Title: The incremental net benefit of lipid-lowering therapy with PCSK9 inhibitors: A Systematic Review and Meta-analysis of cost-utility studies

Short title: cost-effectiveness of pcsk9i an SRMA

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Abstract

Introduction: Proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) are monoclonal antibodies that lower lipid levels by inhibiting PCSK9. Although several cardiovascular outcome trials reported beneficial clinical effectiveness of PCSK9i, the evidence on cost-effectiveness is mixed. We systematically reviewed the evidence on cost-effectiveness and synthesized incremental net benefit (INB) to quantify the pooled cost-effectiveness of PCSK9i lipid-lowering therapy.

Methods: We systematically searched for full economic evaluation studies reporting outcomes of PCSK9 inhibitors compared with any other lipid-lowering pharmacotherapies. We searched PubMed, Embase, Scopus, and Tufts Registry for eligible studies up-to September 2020, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. We pooled the INB with a 95% confidence interval using a random-effects model. We assessed the Heterogeneity using the Cochrane-Q test and I^2 statistic. We used the modified economic evaluations bias (ECOBias) checklist to evaluate the quality of the selected studies.

Results: A total of 20 studies were eligible, mainly from high-income countries (HIC). The pooled INB of PCSK9i versus other lipid-lowering pharmacotherapies were estimated from $n=21$ comparisons; with high heterogeneity ($I^2=98.04$). The INBp (95% CI) was US\$ -46,665 (-196,203; 102,874), PCSK9i was found to be not cost-effective when compared with other standard therapies; however, this finding was not statistically significant. On subgroup analysis PCSK9i was significantly not cost-effective [US\$ -25,686 (-26,085; -25,287), $I^2=0$] compared to other lipid-lowering pharmacotherapies among HICs, with payer's perspective [US\$ -25,686 (-26,086; -25,287), $I^2=0$] and with higher discount rates of 5% for cost [US\$ -25,686 (-26,086; -25,287), $I^2=0$]. The sensitivity analysis revealed that the subgroup findings are not robust.

Conclusion: PCSK9is' are not cost-effective compared to other lipid-lowering pharmacotherapies in HICs. Further, current pieces of evidence are predominantly from HICs with largely lacking evidence from other economies.

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Introduction:

Hyperlipidemia is a long-established risk factor for developing cardiovascular disease (CVD) and cardiovascular events¹⁻³. Statins are the most prescribed drugs to lower the low-density lipoprotein cholesterol (LDL-C) levels⁴. Evidence shows that they reduce cardiovascular risk across all risk factor categories⁵ and reduce the risk of developing CVD events^{6,7}. Despite intensive statin regimens to lower the risk for cardiovascular complications, a sizable proportion of statin-treated patients does not achieve recommended target LDL-C levels. Some are intolerant to statin therapy or may discontinue treatment because of drug-related side effects^{8,9}.

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are monoclonal antibodies that lower lipid levels by inhibiting the PCSK9 enzyme¹⁰. PCSK9i lower the LDL-C levels and help to prevent, treat atherosclerotic cardiovascular diseases^{2,11,12}. Currently, at least six monoclonal antibodies (mAb) have been or are being developed and tested; alirocumab (formerly called SAR236553/REGN727), evolocumab (previously called AMG145), RG7652¹³, LGT209 (NCT01979601, NCT01859455), 1B20¹⁴ and bococizumab (formerly called RN316/PF-049 50615)^{10,15,16}. The US-Food and Drug Administration has approved two (alirocumab and evolocumab) of the PCSK9 inhibitors in patients with clinically significant atherosclerotic CVD or heterozygous familial hypercholesterolemia (FH) requiring additional LDL lowering after being on diet control and maximally tolerated statin therapy¹⁰.

Cardiovascular outcome trials with evolocumab¹², alirocumab¹⁷ bococizumab¹⁶, and inclisiran¹⁸ proved superior to placebo at reducing major adverse cardiovascular events (MACE) among patients with elevated cardiovascular risk and on statin therapy but with no benefit on cardiovascular or all-cause mortality. Meta-analyses of randomized controlled trials (RCTs) suggest that PCSK9i effectively reduce LDL cholesterol^{19,20} as well as reduction of major cardiovascular events^{2,21-23} and reduce the incidence of all-cause mortality compared to placebo²¹.

A Cochrane review, including cardiovascular trials, found that PCSK9i when compared with placebo, reduced MACE but had no effect on cardiovascular or all-cause mortality²⁴. Updated analysis shows that there is evidence for treating patients with PCSK9i, who are not eligible for other drugs or who cannot reduce LDL-C on traditional therapies. However, the evidence base of PCSK9i against other active treatments is weaker²⁵.

PCSK9is' are newer lipid-lowering drugs with indubitable clinical effectiveness but are expensive²⁶. Primary economic evaluations of PCSK9i have reported conflicting results. Some studies reported PCSK9i as cost-effective^{27,28}, while others concluded as not-cost effective^{26,29-31}. The reviews of PCSK9i also noted the higher out-of-pocket costs of PCSK9i for individuals and the enormous economic impact if all potentially eligible patients are to be treated. This is a dilemma for policymakers, payers, and society. Synthesized evidence on the cost-effectiveness of PCSK9i treatment could provide appropriate evidence to aid the policy decision. We systematically reviewed the evidence on the cost-effectiveness of PCSK9 inhibitors. Further, to arrive at a quantitative cost-effectiveness summary measure, we have pooled the incremental net benefit (INB) of PCSK9 therapy.

