# Are PCSK9 inhibitors cost-effective?

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Abstract

The objective of this study was to review available health economic evaluations of PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors. These drugs reduce LDL cholesterol levels and cardiovascular risk, but their cost-effectiveness has been questioned. We searched Medline and Embase for economic evaluation in any language at any time. Studies were included if they analysed any PCSK9 inhibitor compared with either statin alone or in combination with ezetimibe or any other therapy considered standard prior to the introduction of PCSK9 inhibitors. We found 10 full health economic evaluations of PCSK9 inhibitors, two from Europe and eight from United States (US). Six of the eight from the US were from two different consortia that analysed at different stages through the development of evidence. All studies generally reported incremental cost-effectiveness ratios above suggested thresholds for cost-effectiveness, except one study from Spain. The results of this review indicate that PCSK9 inhibitors in general are not cost-effective at the current prices, but lower prices may change the results.

## Key points

- Health economic evaluations have generally not found PCSK9 inhibitors to be cost-effective
- Results are found to be highly sensitive to price.

## Conflicts of interest

## 1. Introduction

Since the introduction of statins in the 1990's, cholesterol-lowering treatment has become one of the cornerstones of prevention of cardiovascular disease (CVD). Statins have played a crucial role in ending CVD's role as the leading cause of death in industrialized countries such as Canada, United Kingdom and France (1). In combination with ezetimibe, up to 60% reduction in low-density lipid (LDL) cholesterol can be achieved. This can bring most patients down to the commonly accepted treatment targets, typically in the range 1.8 to 2.6 mmol/L (2). Still, some patients cannot reach the desired targets for cholesterol reduction and need additional treatment with ezetimibe. Other patients do not tolerate statins due to side effects. Here, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a new treatment opportunity. PCSK9 inhibitors can reduce LDL cholesterol an additional 60% on top of diet, statins and ezetimibe (3). This combination therapy makes it possible, for the first time, to reach treatment targets for the majority of patients with familial hypercholesterolemia (FH) and a history of atherosclerotic cardiovascular disease (ASCVD). Prices may, however, be too high in most countries for general adoption and reimbursement, which makes it an interesting candidate for economic evaluation. The current sparse amount of outcome data on "hard" clinical endpoints, in addition to the controversy as to whether the achievement of very low LDL levels is safe or desirable, mean that economic evaluation of PCSK9 inhibitors is not without its challenges.

The main driver in many economic evaluations is the estimate of effectiveness. For PCSK9 inhibitors, effectiveness was first shown in randomised controlled trials (RCTs) with LDL-C reduction as the primary outcome (4, 5). Later, the FOURIER trial has reported effect on "hard" clinical endpoints such as myocardial infarction and stroke for one of the PCSK9 inhibitors (6), and another RCT has recently been presented and publications are expected shortly (ODYSSEY outcomes; https://clinicaltrials.gov/ct2/show/NCT01663402). It is important to note that the FOURIER trial had relatively short follow-up time, compared to the time it takes to develop cardiovascular disease (7). In the absence of RCTs with longer follow-up, the validity of indirect estimation by modelling risk reduction as a function of LDL reductions is challenging.

Still, PCSK9 inhibitors are used to a limited extent despite wide therapeutic indications (8). For example, in Norway with a population of 5.3 million, in 2016 525,000 individuals redeemed a statin prescription while only 400 redeemed PCSK9 prescriptions (http://www.reseptregisteret.no/Prevalens.aspx). There are at least two major reasons why the sales of PCSK9 inhibitors are still modest despite impressive impact on lipid levels. First, most published clinical studies have surrogate endpoints and not clinical relevant endpoints. The first publication using clinical endpoints reports lower risk reductions than the LDL cholesterol reductions would indicate, and even a small but insignificant increase in CVD mortality (6). Second, the price of PCSK9 inhibitors is so high that payers have questioned whether they represent value for money (9, 10). These two explanations have a clear link, as uncertainty about the clinical effectiveness of the drugs necessarily carries over to the cost-effectiveness analyses.

