79–1.19), but neither risk was statistically significant. For heart failure, the risk was not lower in the PCSK9 inhibitor than the placebo groups of the lipid-lowering trials (OR 0.96; 95% CI: 0.60–1.56) and clinical outcome trials (OR 0.99; 95% CI: 0.84–1.17).

The risk for diabetes mellitus was non-statistically significantly increased in the PCSK9 inhibitor versus placebo groups in the lipid-lowering studies (OR 1.17; 95% CI: 0.75–1.82) and clinical outcomes studies (OR: 1.05; 95% CI: 0.98–1.13). Similarly, the risk for neurocognitive events was non-statistically significantly increased in the lipid-lowering (OR 1.19; 95% CI 0.76- 1.86) and clinical outcomes studies (OR 1.22; 95% CI: 0.70–2.11).

3.3. All-cause serious adverse events and deaths

PCSK9 inhibitors lowered the risk of all-cause SAE compared to placebo in the lipid-lowering studies: the OR was 0.89 (95% CI: 0.80–0.99). This reduction was due to one large bococizumab trial, which contributed a weight of 19%. Without that trial, no difference between PCSK9 inhibitors and placebo was found. In clinical outcomes studies, PCSK9 inhibitors, in general, did not affect the risk of all-cause SAE compared to placebo (OR 0.98; 95% CI: 0.91–1.05), but alirocumab decreased the risk (OR 0.92; 95% CI 0.86–0.98) (Table 3).

The risk of death was not significantly different between the PCSK9 inhibitor versus placebo groups in both the lipid-lowering studies (OR 0.80; 95% CI: 0.51–1.24) and clinical outcomes studies (OR 0.99; 95% CI: 0.84–1.17). However, for evolocumab, the risk of mortality was 1.18 (95% CI 0.46–3.02) in lipid-lowering trials and 1.12 (95% CI 1.00-1.25) in the clinical outcome trial FOURIER (Table 3). The percentage of participants that died in the placebo

Table 2. Effect of PCSK9 inhibitors on clinical outcomes in randomized placebo-controlled trials according to data reported on ClinicalTrials.gov.

Outcome	33 lipid lowering studies* (n = 16,958, mean follow-up = 43 weeks)			4 clinical outcome studies (n = 73,836, mean follow-up = 95 weeks)			Difference between ORs
	PCSK9 group, n/ N (%)	Placebo group, n/ N (%)	Odds ratio (95% CI)	PCSK9 group, n/ N (%)	Placebo group, n/ N (%)	Odds ratio (95% CI)	p-value
Myocardial infarction^	63/10772 (0.6)	45/6186 (0.7)	0.92 (0.64 - 1.30)	190/36921 (0.5)	218/36915 (0.6)	0.88 (0.64 – 1.22)	0.85
Stroke/ TIA	46/10772 (0.4)	19/6186 (0.3)	1.32 (0.83 - 2.09)	185/36921 (0.5)	191/36915 (0.5)	0.97 (0.79 – 1.19)	0.30
Heart failure	29/10772 (0.3)	19/6186 (0.3)	0.96 (0.60 – 1.56)	292/36921 (0.8)	294/36915 (0.8)	0.99 (0.84 – 1.17)	0.91
Diabetes mellitus^	46/6636 (0.7)	26/3702 (0.7)	1.17 (0.75 - 1.82)	1758/22576 (7.8)	1698/22698 (7.5)	1.05 (0.98 - 1.13)	0.66
Neurocognitive events	48/10772 (0.4)	19/6186 (0.3)	1.19 (0.76 - 1.86)	28/36921 (0.1)	23/36915 (0.1)	1.22 (0.70 – 2.11)	0.94
All serious adverse events	982/10772 (9.1)	703/6186 (11.4)	0.89 (0.80-0.99)	7606/36921 (20.6)	7734/36915 (21.0)	0.98 (0.91- 1.05)	0.13
All-cause mortality	31/10772 (0.3)	27/6186 (0.4)	0.80 (0.51- 1.24)	1019/36921 (2.8)	994/36915 (2.7)	0.99 (0.84 - 1.17)	0.35

*One trial (EQUATOR) did not report data on ClinicalTrials.gov; ^ For myocardial infarction and diabetes mellitus random effects models were used due to I^2 > 40%.