Methods:

We have followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA-P)³², and the protocol was registered at PROSPERO (CRD42020206043).

Data Sources and search strategy: Search was performed in Pubmed, Embase, Scopus, and the cost-effective analysis registry³³ by Tufts medical centre, from inception to September 3, 2020 (see Appendix 1), adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Economic evaluation studies were eligible if they met all the following

inclusion criteria: Adult subjects requiring the lipid-lowering therapy and were treated with PCSK9i compared to any other lipid-lowering pharmacotherapies, and reported economic outcomes of incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALY), or INB. We excluded studies related to clinical effectiveness, only cost/burden of illness studies, reviews, or multiple publications. The detailed search terms are reported in Appendix 1.

Titles and abstracts of the studies listed from electronic database search were screened independently by the authors (BSB, AS) for their potential inclusion using the Rayyan-web application³⁴. After screening, authors (BSB, AS) independently reviewed the full-text articles. The Final list of studies meeting the inclusion and exclusion criteria was prepared on authors' mutual consensus (BSB, AS) (Figure 1).

Data extraction and risk of bias assessment: An *a priori* data extraction form (DEF) was constructed consisting of study/patient characteristics, intervention, economic outcomes/parameters, the methods used, and the data for pooling. We have extracted economic parameters; cost (C) or incremental/delta costs (ΔC), clinical effectiveness (E) or its incremental/delta (ΔE), ICERs, measures of dispersion [i.e., standard deviation (SD), standard error (SE), or 95% confidence interval (CI), and willingness to pay (WTP) threshold (K). From the cost-effective (CE) plane graph, we have extracted ΔC and ΔE using web plot digitaliser³⁵. Our intervention of interest was the use of any PCSK9i, and the comparator was any other lipid-lowering pharmacotherapeutic agent or placebo. Two reviewers (BSB and AS) independently extracted the data; any disagreement was resolved by consensus.

We assessed the risk of bias using the modified economic evaluations bias (ECOBias) checklist³⁶. It considers overall biases (11 items) and biases from model-specific aspects, i.e., structure (4 items), data (6 items), and internal consistency (1 item). Each item was graded as yes, partly,

unclear, no, or not applicable.

The outcome of interest: The primary outcome parameter of interest was INB, defined as follows: $INB = K * \Delta E - \Delta C$, where K was the willingness to pay threshold, ΔC -incremental cost (i.e., the difference in costs between intervention and comparator), ΔE -incremental effectiveness (i.e., the difference in effectiveness between intervention and comparator). The positive INB favors treatment, i.e., intervention is cost-effective. In contrast, a negative INB suggests favoring the comparator, i.e., intervention is not-cost effective^{37,38}. We used INB instead of ICER as the effect measure because of limitations with ICER³⁹ and the ambiguity in interpreting them. Since all monetary units were being reported in different currencies (i.e., US\$, €, £, ¥) and at different time points (years), we converted them to purchasing power parity (PPP), adjusted to US\$ for the year 2019 before calculating INB, as detailed in Appendix II.

Data preparation and statistical analysis: We followed the data preparation method and analysis as detailed in Bagepally et al.⁴⁰. Briefly, to calculate the INB and its variance, means along with dispersions (SD, SE, 95% CI) of ΔC and ΔE were required. However, economic studies reported different parameters; therefore, we designed five scenarios to deal with data⁴⁰⁻⁴³. Using the data as reported by the primary research publications and following the approach as detailed in Bagepally et al., we calculated the INB and its variances for each intervention comparator duos.

Following, INBs were pooled across studies stratified by low (LIC), lower-middle (LMIC), upper-middle (UMIC), and high (HIC) income countries as per the World Bank classification⁴⁴. Meta-analysis was applied to pool the INBs^{37,41} using a random-effects model if heterogeneity was present (i.e., $I^2 \geq 25\%$ or Q p-value < 0.1). We did subgroup analysis wherever appropriate to explore the source of heterogeneity and provide subgroup-specific pooled INBs. Subsequently, we assessed the publication bias using funnel plots and Egger's test. Further, we explored the sources

of asymmetry using contour-enhanced funnel plots. All data were prepared using Microsoft Excel version 2016 and analyzed by Stata software version 16⁴⁵. Two-sided $p < 0.05$ was considered statistically significant except for the heterogeneity test, in which $p < 0.10$ was used.

Results:

We retrieved 2,048 potentially relevant articles through our search. Of the identified studies, 20 studies were eligible for the meta-analysis, as shown in the PRISMA flow diagram (Figure 1). Among the twenty studies, twenty-one comparisons were assessed, including sixteen comparisons of PCSK9i versus standard^{27–29,31,46–56}; three comparisons were assessed including PCSK9i versus placebo^{17,57,58} and two comparisons were assessed, including PCSK9i versus ezetimibe^{30,54}. We considered all studies with PCSK9i versus statin or ezetimibe or placebo for pooling, included the PCSK9i versus no treatment comparator under placebo for pooling⁵⁸. The ‘standard treatment’ defined here as the comparator with statin therapy.

The INB variance was used from the most similar studies for further study calculations under scenario five. The INB variance of Cheng et al. was used for four studies^{27,31,48,51}, Bhatt et al. was used for two studies^{57,58}. Stam-Slob et al.⁴⁹, Villa et al.⁵⁰, Korman and Wisløff³¹ used Dressel et al.⁴⁷, Toth et al.²⁸, and Kazi et al.⁵⁴, respectively.