The objective of this review was to identify published health economic evaluation of PCSK9 inhibitors in order to explore the evidence that these drugs are cost-effective.

## 2. Methods

We searched Medline and Embase on November 2$^{nd}$ 2017 for economic evaluations of PCSK9 inhibitors using key words for economic evaluation and PCSK9 inhibitors (detail in appendix 1). Given the limited nature of the currently available literature on the subject, we sought to include any full economic evaluation of PCSK9 inhibitors where time was captured in the health outcome, i.e. life years or quality-adjusted life-years. The only PCSK9 inhibitors explicitly included in the search strategy were evolocumab and alirocumab, as these are the only drugs approved for the market at the date of our search. Studies in any jurisdiction were included and there were no limitations regarding language or time. Titles were reviewed by two authors independently (MJK and TW) and inclusion was based on agreement between the same two authors. Reference lists were searched for further references, which were included if found.

Population criteria was broadly defined as any group with increased risk of CVD or with history of CVD. Intervention criteria were the use of evolocumab, alirocumab, or both. Comparator criteria were use of statins, ezetimibe or a combination of the two. Outcome criteria were cost per quality adjusted life-year (QALY) or cost per life-year, compared with a cost-effectiveness threshold (which implicitly includes net health benefit or net monetary benefit). Studies could be either model based, RCT based or a combination of the two. Reviews of any kind were excluded, as were other publications without original reporting of results.

We used a standardised extraction form inspired by the Drummond checklist to collect information (11). We collected information on publication year, country of focus, time horizon, interventions, comparators, patient population, methods for how effectiveness was estimated, methods and sources for determining costs, drug price, health states included, discount rates applied, utility estimation, model type, outcomes, uncertainty (including methods, sources for parameters, and impact), conclusions, and sources of funding.

## 3. Results

In total 253 total references were identified in either Embase or Medline (including duplicates). Titles were reviewed and 18 references were found to possibly contain a full article of an economic evaluation of PCSK9 inhibitors. Eight articles were excluded for reasons such as health outcome not capturing time, article not reporting original analyses and not analysing PCSK9 inhibitors (appendix 2). Finally, 10 different publications were included in the review, including two references found in the reference list of one of the included articles (Figure 1).

The included studies stemmed from US (n=8), Spain (n=1) and Norway (n=1) (Table 1). We also identified one review of a study from the UK, but as the primary publication of that study was not published, it was excluded. Six of the eight publications from the US were essentially from two consortia that made analyses at different stages through the development of evidence. The last two US publications and the Spanish publications were both sponsored by Amgen and co-authored by Amgen employees. The last publication was from Norwegian authors (ourselves).

All publications were from 2015, 2016 and 2017, with costs given in Euros or US dollars for either the year 2015 or later (Table 2). Given that Euros and dollars for 2015 and 2016 are relatively similar, with yearly Euro to Dollar exchange rates reported to be EUR€1=US$1.11, we chose not to convert to a common currency in our reporting of results.

The three Amgen papers analysed evolocumab compared with standard of care (typically statins) from a Spanish perspective in one paper and a US perspective in two others (12-14). The main

differences between the two US papers were that the one by Fonarow and colleagues from 2017 (12) had incorporated results from the recently published FOURIER trial, which reported effect on myocardial infarction and stroke. In comparison, the US paper by Gandra and colleagues from 2016 (13) did not have access to these data, and therefore modelled clinical outcomes indirectly using LDL cholesterol reductions and CTTC meta-analysis results. In addition, a major difference between these two US studies was that the latest study had a societal perspective, while the other had a payer perspective. These two studies (12, 13) reported markedly different incremental QALYs, with for instance 1.12 (Gandra et al.) and 0.39 (Fonarow et al.) for patients with a history of ASCVD, possibly due to their mentioned take on modelling effectiveness of evolocumab. The first reported "intermediate cost-effectiveness of evolocumab" (13), while the most recent concluded it was not cost-effective (12). The Spanish Amgen study also modelled through LDL reductions based on Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis (15) and found incremental QALYs among CVD patients similar to Gandra and colleagues, who used a similar modelling assumption. The Spanish study concluded that evolocumab was cost-effective for a population of FH patients where the majority had established CVD with an ICER at EUR€30,893 per QALY. For secondary prevention of non-FH patients, it reported an ICER of EUR€45,340 per QALY, which would typically be considered not cost-effective according to cost-effectiveness thresholds in Spain (14).