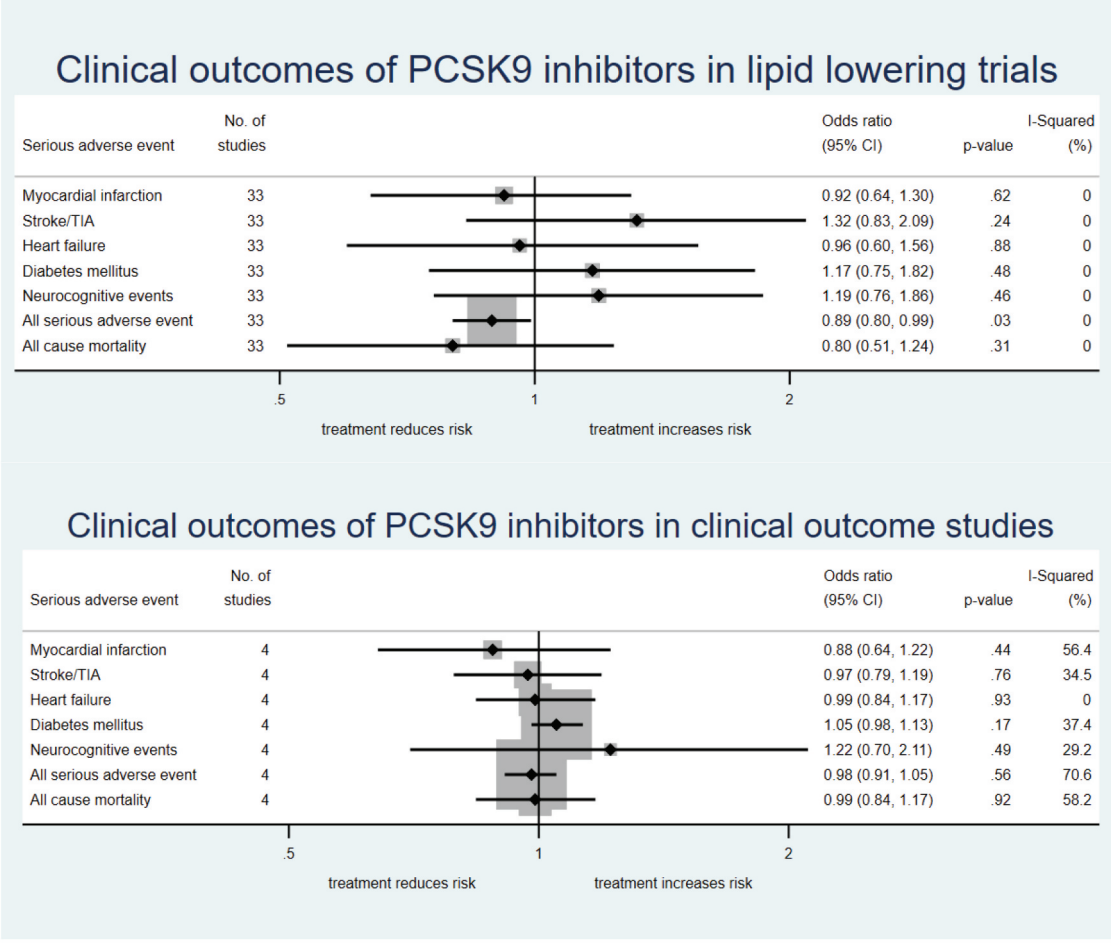

Figure 2. Risk for individual SAE, all-cause SAE, and all-cause mortality for PCSK9 inhibitors versus placebo in (a) lipid-lowering trials and (b) clinical outcome studies.

group of FOURIER was 4.3% and in the evolocumab group 4.8%. This amounts to a number needed to harm of 213 for a median follow-up of 2.2 years.