Table 1 provides the study characteristics of included studies. The majority of selected economic evaluation studies reported payer’s perspective. One study⁴⁷ did not report the study perspective and for Kongpakwattana et al., we considered the societal perspective for INB pooling⁵².

All studies were from HICs, except one⁵² from a UMIC country. All of the comparisons used model-based economic evaluations, including a Future Elderly Model (FEM) (n=1)⁴⁶, Nor CAD-Norwegian Cardiovascular Disease Model (n=1)⁵¹, SMART-REACH Model (n=1) and Cardio

Vascular Disease Policy Model (CVDPM) (n=4)^{30,54,55}.

Except for two studies^{57,59}, all other studies used lifetime horizon. All studies reported direct medical costs; three studies reported direct non-medical costs^{28,49,52}. All studies used discounting for costs and outcomes, except for one study⁴⁸. Sources of data for model input parameters were based on multiple-study-based estimates for the majority of studies^{27,28,30,46,47,49–51,54,56–59} except five studies which used synthesis-based estimates^{29,31,48,52,53} and two studies used single-study-based effectiveness^{55,60}. All the studies reported the use of country-specific thresholds as the willingness to pay (WTP) except one study that used GDP based WTP⁴⁶. We used the World Health Organization's (WHO) recommendation of one gross domestic product (GDP) per capita for studies that did not provide a WTP threshold.

Sensitivity analysis was done using one-way and probabilistic sensitivity analysis in all but one study⁴⁸. The cost-effectiveness of PCSK9i reported varied in individual studies. Ten studies^{29,30,49,52–57,59} reported that PCSK9i was not cost-effective compared with other treatments or placebo. While eight studies^{27,28,47,48,50,51,58,60} reported that PCSK9i was cost-effective. Cheng et al. reported that PCSK9 to be cost-effective for patients with a higher absolute risk of CVD⁴⁶, and Korman et al. reported that PCSK9i is cost-effective for secondary prevention among older patients with an increased risk of CVD³¹, but not cost-effective for primary prevention.

Risk of bias assessment: Our assessment shows that most of the studies, reported the use of comparators that reflects current practice, deriving QALYs from justifiable sources, clear presentation of data that was used in the model, provided sufficient detail for the methods costs and ICER estimation, applied recommended discount rates, and outwardly disclosed any sponsors related to the studies' (see Supl. Figure 1). Bias related to a time horizon was limited because most of the studies except two^{57,59} used a lifetime horizon. However, some studies failed in providing a

full justification for not choosing the societal perspective^{28,30,46–48,50,51,57,58} or detailed cost calculation^{53,54,57–59}. Only three studies used a pre-specified protocol while doing the study^{30,47,53}. All the five studies which received funding from pharma companies reported PCSK9i to be cost-effective^{27,28,48,50,51}. Studies failed to explain the justification for deciding which data to include in the model, leading to biases related to the data. The transformation process to align data with the model was not clearly explained. Limited scope bias is very likely in almost all studies. In this review, it was unclear whether any study pre-tested the model (Internal consistency) before they had used it for the main study.

PCSK9 versus others: INB of PCSK9i versus other standard therapies estimated from n=21 comparisons showed high heterogeneity ($I^2=98.04$) (Figure 2). The INBp (95% CI) was US\$ -46,665 (-196,203; 102,874), where INBp is not cost-effective; however, this finding was not statistically significant. Several subgroup analyses were conducted to explore the heterogeneity and provide the subgroup-specific INBp (Supp Table 1).

On subgroup analysis with countries income status (n=21), the INBp among studies from HICs (n=20)^{27–31,46–51,53–60} showed that PCSK9i therapy was significantly not cost-effective in the subgroup with INBp \$-25,686 (-26,085;-25,287) with low heterogeneity ($I^2=0$) (Supp Figure 3). However, since we found only one study⁵³ among HICs, which showed that the PCSK9i is significantly not cost-effective. However, on sensitivity analysis by pooling studies excluding the study by Kam et al, the statistical significance of pooled estimate did not sustain.

On subgroup analysis based on study perspective, the INBp among the subgroup with payer's perspective showed that the PCSK9i therapy was significantly not cost-effective. The INBp was \$-25,686 (-26,086;-25,287) with low heterogeneity ($I^2=0$) (Supp Figure 4). The studies with societal perspective⁵² and studies with no mention of perspective⁴⁷ showed that the mean INBp in

these subgroups was not cost-effective; however, the results were not statistically significant.

On subgroup analysis based on target population, the INBp among all the subgroups viz, target population of CVD (n=9)^{48,52–55,58–60} showed high heterogeneity ($I^2=99.26$, hypercholesterolemia (n=5)^{27,31,49–51} low heterogeneity ($I^2=0$) and mixed population (n=7)^{28–30,46,47,56,57} low heterogeneity ($I^2=0$). The mean INBp in these subgroups were not cost-effective. This sub-group analysis identified that the target group is one of the sources of heterogeneity, however within individual subgroups the results were not statistically significant (Supp Figure 5).

On subgroup analysis based on discount rate used in the model, the INBp among subgroups viz, discount rates of 2% (n=1)⁵⁹, 3% (n=14)^{27–30,46,47,49,50,52,54–56,60} with high heterogeneity ($I^2=92.50$) and 4% (n=3)^{31,51,58} with low heterogeneity ($I^2=0$) showed that the mean INBp was not cost-effective, however the results were not statistically significant (Supp Figure 6). However, among the subgroup of studies that used the highest discount rate of 5% (n=2)^{53,57} PCSK9i was significantly not cost-effective, with INBp \$-25,687 (-26,086;-25,288) and with low heterogeneity ($I^2=0$) compared to other therapies.