The Norwegian publication was authored by Korman and Wisløff (16). In the study, we analysed cost-effectiveness for six different age groups and eight different risk groups, in total 48 different groups stratified by diagnosis and age at which treatment begins. We found that among these groups, only 65 year-old FH patients with a previous CVD event were estimated to be cost-effective candidates for evolocumab, which seemed to be the most cost-effective PCSK9 inhibitor. We found that treatment of younger patients generally was not cost-effective due to the high number of years for which this costly treatment was required, despite significant gains in both life-years and QALYs. Given that payers increasingly negotiate prices or put pharmaceuticals on tender, price reductions could be expected. With a 50% discount, the number of patient groups in which PCSK9 was estimated to be cost-effective could increase from 1 to 33 (out of 48). Willingness-to-pay thresholds (WTP) of approximately €67,000 were used to determine likelihood of cost-effectiveness in all analyses, which is standard in Norway.

Four publications used the Cardiovascular Disease Policy Model (CVDPM) to evaluate the cost-effectiveness of PCSK9 inhibitors in the United States (17-20). The Institute for Clinical and Economic Review's original draft report and a separate cost-effectiveness analysis were published prior to the FOURIER Trial, and therefore modelled clinical outcomes indirectly using CTTC meta-analysis results. Two updated cost-effectiveness analyses were published after the results of FOURIER, and each modelled cost-effectiveness based on outcomes on hard clinical endpoints in FOURIER. Broadly speaking, two main treatment groups were analysed: FH patients and patients with a history of CVD. Statins were assumed to be baseline treatment for all patients, though statin intolerance was assumed in 10% of the population for some analyses. Ezetimibe plus statin was included as a comparator in addition to statins in all but one publication. PCSK9 inhibitors were never found to be cost-effective given current market prices and standard willingness-to-pay thresholds. The ICERs varied between approximately US$275,000 and US$500,000 per QALY. In some cases, the ICER was close to or above US$1,000,000 per QALY, while standard WTP's in the US are $50,000, $100,000, and $150,000 per additional QALY gained. The authors found that substantial price reductions would be necessary—ranging from 42% to 88%—in order for the drugs to be considered cost-effective. Introduction of data on clinical relevant endpoints from FOURIER resulted in a reduced likelihood of cost-effectiveness and higher costs per QALY, as compared to the original analyses modelled according to LDL reductions and CTTC data.

Arrieta and co-workers performed two cost-effectiveness analyses (21,22). In the baseline scenario of the first analysis the effect of PCSK9 inhibitors was modelled directly according to 2015 outcome data on cardiovascular events, while in an alternate scenario the effect of PCSK9 on outcomes was modelled indirectly through to LDL reductions (21). The second analysis, an update of the original cost-effectiveness assessment, integrates evidence from the FOURIER trial (22). Each analysis used the Framingham risk equations to model risk of CVD, and each included a number of scenario analyses. The results were highly sensitive to price and estimate of effect. In the baseline scenario of the original analysis the ICER was about $350,000 per QALY, given current market prices. This baseline scenario assumed the relative risk reduction of CVD events was 49.2%, based on 2015 outcome data. When the estimate of effect was modelled through LDL reductions in the alternative analysis, the ICER was over $600,000 per QALY. The estimate of effect in the baseline scenario assumes a stronger effect on CVD events than FOURIER suggests. Integration of effectiveness evidence from the FOURIER trial in the updated analysis lead to a higher ICER of nearly $500,000 per QALY. The updated analysis found the ICER to be significantly lower, about $340,000 per QALY, under the assumption that patent protection would expire generics would enter the market after a number of years. Scenario analyses indicate that the ICERs are highly sensitive to price and estimate of effect, in addition to the introduction of revascularization as a health state. The results were not very sensitive to increases in cardiovascular event costs or baseline QALYs, which yielded only small effects on the ICER. Probabilistic sensitivity analysis suggests zero or near zero probability of cost-effectiveness given current market prices, and new price tags of $4250 in the original analysis and $5500 in the updated analysis were necessary for cost-effectiveness given a $100,000 WTP threshold.