4. Discussion

In this study, we reviewed 38 randomized placebo-controlled trials of PCSK9 inhibitors, and used results of 37 trials reported

Table 3. Risk of clinical outcomes of evolocumab and alirocumab in randomized placebo-controlled trials according to data reported on ClinicalTrials.gov.

	Evolocumab		Alirocumab	
Outcome	**12 lipid lowering studies, OR (95% CI)**	**1 clinical outcome study, OR (95% CI)**	**13 lipid lowering studies, OR (95% CI)**	**1 clinical outcome study, OR (95% CI)**
Myocardial infarction^	1.00 (0.48 – 2.06)	0.74 (0.50 – 1.10)	0.63 (0.37 – 1.06)	1.14 (0.41 – 3.15)
Stroke/ TIA	0.77 (0.31 – 1.88)	1.19 (0.87 – 1.63)	2.04 (0.94 – 4.42)	1.75 (0.51 – 5.98)
Heart failure	0.89 (0.33 – 2.46)	1.07 (0.87 – 1.33)	1.23 (0.60 – 2.55)	0.90 (0.48 – 1.70)
Diabetes mellitus^	1.15 (0.40 – 3.29)	1.08 (0.99 – 1.17)	1.24 (0.68 – 2.25)	1.04 (0.67 - 1.62)
Neurocognitive events	1.01 (0.47 – 2.18)	0.80 (0.22 – 2.98)	1.55 (0.77 – 3.12)	1.89 (0.84 – 4.24)
All serious adverse events	0.97 (0.78 – 1.22)	1.00 (0.95 – 1.06)	0.91 (0.77 – 1.08)	0.92 (0.86 – 0.98)#
All-cause mortality	1.18 (0.46 – 3.02)	1.12 (1.00 – 1.25)	0.79 (0.41 – 1.54)	0.85 (0.72 – 1.02)

^For myocardial infarction and diabetes mellitus random effects models were used due to $I^2 > 40\%$; # $p < 0.05$.

on ClinicalTrials.gov. PCSK9 inhibitors did not reduce the risk of major cardiovascular and non-cardiovascular diseases. PCSK9 inhibitors in general did not affect the risk of all-cause mortality, but evolocumab probably increased it.

4.1. Cardiovascular outcomes

Despite the effect of PCSK9 inhibitors on LDL-cholesterol, our review found that these drugs did not improve cardiovascular health. In contrast, previous meta-analyses have presented a statistically significantly reduced risk of major adverse cardiovascular events (MACE) [11,12,15,63]. MACE is a heterogeneously defined composite outcome that often includes interventions and may be susceptible to bias [64,65]. Some authors have proposed to use only the individual components relating to morbidity [23]. Also, the previous reviews excluded (short-term) studies that did not report MACE, thus potentially introducing bias due to selective reporting [11,15].

Nevertheless, one previous systematic review about individual outcomes reported that PCSK9 inhibitors decreased the risk of MI (RR: 0.83; 95% CI: 0.74–0.93) and stroke (RR: 0.75; 95% CI: 0.65–0.85) versus placebo [12]. This review pooled clinical outcome studies and lipid-lowering studies, and it excluded 16 zero-event studies. As a result, two trials – FOURIER and ODYSSEY OUTCOMES – accounted for >80% of the pooled risk. In addition, outcome data were extracted from published articles, which reported many more events than ClinicalTrials.gov: e.g., respectively, 2493 versus 516 MIs. Moreover, FOURIER and ODYSSEY OUTCOMES trials included other than spontaneous atherosclerotic MIs, which represented >30% of the events [13,14].