On subgroup analysis based on the measure of clinical effectiveness used in the model, the INBp among all the subgroups viz, model input synthesized (n=5)^{29,31,48,52,53} with high heterogeneity ($I^2=99.63$), model input from multiple studies (n=14)^{27,28,30,46,47,49–51,54,56–59} with low heterogeneity ($I^2=0$) and model input from single study (n=2)^{55,60} with low heterogeneity ($I^2=0$) showed that the mean INBps in these subgroups were not cost-effective, however the results were not statistically significant (Supp Figure 7).

On subgroup analysis based on scenario used to calculate the INBs, the INBp among all the subgroups viz, scenarios two (n=9)^{28,30,46,47,54,55,59,60} with low heterogeneity ($I^2=0$), four (n=2)^{52,53} with high heterogeneity ($I^2=99.91$) and five (n=10)^{27,29,31,48–51,56–58} with low heterogeneity ($I^2=0$),

showed that the mean INBps in these subgroups were not cost-effective, however the results were not statistically significant (Supp Figure 8).

The thresholds used in the comparisons range from PPP adjusted US\$ 6,995 to 203,252 with the median threshold of US\$ 100,000. On subgroup analysis based on the median threshold, the mean INBp among both the subgroups viz, thresholds of >100,000 US\$ (n=13)^{27-30,46-49,54-56,60} with low heterogeneity ($I^2=0$) as well as thresholds of $\leq 100,000$ US\$ (n=8)^{31,50-53,57-59} with high heterogeneity ($I^2=99.31$) were not cost-effective; however, within subgroup results were not statistically significant (Supp Figure 9).

On subgroup analysis based on the study countries in which the studies have been conducted, the majority of the studies were from the USA (n=11)^{27-30,46,48,54-56,60}, followed by two studies each from the Netherlands^{49,58}, Norway^{31,51} and Australia^{53,57}, and one study each from Germany⁴⁷, Japan⁵⁹, Spain⁵⁰ and Thailand⁵². The mean INBs among subgroups from the USA with low heterogeneity ($I^2=0$) were not cost-effective; however, within subgroup results were not statistically significant. There is not enough studies from other countries for providing an interpretation. (Supp Figure 10).

On subgroup analysis based on treatment comparisons, the INBp among both the subgroups viz, PCSK9 versus placebo (n=3)^{57,58,60} with INBp \$-12,198 (-214,069;189,673) with low heterogeneity ($I^2=0$), a PCSK9 versus ezetimibe (n=2)^{30,54} with INBp \$-102,393 (-1,260,761; 1,055,974) with low heterogeneity ($I^2=0$), as well as PCSK9 versus other standard therapies (n=16)^{27-29,31,46-56,59} with INBp \$-51,326 (-215,427; 112,775) with high heterogeneity ($I^2=98.53$) were not cost-effective, however the results were not statistically significant (Supp Figure 11).

Examination for the evidence of asymmetry on funnel plot and the Eggers test indicated the presence of publication bias p=0.34 (Supp Figure 2). On contour enhanced funnel plot, only one

study lies in the area of significance. All the other studies broadly lie in non-significance, making publication bias plausible. To distinguish between publication bias or other causes would be challenging due to high between study heterogeneity.

Discussion:

The PCSK9is' are newer lipid-lowering drugs that are clinically effective but expensive. To examine PCSK9is' cost-effectiveness, we pooled the incremental net benefits of PCSK9i lipid-lowering therapies across cost-utility studies. We observed that the PCSK9i are not cost-effective, but the results are not statistically significant across all studies. On subgroup analysis, PCSK9is were significantly not cost-effective in HIC's, with the payer's perspective and the use of high discount rates, however the results were highly sensitive; the statistical significance of results among HIC was not sustained on omitting a single study from the pooled analysis.

Since PCSK9i is a relatively new and expensive treatment, policymakers, payers, and society need cost-effectiveness evidence. Such expensive therapy challenges the affordability for self-financed individuals with higher out-of-pocket expenditures and enormous budgetary constraints for the public payers or government. Although there is evidence on the clinical effectiveness of PCSK9i, there is a lack of synthesized cost-effectiveness evidence as well as primary economic studies from low and middle-income economies. The challenges in synthesizing economic evaluation studies are inherent because of differences in economic parameters, level of income countries/thresholds, study perspectives, costs and measurements, and variations in result reporting. We have attempted to address these critical challenges by standardization of data extraction & pre-processing from various published studies.

The pooled mean INB indicated that PCSK9i is not cost-effective compared to statins or ezetimibe,

or placebo; however, the results were not statistically significant. Only two^{52,53} of the twenty included studies showed that the PCSK9i was significantly not cost-effective; interestingly, it included study from HIC⁵³ and UMC⁵². The studies that reported PCSK9i as cost-effective are mainly by interpreting the point estimates (mean) of ICER, overlooking the confidence intervals of the point estimate. Further subgroup analysis based on the target population, different discount rates, model input clinical effectiveness data, scenario, thresholds, countries, and treatment comparisons' pooled INB indicated that PCSK9i were not cost-effective; however, the subgroup results too were not statistically significant.

There is strong evidence for clinical endpoint results and prescribing PCSK9i to those who might not be eligible for other lipid-lowering drugs from various cardiovascular outcomes research^{12,16-18}. Still, it is not clear whether PCSK9i can be used effectively as replacement therapies. As per available literature, PCSK9i is effective on lipid profile in selected patients with difficulties in management, so careful consideration of alternative lipid-lowering treatments is essential.