Analyses performed with updated FOURIER data generally report lower effect of PCSK9 than those performed before this evidence was available (Table 3). With indirect modelling through LDL level reductions, these studies reported incremental QALYs ranging from 0.66 to 1.12, while with direct modelling of effect, similar results were almost halved, ranging from 0.27 to 0.62. It is worth noting, however, that updated analyses based on the FOURIER trial were only performed for patients with established CVD and not for FH populations.

## 4. Discussion

The cost-effectiveness of PCSK9 inhibitors remains uncertain because only one large randomized clinical trial has reported results. The currently published economic evaluations vary with respect to basis for effectiveness estimates (LDL or clinical outcomes), economic perspective (societal versus payer perspective), comparator, epidemiologic basis for risk of CVD events (national register data, Framingham equations, etc.) and patient groups. Still, most of the studies analysed here conclude that PCSK9 inhibitors are not cost-effective for most patient groups, given a threshold in the order of US$100,000 per QALY.

The cost-effectiveness of interventions to reduce the risk of CVD needs to take account of long-term cost and health consequences, CVD risk and medical practice, and cost level for the relevant country or area. This means that no randomized study alone is sufficient to evaluate cost-effectiveness, and policy makers have to use mathematical or numerical models for informed decision-making. The cost-effectiveness analyst then has to make a number of choices that will influence the long-term cost as well as effectiveness estimate. A starting point is the short-term and long-term risk of CVD events in the patient group the analyst aims to study. The majority of studies uses Framingham equations (17-22). There are important limitations to consider, however, when using Framingham scores in this context. These equations are not validated for use in wider populations, or for

secondary prevention. Local or national register data likely better reflects the actual risk of specific populations, but a lack of registry data in most countries limits this option. Another important factor may be the number of different types of clinical events that are modelled. The more relevant events that are included (e.g. heart failure or angina), the greater the estimated benefit because such additional benefits and avoided costs come at no additional treatment cost.

The impact of PCSK9 inhibitors may be modelled though LDL cholesterol level reductions or more directly with relative hazards from clinical trials. Two of the groups that have analysed cost-effectiveness of PCSK9 inhibitors have performed updated analyses after the publication of the FOURIER trial with data on hard clinical endpoints. These updated analyses indicate that modelling of effectiveness of PCSK9 inhibitors based only on randomized evidence on LDL-C reduction gives more favourable results—i.e. high likelihood of cost-effectiveness and lower ICERs—compared to modelling based on actual reductions in AMI and stroke. The lower ICERs are a result of the higher incremental effects, which we have shown to be approximately doubled if based on modelling through LDL reduction. It should again be noted that the follow-up time of FOURIER patients still is limited, and valid only for a short follow-up period. The finding of a small, non-significant increase in mortality in the FOURIER trial may be explained by chance given that that there was a statistically significant reduction in all-cause death in another recent trial with longer follow-up, the ODYSSEY outcomes trial (https://clinicaltrials.gov/ct2/show/NCT01663402). This study confirms the effect on CVD events and further re-analyses may be warranted to show the effect of this result on cost-effectiveness (http://clinicaltrialresults.org/Slides/ACC2018/ODYSSEY_Steg.pdf).