4.2. Non-cardiovascular outcomes

Our review did not yield an increased risk for diabetes mellitus or neurocognitive events in PCSK9 inhibitor use compared to placebo in line with most published reviews [3,11,66]. One previous review showed that alirocumab had a higher risk of neurocognitive disorders. This may be explained by the fact that the results of the ODYSSEY OUTCOMES trial, which showed no increased risk for neurocognitive events, were not included in this review [2].

PCSK9 inhibitors did not decrease the risk of all-cause SAE, i.e., all-cause serious morbidity. This means that the prevention of cardiovascular diseases – if present at all – was annihilated by an increased risk of non-cardiovascular diseases. In other words, there is no net health gain. This interpretation differs from those of previous reviews [1,11,67]. They concluded that the lack of an increased risk of SAE indicated that PCSK9 inhibitors were safe to use, even though this outcome included cardiovascular diseases that PCSK9 inhibitors are supposed to prevent. In contrast to other PCSK9 inhibitors, alirocumab decreased the risk of all-cause SAE, but this did not translate into a decreased risk of death.

PCSK9 inhibitors in general did not decrease the risk of all-cause mortality in our review. Some previous reviews reported a decreased risk of all-cause mortality, but these studies had excluded 15 trials due to zero deaths in both arms, and included trials with ezetimibe or (non-blinded) usual care as control intervention [2,3,34]. Pooling placebo with other control interventions groups might have erroneously suggested a beneficial effect of PCSK9 inhibitors versus placebo on all-cause mortality.

Evolocumab probably increased the risk of all-cause mortality in the FOURIER trial. The main results article presented mortality data censored at the median follow-up (2.2 years), and this was used in previous reviews [7]. Clinicaltrials.gov provided mortality data for 3.0 years of follow-up. Follow-up was at least 3 years and 2 months in some of the participants.

4.3. Strengths and limitations

The major strength of our review is the use of data registered on ClinicalTrials.gov. Availability of primary outcome data on this website for all but one of the 38 trials decreased bias due to unpublished trials and selective reporting. We are

convinced that the SAE data are a valid representation of diseases that occurred during the trials. For each site, a blinded Primary Investigator needs to sign off all diagnoses of anticipated and unanticipated SAE made by the attending physicians [68]. Furthermore, cardiovascular events had been adjudicated by an independent committee in the largest trials [7,8,40,59], as were sometimes diabetes and neurocognitive events. Finally, the investigators need to ensure that the data submitted to ClinicalTrials.gov are accurate and complete [69].

Nevertheless, discrepancies in numbers of individual SAE between ClinicalTrials.gov and articles seem to have occurred in some trials. This problem has been reported by others before [70–72]. Mostly, the number of adjudicated events in articles was higher than the number of unadjudicated events on ClinicalTrials.gov, which is unexpected. What the discrepancies question is who decided to present which events to the adjudication committee and when. This process should be described in trial protocols.

Another strength of our review is that it shows the added value of the lipid-lowering trials, which represented 19% of all trial participants despite their relatively small sample sizes. The yearly baseline rate of targeted cardiovascular events (in the placebo groups) was very similar for the lipid-lowering and clinical outcomes studies (see supplementary Table 2). In addition, the average follow-up periods of both types of trials were short (0.8 and 1.8 year) compared to the usual reference timeframe of at least 5 years for cardiovascular risk prevention. Some results including the increased point estimate for the risk of all-cause mortality in the clinical outcomes trial of evolocumab were already consistently appearing in the early available lipid-lowering trial.

One limitation of our study was that our analysis had less power compared to other reviews due to the lower number of individual cardiovascular events reported on ClinicalTrials.gov. Another limitation of our study was that study investigators seldom describe the process of collecting SAE data in study protocols and articles.