With the current evidence, we conclude PCSK9i is not cost-effective. We found that the cost-effectiveness of PCSK9i depends heavily on the way the effectiveness is modeled. The difference in input parameters, insufficient data to model all the events considered, and short-term trials used will be underestimating the actual cardiovascular benefits. Further, the studies neither include indirect costs nor captured the real-world burden of CVD. Previously published studies suggest that PCSK9i is cost-effective for secondary prevention³¹ and among patients with a high risk of CVD⁴⁶ or if the threshold price is increased or the drugs are made available at a lesser cost^{54,56}. Higher medication cost is the primary factor that affects cost-effectiveness. Studies from the USA reported that PCSK9i price has to be discounted by more than 20%²⁸, Arrieta et al. found overpricing to be 62%⁵⁶, and Kazi et al. suggested a reduction by 86%⁵⁴ to meet a conventional

WTP of \$100,000 per QALY. Lowering the price of these PCSK9i seems to be the most effective way for PCSK9i to be cost-effective. The available evidence is not sufficient for making any policy decision regarding the use of PCSK9i. Many factors need to be weighed in before policy decisions because this evidence synthesis does not reveal PCSK9i to be not cost-effective with statistical significance, neither does it provide evidence against it. The limitations of our study are that our findings may be generalizable to only high-income countries because most of the included studies were from HIC, except one study. We could not do separate analysis on primary and secondary prevention due to lack of published studies. Also, most of the inputs used for the selected economic evaluation studies are from clinical trials that preferentially enrolled people with either established CVD or at a high risk already, hence there is no evidence for a low- to medium-risk setting.

Conclusion: PCSK9 inhibitors are not cost-effective than other lipid-lowering therapies; however, this result is not statistically significant. However, PCSK9i are significantly not cost-effective in HIC's, with payer's perspective and the use of high discount rates. There is a scarcity of evidence on this, particularly from LMIC and UMC. This evidence synthesis could guide policymakers at a macro level on the direction of cost-effectiveness of PCSK9-inhibitor therapy. However, specific primary economic evaluation studies are indicated if context-specific evidence is required. Cost-effectiveness evaluation of such newer treatments on time may positively influence the pricing and adoption of those interventions for more considerable societal benefit.

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Figure 1: Study selection

Figure 2:

Table 1: Characteristics of included studies

Study	Country	Time Horizon	Model	Type of population	Target population	Intervention	Comparator	Discounting (cost; outcome) (%)	Reference year	WTP	WTP (PPP - 2019 US \$)
Arrieta et al ¹	USA	Lifetime	Markov	Fourier Trial with ASCVD	Mixed	pcsk9i +statin	Std	3;3	2016	100,000 \$	100,000
Berkelman et al ²	Netherlands	Lifetime	SMART-REACH	Adults with stable CVD	CVD	pcsk9i	no Rx	4;1.5	2016	50,000 €	63,452
Bhatt et al ³	USA	Lifetime	Markov	Acute coronary syndrome from Odyssey outcomes Trial	CVD	Ali	placebo	3;3	2018	100,000 \$	100,000
Dressel et al ⁴	Germany	Lifetime	Markov	Stable CAD from LURIC Study	Mixed	pcsk9i	Std	3;3	-	150,000 €	203,252
Fonarow et al ⁵	USA	Lifetime	Markov	ASCVD	Mixed	Evol+Std	Std	3;3	-	150,000 \$	150,000
Fonarow et al ⁶	USA	Lifetime	Markov	very high risk ASCVD	CVD	Evol+Std	Std	-	2018	150,000 \$	150,000
Gandra et al ⁷	USA	Lifetime	Markov	Heterozygous FH, ASCVD, ASCVD (Statin intolerant)	Hypercholesterolemia	Evol+Std	Std	3;3	2014	150,000 \$	150,000
Kam et al ⁸	Australia	Lifetime	Markov	ORION-10 Trial	CVD	Inc+Statin	Std	5;5	2020	50,000AUS \$	33,738
Kazi et al ⁹	USA	Lifetime	CVDPM	US population for whom lipid lowering therapy is indicated	Mixed	pcsk9i+statin	Ezet	3;3	2015	100,000 \$	100,000
Kazi et al ¹⁰	USA	Lifetime	CVDPM	NHANES (Fourier inclusion criteria)	CVD	pcsk9i+Statin	Std	3;3	2017	100,000 \$	100,000
Kazi et al ¹¹	USA	Lifetime	CVDPM	NHANES& Odyssey outcomes trial	CVD	Ali+Statin	Std	3;3	2018	100,000 \$	100,000
						Ali+Statin	Ezet				
Kodera et al ¹²	Japan	30 years	Markov	High risk group with triple vessel CVD from CREDO Kyoto registry	CVD	Ali+Statin	Ezet	2;2	-	5,000,000 JPY	49,215
Kongpakwattana et al ¹³	Thailand	Lifetime	Markov	Statin treated patients	CVD	pcsk9i+Statin	Std	3;3	2018	160,000 THB	12,701
Korman et al ¹⁴	Norway	Lifetime	Markov	High-risk population	Hypercholesterolemia	pcsk9i+Statin	Std	4;4	2015	600,000 NOK	59,958

Study	Country	Time Horizon	Model	Type of population	Target population	Intervention	Comparator	Discounting (cost; outcome) (%)	Reference year	WTP	WTP (PPP - 2019 US \$)
Kumar et al ¹⁵	Australia	25 years	Markov	Fourier Trial	Mixed	Ali & Evol	Std	5;5	2017	50,000 AUS \$	33,738
Stam-Slob et al ¹⁶	Netherlands	Lifetime	Markov	Familial Hypercholesterolemia	Hypercholesterolemia	pcsk9i	placebo	3;3	2014	100,000 €	126,904
Toth et al ¹⁷	USA	Lifetime	Markov	CPRD Database-UK	Mixed	pcsk9i	Std	3;3	-	150,000 \$	150,000
Villa et al ¹⁸	Spain	Lifetime	Markov	High risk of CVD	Hypercholesterolemia	Evol+Statin	Std	3;3	2016	30,000€	48,309
Cheng et al ¹⁹	USA	Lifetime	FE	older Americans > 51 years	Mixed	Evol+Statin	Std	3;3	2015	150000 \$	161,803
Wisløff et al ²⁰	Norway	Lifetime	Nor CAD	Fourier Trial	Hypercholesterolemia	pcsk9i	Std	4;4	2017	70,000 €	6,995

FEM - Future Elderly Model, CVDPM - Cardio Vascular Disease Policy Model, Nor CAD - Norwegian Cardiovascular Disease Model, CPRD - Clinical Practice Research Datalink

Mixed population included Hypercholesterolemia, CVD, Dyslipidemia or Heterozygous FH, ASCVD, primary prevention-CVD high risk equivalents.

Std - Standard of care (statin), Evol - Evolocumab, Ali - Alirocumab, Inc - Inclisiran

ONLINE ONLY MATERIAL

Supplementary Figures and Tables & Appendix I and II & Prisma Checklist

Supplementary Figure 1: Assessment of Risk of Bias using ECOBIAS Checklist

Issue addressed	Arrieta et al ¹	Berkelman et al ²	(Bhatt et al ³	(Dressel et al ⁴	(Fonarow et al ⁵	(Fonarow et al ⁶	Gandra et al ⁷	Kam et al ⁸	Kazi et al ⁹	Kazi et al ¹⁰	Kazi et al ¹¹	Kodera et al ¹²	Kongpakwattana et al ¹³	Korman et al ¹⁴	Kumar et al ¹⁵	Stam-Slob et al ¹⁶	Toth et al ¹⁷	Villa et al ¹⁸	Cheng et al ¹⁹	Wisløff et al ²⁰
Narrow perspective bias	yes	partly	yes	unclear	yes	partly	yes	yes	partly	partly	yes	yes	yes	yes	partly	yes	partly	partly	unclear	partly
Inefficient comparator bias*	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	partly	yes	yes	yes	yes	yes	yes
Cost measurement omission bias	yes	partly	yes	yes	yes	yes	yes	partly	yes	yes	partly	partly	yes	yes	partly	yes	yes	yes	yes	yes
Intermittent data collection bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	unclear	yes	yes	unclear	yes	yes	yes	yes	yes
Invalid valuation bias	yes	yes	yes	partly	yes	yes	yes	yes	yes	yes	unclear	unclear	yes	partly	yes	yes	yes	yes	yes	partly
Ordinal ICER bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Double-counting bias	unclear	unclear	unclear	partly	partly	unclear	partly	unclear	yes	yes	unclear	unclear	unclear	unclear	unclear	partly	partly	partly	partly	partly
Inappropriate discounting bias	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Limited sensitivity analysis bias§	partly	partly	partly	partly	partly	partly	yes	partly	partly	partly	partly	partly	yes	partly	partly	partly	partly	partly	partly	partly
Sponsor bias	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Reporting and dissemination bias	unclear	unclear	unclear	yes	unclear	unclear	unclear	yes	yes	yes	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear
Structural assumptions bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
No treatment comparator bias*	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Wrong model bias	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Limited time horizon bias	partly	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	partly	yes	yes	yes	yes	yes
Bias related to data identification	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	partly	yes	partly	yes	yes	yes	yes
Bias related to baseline data	yes	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	yes	partly	yes	yes	yes	yes	yes	yes
Bias related to treatment effects	partly	partly	partly	yes	yes	yes	yes	Yes	partly	partly	partly	partly	yes	partly	partly	yes	yes	partly	yes	yes
Bias related to quality-of-life weights (utilities)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Non-transparent data incorporation bias	yes	yes	yes	yes	yes	partly	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Limited scope bias§	partly	partly	partly	partly	partly	partly	yes	partly	partly	partly	partly	partly	partly	partly	partly	partly	partly	partly	partly	partly
Bias related to internal consistency	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear

Supplementary Figure 2: Funnel and contour-enhanced funnel plots of PCSK9 Inhibitors versus others

Supplementary Figure 3: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by country income classification

Supplementary Figure 4: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Study perspective.

Supplementary Figure 5: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Target population.

Supplementary Figure 6: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by rate of discount.

Supplementary Figure 7: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by measure of clinical effectiveness.

Supplementary Figure 8: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Scenario.

Supplementary Figure 9: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Threshold.

Supplementary Figure 10: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Country.

Supplementary Figure 11: Subgroup analysis of INBp of PCSK9 Inhibitors versus others by Treatment comparisons.

Supplementary Table 1: Results of subgroup analysis of INBp of PCSK9 Inhibitors versus others.