4.4. Conclusions

ClinicalTrials.gov is an important open source that reports trial results in a structured way and enables the inclusion of unpublished data in reviews. Our review did not yield evidence that PCSK9 inhibitors decreased the risk of individual targeted and unintended serious diseases. However, in the clinical outcomes studies, alirocumab decreased the risk of all-cause serious morbidity but not of all-cause mortality, whereas evolocumab did not affect the risk of all-cause serious morbidity but probably increased the risk of death. Differences in numbers of events in articles and on ClinicalTrials.gov deserve more attention.

Preventive therapies require elaborate safety analysis before massive use. Regulatory agencies had a special interest in new-onset DM and neurocognitive disorders when reviewing PCSK9 inhibitors. Systematic reviews based on articles about PCSK9 inhibitor trials found no increased risk for these conditions. In addition, no differences in all-cause serious adverse events (SAE) and all-cause mortality between intervention and control groups were found. Hence, alirocumab and evolocumab were considered to be safe and found their way to the market and international treatment guidelines [73,74]. The published results of two large clinical outcomes trials later confirmed the safety profile.

Although our review based on ClinicalTrials.gov data confirmed the initial findings for new-onset DM, neurocognitive events, and all-cause SAE for evolocumab and alirocumab, we found an increased risk of all-cause mortality for evolocumab. ClinicalTrials.gov reported the number of deaths for 3.0 years of follow-up of the FOURIER-trial while the article reported deaths until 2.2 years of follow-up. The number needed to harm was 213. For a preventive therapy, this reflects an unacceptable lack of safety, which questions whether evolocumab should be recalled from the market.

In addition to being safe, preventive medications should also have unambiguous health benefits. Several systematic reviews based on composite outcome data from articles reported a reduction in the risk of cardiovascular events. Therefore, PCSK9 inhibitors are considered to be effective in improving cardiovascular health.

In contrast to trial results reported in articles, trial results registered on ClinicalTrials.gov enable an analysis of individual cardiovascular events. The attending physicians of the trial participants need to record all SAE including (potentially fatal) targeted cardiovascular diseases and (potentially fatal) non-cardiovascular events. The disorders are coded according to the regularly updated, clinically validated dictionary for medical terminology MedDRA, which is imposed by regulatory authorities for use in pharmaceutical trials. We found that PCSK9 inhibitors did not reduce the risk of myocardial infarction, stroke/TIA, and heart failure.

5. Measuring safety

PCSK9 inhibitors are deemed safe because they were not shown to increase the risk of a number of unintended SAE, such as new-onset DM and neurocognitive dysfunction. It is common that unintended SAE are not grouped together in a composite outcome as are targeted cardiovascular diseases. As such diseases occur less frequently than the cardiovascular events, it is likely that power to detect an increased risk will be insufficient. Moreover, some serious side-effects may not yet be expected beforehand and would be missed too.

PCKS9 inhibitors are also thought to be safe because they did not increase the risk of all-cause SAE in trials. However, this is a conclusion based on an inconsistent interpretation of the outcome all-cause SAE. Previous reviews reported a positive effect of PCSK9 inhibitors on cardiovascular health but a lack of effect on all-cause SAE [1,11,67]. As all-cause SAE cover both serious cardiovascular and non-cardiovascular events, no effect on all-cause SAE implies that the reduction in cardiovascular events was countered by an increase in non-cardiovascular events (Figure 3).

An outcome that leaves little room for misinterpretation is death. All-cause deaths include (prevented) deaths due to cardiovascular disease and (induced) deaths due to yet

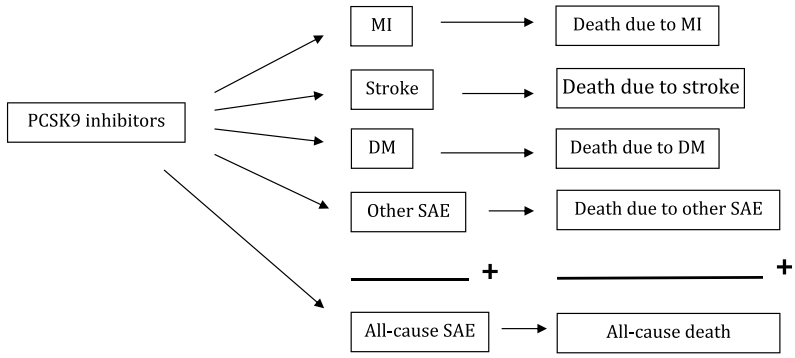

Figure 3. All-cause SAE and all-cause death as outcomes of PCSK9 inhibitors.