	Sub-group (no. of comparisons)	INB (CI) *10 ³ US\$	I ² (%)	Q
PCSK9 vs Others	Overall (21) ¹⁻²⁰	-46.67 (-196.20 to 102.87)	98.16	1088.39
Country's Income	High income countries (20) ¹⁻¹⁹	-25.67 (-26.09 to -25.29)	0	3.06
	Upper middle income countries (1) ²⁰	-524.56 (-554.24 to -494.88)	-	-
Perspective	Not mentioned (1) ¹²	-63.47 (-171.07 to 298.00)	-	-
	Payers (18) ^{1-3,5-11,13-19}	-25.67 (-26.07 to -25.28)	0	2.44
	Societal (2) ^{4,20}	-343.65 (-774.97 to 87.68)	80.43	5.11
Target population	CVD (9) ^{8,11,13,16-20}	-106.96 (-353.99 to 140.08)	99.26	1086.24
	Hypercholesterolemia (5) ^{1,6,10,14,15}	9.23 (-84.02 to 102.48)	0	0.62
	Mixed (7) ^{2-5,7,9,12}	-3.06 (-101.65 to 95.53)	0	0.79
Discount Rate for costs	2 percent (1) ¹¹	-40.88 (-141.69 to 59.94)	-	-
	3 percent (14) ^{1-6,8-10,12,16,19,20}	-74.02 (-282.51 to 134.46)	92.50	173.31
	4 percent (3) ^{14,15,17}	28.29 (-126.23 to 182.71)	0	0.18
	5 percent (2) ^{7,18}	-25.69 (-26.09 to -25.29)	0	0
	Not mentioned (1) ¹³	36.00 (-207.51 to 279.51)	-	-
Measure of Clinical Effectiveness	Synthesised (5) ^{4,13,14,18,20}	-113.52 (-432.51 to 205.46)	99.63	1086.21
	Multiple studies (14) ^{1-3,5-7,9-12,15-17}	-14.09 (-71.05 to 42.87)	0	1.48
	Single study (2) ^{8,19}	-60.99 (-357.98 to 235.99)	0	0.48
Scenario	Five (10) ^{1,4,6,7,9,10,13-15,17}	1.30 (-77.38 to 79.99)	0	1.17
	Four (2) ^{18,20}	-274.89 (-763.78 to 213.99)	99.91	1085.32
	Two (9) ^{2,3,5,8,11,12,16,19}	-20.06 (-91.05 to 50.94)	0	1.42
Threshold (100k US\$)	>100K US\$ (13) ^{1-5,8-10,12,13,16,19,19}	1.19 (-76.60 to 78.99)	0	1.85
	<100K US\$ (8) ^{6,7,11,14,15,17,18,20}	-79.94 (-312.24 to 157.22)	99.36	1086.08
Country	Australia (2) ^{7,18}	-25.69 (-26.09 to -25.29)	0	0
	Germany (1) ¹²	63.47 (-171.07 to 298.00)	-	-
	Japan (1) ¹¹	-40.88 (-141.69 to 59.94)	-	-
	Netherlands (2) ^{10,17}	-14.39 (-209.17 to 180.39)	0	0.01
	Norway (2) ^{14,15}	34.53 (-137.65 to 206.72)	0	0.15
	Spain (1) ⁶	-16.82 (-163.89 to 130.26)	-	-
	Thailand (1) ²⁰	-524.56 (-554.24 to -494.88)	-	-
	USA (11) ^{1-5,8,9,13,16,19}	-4.33 (-92.43 to 83.77)	0	1.52
Treatment	pcsk9 vs placebo (3) ^{7,17,19}	-12.19 (-214.07 to 189.67)	0	0.02
	pcsk9 vs standard (16) ^{1,3-6,8-16,18,20}	-51.33 (-215.43 to 112.78)	98.62	1088.39
	pcsk9 vs ezetimibe (2) ^{2,16}	-102.39 (-1260.76 to 1055.97)	0	0.02

APPENDIX I

SEARCH STRATEGIES

	Pubmed Search	Hits as on 03-09-2020
I	pcsk9 OR "Pro-protein convertase subtilisin-kexin type 9" OR Alirocumab OR Praluent OR Evolocumab OR Repatha OR 1B20 OR Bococizumab	3,873
O	"quality of life" OR "QALY" OR "quality adjusted" OR "life year" OR "life years" OR "DALY" OR "disability adjusted" OR "cost effective" OR utility OR "ICER" OR "ICERS" OR INB OR "economics"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms]	4,292,002
	P & O	682

	Embase Search	Hits as on 03-09-2020
I	'proprotein convertase 9'/exp OR 'pcsk9 protein' OR 'neural apoptosis regulated convertase 1' OR 'proprotein convertase 9' OR 'proprotein convertase subtilisin/kexin type 9' OR 'protein pcsk9' OR 'subtilisin/kexin like protease pc9' OR 'pcsk9 inhibitor'/exp OR 'alirocumab'/exp OR 'alirocumab' OR 'praluent' OR 'regn 727' OR 'regn727' OR 'sar 236553' OR 'sar236553' OR 'evolocumab'/exp OR 'amg 145' OR 'amg145' OR 'evolocumab' OR 'repatha' OR 'bococizumab'/exp OR 'bococizumab' OR 'pf 04950615' OR 'pf 4950615' OR 'pf04950615' OR 'pf4950615' OR 'rn 316' OR 'rn316'	9,519
O	'cost benefit analysis'/exp OR 'cost analysis' OR 'cost benefit' OR 'cost benefit analysis' OR 'cost benefit ratio' OR 'cost-benefit analysis' OR 'cost minimization analysis'/exp OR 'cost minimization' OR 'cost minimization analysis' OR 'quality of life' OR 'QALY' OR 'quality adjusted' OR 'life year' OR 'life years' OR 'DALY' OR 'disability adjusted' OR 'ICER' OR 'ICERS' OR INB OR 'cost effectiveness analysis'/exp OR 'cost effectiveness' OR 'cost effectiveness analysis' OR 'cost effectiveness ratio' OR 'cost efficiency analysis' OR 'willingness to pay' OR 'cost utility analysis'/exp OR 'cost utility' OR 'cost utility analysis'	843,025
	P & O	374