unknown or rare unintended serious adverse events (Figure 3). It is also a clinically relevant outcome because most preventive interventions have been introduced for potentially fatal diseases. Moreover, the outcome death is not vulnerable to biased measurement or participant drop-out. PCSK9 inhibitors have not been shown to decrease the risk of mortality in our or any previous review.

5.1. Five-year view

ClinicalTrials.gov facilitates transparency about trial results. The posted data offer researchers the opportunity to analyze unpublished data as well as individual rather than composite clinical outcomes. In contrast to reviews based on published articles, our review did not show that PCSK9 inhibitors decreased the risk of myocardial infarction and stroke, and it showed that evolocumab probably increased the risk of all-cause mortality. These findings underline the relevance of ClinicalTrials.gov.

Discrepancies in trial results between online trial registers and articles are not confined to approved PCSK9 inhibitors. Previous studies found that, generally, a higher number of all-cause SAE was reported on ClinicalTrials.gov [71]. Unless participating physicians have mistakenly coded events as an SAE, this discrepancy suggests that the data on ClinicalTrials.gov were more accurate. We, on the other hand, found a (remarkably) lower number of individual cardiovascular events on ClinicalTrials.gov than in the matching articles about clinical outcome trials of PCSK9 inhibitors.

Whatever accounts for the discrepancies between trial data from ClinicalTrials.gov and matching publications, it is important that the data becomes better aligned. Several stakeholders are involved. Investigators and sponsors are responsible for complete and accurate data posted on online trial registers. Regulatory agencies should include the online data in their reviews, and question discrepancies between online data and data provided by the sponsors, which in the case of PCSK9 inhibitors seemed to match the article data well.

ClinicalTrials.gov is continually being updated. For instance, the outcome all-cause mortality was included in the standard format of the website in 2017. We advocate systematic reviews with data from online trial registers. Such reviews may strengthen the evidence base underlying medical care in the upcoming years.

Author contributions

F. van Bruggen performed the search, extracted the data and assessed the risk of bias, analyzed the data and drafted the manuscript. G. Nijhuis performed the search, extracted the data and assessed risk of bias, and helped draft the manuscript. S. Zuidema helped draft the manuscript. H. Luijendijk designed the study, performed the search, extracted data and assessed risk of bias, analyzed the data, and helped draft the manuscript. H. Luijendijk is the guarantor of the paper and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors have approved the final manuscript and consented to its publication.

Funding

This paper has not been funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

A reviewer has declared consulting for Pharma in respect of PCSK9 inhibitors and has received funding support from Amgen, Sanofi, and Regeneron. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Li C, Lin L, Zhang W, et al. Efficiency and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials. J Am Heart Assoc. 2015;4(6):e001937.
2. Lipinski MJ, Benedetto U, Escarcega RO, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. Eur Heart J. 2016;37:536–545.
3. Zhang X-L, Zhu -Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015 June;13:123.