	Scopus search	Hits as on 03-09-2020
I	pcsk9 OR "Pro-protein convertase subtilisin-kexin type 9" OR Alirocumab OR Praluent OR Evolocumab OR Repatha OR 1B20 OR Bococizumab	13,750
O	"cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year\$" OR daly OR "disability adjusted" OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR "benefit ratio" OR 'cost benefit' OR 'cost minimi?ation' OR "cost-effectiveness" OR "cost effectiveness ratio" OR "cost efficiency analys?s" OR "cost utility"	563,690
	P & O	979

Appendix II

A) Estimation of incremental net benefit Incremental net benefit (INB)¹ can be estimated as follows:

$$INB = K \Delta E - \Delta C \text{ --- (1)}$$

or

$$INB = \Delta E (K - ICER) \text{ --- (2)}$$

$$Var(INB) = K^2 \sigma_{\Delta E}^2 + \sigma_{ICER}^2 \text{ --- (3)}$$

or

$$Var(INB) = K^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2K \rho_{\Delta E \Delta C} \text{ --- (4)}$$

K is the Willingness to pay (WTP), ΔC and ΔE are incremental cost and incremental effectiveness, $\sigma_{\Delta C}^2$, $\sigma_{\Delta E}^2$, $\rho_{\Delta C \Delta E}$ were variances of ΔC and ΔE and their covariance, and σ_{ICER}^2 was variance of ICER. The WTP was used as reported in the original included studies, i.e., a standard/country specific or GDP based WTP threshold. A positive INB favours treatment, i.e., intervention is cost-effective, whereas a negative INB favours the comparator, i.e., intervention is not cost-effective¹.

Currency conversions and standardization

The monetary units were converted to purchasing power parity (PPP), adjusted to US\$ for the year 2019 before INB calculation. For instance, if a study reported cost, ICER, and thresholds in Euros for 2012, this currency was first converted to 2019 Euros using the historical consumer price index (CPI) of that country. The Euro 2019 value was next converted to PPP adjusted US\$ rate using conversion rates from the International Monetary Fund². In addition, the K value from GDP-based threshold was corrected for both latest CPI (2019) and PPP, while for standard/country specific or fixed K, only PPP was corrected. For the variance monetary value conversion, the specific study variance was multiplied by the square of total factors (i.e., CPI and PPP) for the year

2019. For example, if Y is variance of ICER in Euros 2012, this was converted into 2019 PPP adjusted US\$ as

$$Var_{PPP_{2019}} = Var_{Euro_{2012}} \times \left(\frac{CPI_{Euro_{2019}}}{CPI_{Euro_{2012}}} \times \frac{1}{PPP_{2019}} \right)^2 \text{-----} (5)$$

We did not adjust PPP for year 2020 or 2021 due to the uncertainties in economies due to the COVID-19 Pandemic.

B) Meta-analysis

i. A fixed effect model

$$INB_p = \frac{\sum_{i=1}^S w_i \cdot INB_i}{\sum_{i=1}^S w_i} \text{-----} (1)$$

$$w_i = \frac{1}{Var(INB_i)} \text{-----} (2)$$

ii. A random effect model

$$INB_p = \frac{\sum_{i=1}^S w_i^* \cdot INB_i}{\sum_{i=1}^S w_i^*} \text{-----} (3)$$

$$w_i^* = \frac{1}{Var(INB_i) + \tau^2} \text{-----} (4)$$

$$\tau^2 = \frac{Q - (S - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \text{-----} (5)$$

Q is the Cochran Q-statistic, where $Q = 0$ if $Q < S - 1$; and s is the number of included studies/comparisons. The heterogeneity of INB was assessed using Cochran Q-test and I^2 statistic calculated as equations below.

$$Q = \sum_{i=1}^S w_i (INB_i - INB_p)^2 \text{-----} (6)$$

$$I^2 = 100\% \times \frac{Q - (S - 1)}{Q} \text{-----} (7)$$

1. Crespo C, Monleon A, Díaz W, Ríos M. Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies. BMC medical research methodology. 2014;14(1):1–9.
2. International Monetary Fund. World Economic Outlook Databases [Internet]. 2021 [cited 2021 Apr 20]. Available from: <https://www.imf.org/en/Publications/SPROLLS/world-economic-outlook-databases>

Prisma Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE : The incremental net benefit of lipid-lowering therapy with PCSK9 inhibitors: A Systematic Review and Meta-analysis of cost-utility studies			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes, 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes, 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes, 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes, 4, Appendix 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes, 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes, 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes, 4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes, 5 & appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes, 5, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes, 5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes, 5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes, 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes, 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Yes, 6-7

Prisma Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes 5 & 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Yes, 6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes, 7 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes, 7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes, 8-9, Supl fig 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes, 7-9 Figure 2 Table 1 Supls Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Yes, 9-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes, 10-15 Supp Figures 4,14,17,20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supp Table 1, Supp Figures
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes, 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes, 13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes, 14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes, 1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097