4. Dicembrini I, Giannini S, Ragghianti B, et al. Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Endocrinol Invest. 2019;42 (9):1029–1039.
5. Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. J Am Heart Assoc. 2017;6. DOI:10.1161/JAHA.117.006910
6. Reiner Ž. PCSK9 inhibitors in clinical practice: expectations and reality. Atherosclerosis. 2018;270:187–188.
7. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–1722.
8. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–2107.
9. Kip KE, Hollabaugh K, Marroquin OC, et al. The problem with composite end points in cardiovascular studies. The story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol. 2008;51(7):701–707.
•• **Calls into question the use of MACE in cardiology research.**
10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–269.
11. Turgeon RD, Tsuyuki RT, Gyenes GT, et al. Cardiovascular efficacy and safety of PCSK9 inhibitors: systematic review and meta-analysis including the ODYSSEY OUTCOMES Trial. Can J Cardiol. 2018;34 (12):1600–1605.
12. Du H, Li X, Su N, et al. Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis. Heart. 2019. DOI:10.1136/heartjnl-2019-314763
13. White HD, Gabriel Steg P, Szarek M, et al. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. Eur Heart J. 2019;40(33):2801–2809.
14. Wiviott SD, Giugliano RP, Morrow DA, et al. Characterization of types and sizes of myocardial infarction reduced with evolocumab in FOURIER. Circulation [Internet]. 2017;136:A16714.
• **Demonstrated that many of the included MIs in FOURIER were of the non-atherosclerotic type.**
15. Schmidt AF, Pearce LS, Wilkins JT, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017 Apr 28;4(4):CD011748.
16. DHHS. 42 CFR part 11 - clinical trials registration and results information submission. Fed Regist; 2016.
17. No Title [Internet]. 2016. [cited 2017 May 8]. Available from: https://prsinfo.clinicaltrials.gov/FinalRuleChanges-12Dec2016.pdf
18. For A, Disclosure P, Redaction W. FDA endocrinologic and metabolic drugs advisory committee. Briefing Document; 2015 May:1–152.
19. FDA. FDA ADVISORY COMMITTEE BRIEFING DOCUMENT PRALUENT TM (alirocumab); 2015.
20. EMA. Assessment report repatha; 2015.
21. Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5. The Cochrane Collaboration; 2011.
22. Mansournia MA, Higgins JPT, Sterne JAC, et al. Trials, biases in randomized epidemiologists, a conversation between trialists. Epidemiology. 2017;28(1):54–59.
23. Cordoba G, Schwartz L, Woloshin S, et al. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ. 2010;341(7769):381.
24. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161(7):996–1002.
25. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J. 2002;143 (3):398–405.
26. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J. 1997;133(6):703–712.
27. Qureshi WT, Zhang Z-M, Chang PP, et al. Silent myocardial infarction and long-term risk of heart failure. J Am Coll Cardiol. 2018;71(1):1–8.
28. WHO. World heart federation. World Stroke Organization. Global Atlas on Cardiovascular disease prevention and control; 2011.
29. EMA. EPAR praluent final; 2013.
30. Cheng J, Pullenayegum E, Marshall JK, et al. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. BMJ Open. 2016;6(8):e010983.
• **Explains why zero-event studies should not be exluded from meta-analysis.**
31. Friedrich JO, Adhikari NKJ, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol. 2007;7(1):5.
32. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351–1375.
33. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):150315080057008.
34. Navarese EP, Kołodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med. 2015;163(1):40–51.
35. McKenney JM, Koren MJ, Kereiakes DJ, et al. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012 June;59(25):2344–2353.
36. Teramoto T, Kondo A, Kiyosue A, et al. Efficacy and safety of alirocumab in patients with hypercholesterolemia not adequately controlled with non-statin lipid-lowering therapy or the lowest strength of statin: ODYSSEY NIPPON study design and rationale. Lipids Health Dis. 2017;16(1). DOI:10.1186/s12944-017-0513-7
37. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY Outcomes trial. Am Heart J. 2014;168(5):682–689.e1.
38. Ballantyne CM, Neutel J, Cropp A, et al. Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomized, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. Am J Cardiol. 2015 May;115(9):1212–1221.
39. Ridker PM, Tardif JC, Amarenco P, et al. Lipid-reduction variability and antidrug- antibody formation with bococizumab. N Engl J Med. 2017;376:1517–1526.
40. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017;376 (16):1527–1539.
41. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet. 2012;380 (9858):2007–2017.
42. Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2012;380(9858):1995–2006.
43. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the reduction of LDL-C with PCSK9 inhibition heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation. 2012 Nov;126(20):2408–2417.
44. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on Low-density lipoprotein cholesterol levels in statin-intolerant patients. JAMA. 2012;308(23):2497.

45. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370 (19):1809–1819.
46. Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012 Nov;367(20):1891–1900.
47. Hirayama A, Honarpour N, Yoshida M, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk–primary results from the phase 2 YUKAWA study. Circ J. 2014;78 (5):1073–1082.
48. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531–2540.
49. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia. Jama. 2014;311(18):1870.
50. Kiyosue A, Honarpour N, Xue A, et al. Effects of evolocumab (Amg 145) in hypercholesterolemic, statin-treated, japanese patients at high cardiovascular risk: results from the phase III yukawa 2 study. J Am Coll Cardiol. 2015;65(10):A1369.
51. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385(9965):331–340.
52. Amgen. FLOREY trial; 2016.
53. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA. 2016;316 (22):2373–2384.
54. Kastelein JJP, Nissen SE, Rader DJ, et al. Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9): a randomized, placebo-controlled Phase 2 study. Eur Heart J. 2016 May;37 (17):1360–1369.
55. Baruch A, Mosesova S, Davis JD, et al. Effects of RG7652, a monoclonal antibody against PCSK9, on LDL-C, LDL-C subfractions, and inflammatory biomarkers in patients at high risk of or with established coronary heart disease (from the phase 2 EQUATOR study). Am J Cardiol. 2017;119(10):1576–1583.
56. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012 July;380 (9836):29–36.
57. Kastelein JJP, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J. 2015 Nov;36(43):2996–3003.
58. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J. 2015 June;169(6):906–915.e13.
59. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1500–1509.
60. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovasc Drugs Ther. 2016 Oct;30(5):473–483.
61. Stroes E, Guyton JR, Lepor N, et al. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II study. J Am Heart Assoc. 2016;5(9):e003421.
62. Teramoto T, Kobayashi M, Tasaki H, et al. Efficacy and safety of alirocumab in Japanese patients with heterozygous familial hypercholesterolemia or at high cardiovascular risk with hypercholesterolemia not adequately controlled with statins- ODYSSEY JAPAN randomized controlled trial. Circ J. 2016 Aug;80(9):1980–1987.
63. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. Jama. 2016;316(12):1289–1297.
64. Schroll JB, Penninga EI, Gøtzsche PC, et al. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of orlistat: a document analysis. PLOS Med. 2016;13(8):e1002101.
65. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. PLoS One. 2012;7(7):e41174.
66. Bajaj NS, Patel N, Kalra R, et al. Neurological effects of proprotein convertase subtilisin/kexin type 9 inhibitors: direct comparisons. Eur Hear J. 2018;4(2):132–141.
67. He XX, Zhang R, Zuo PY, et al. The efficacy advantage of evolocumab (AMG 145) dosed at 140 mg every 2 weeks versus 420 mg every 4 weeks in patients with hypercholesterolemia: evidence from a meta-analysis. Eur J Intern Med. 2017;38:52–60.
68. Sfera D and Sauber C. The comprehensive guide to clinical research: a practical handbook for gaining insight into the clinical research industry kindle edition. LLC DSCS Sweat Equity & Investments; 2019.
69. Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. Chest. 2009;136:295–303.
70. Hartung DM, Zarin DA, Guise JM, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med. 2014;160(7):477–483.
71. Tang E, Ravaud P, Riveros C, et al. Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles. BMC Med. 2015;13(1). DOI:10.1186/s12916-015-0430-4
    - **Demonstrated that ClinicalTrials.gov reported more SAEs compared to corresponding publications.**
72. Becker JE, Krumholz HM, Ben-Josef G, et al. Reporting of results in ClinicalTrials.gov and high-impact journals. JAMA. 2014;311 (10):1063–1065.
73. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):e285–350.
74. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–188.