The primary drivers of these analyses are the PCSK9 price and the estimate of effectiveness. The CVDPM analyses utilize significantly higher CVD cost estimates for acute MI and post-stroke treatment, in addition to generally higher utilities for chronic CVD states as compared to the Arrieta analyses. In spite of this, the incremental cost-effectiveness ratios reported from their respective updated analyses that integrated the FOURIER evidence were quite comparable (approximately $450,000 per QALY for CVDPM and $500,000 per QALY for Arrieta), assuming similar drug prices and no price reductions. This means that utilization of the same outcome data when modelling the estimate of effect leads to similar results in spite of differences in key cost and utility estimates. All these analyses assumed that PCSK9 inhibitors would have an effect on cardiovascular mortality. When the CVDPM was modelled assuming no effect on CVD mortality, as was the case in the FOURIER trials, the ICERs rose significantly to roughly $1,300,000 per QALY. When the cost of the drugs was then discounted from $14,500 to $9000, the ICERs dropped to approximately $800,000 per QALY. This demonstrates quite clearly that estimate of effect and drug costs are the key drivers in cost-effectiveness analysis of PCSK9 inhibitors.

All analysis results included in this review are highly sensitive to changes in price, such that significant price breaks lead to major reductions in ICERs and increases in likelihood of cost-effectiveness. Price breaks in the order of 50-70% were necessary in most analyses for PCSK9 inhibitors to be considered cost-effective at the stated WTP levels (e.g. $100 000 in the US). Treatment with PCSK9 inhibitors was assumed a long-term treatment by all analyses, and time horizons were universally quite long. It is not surprising that the accumulation of costs of many years of treatment has a powerful effect on cost-effectiveness results. This was, for example, why our own Norwegian analysis found that initiating treatment in older patients was more cost-effective. These patients have fewer total years of treatment and their absolute risk levels is generally higher.

Another important driver of results is the baseline risks of events. Model analyses have generally modelled patients with either established CVD or FH. Although each of these populations consists of a number of individuals with the other condition (i.e. the CVD population also has some FH patients

and the FH population also has some CVD patients), only a few models have explicitly modelled the joint risk of having these two conditions simultaneously. The Korman analysis explicitly models FH separately and in combination with CVD and shows that patients with both conditions are more cost-effective to treat than FH patients without established CVD. Given that the FH population modelled by Villa has a high proportion of CVD, this may be a factor that explains why this analysis suggests that PCSK9 treatment is cost-effective.

As has been reported by others, cardiovascular disease has been modelled with a range of different CVD events and health states (23). The modelling of PSCK9 inhibitors generally included modelling through the health states post-MI and post-stroke, with some alterations and additions in some models (e.g. heart failure). We did not find any clear connection between number of health states modelled and cost-effectiveness, although one of the papers had a scenario analysis which indicated that including another event (revascularisation) would reduce the ICER (22). Patients that experience recurrent CVD events despite maximal intensive treatment are at considerably higher risk than those who have experienced just one event. Further, advanced atherosclerosis in young patients is typically more aggressive than in older patients. It is possible that more targeted modelling of groups such as these could yield more favourable cost-effectiveness results for PCSK9 inhibitors. However, if this kind of modelling is to be performed, it would either have to be based on the identification of high-risk subgroups in RCTs, which to date has not been performed, or based on some kind of assumption with the limitations that follow.

Funding from one of the manufacturer of PCSK9 inhibitor was present in 3 of 10 analyses. Among the 3 industry funded analyses, 1 concluded that PCSK9 inhibitors were cost-effective, compared to 0 among 7 studies not funded by industry. Hence, this review gives some indication that industry funded analyses conclude in favour of cost-effectiveness to a greater extent than non-funded analyses, although the numbers here are too small to make any clear conclusion.

All analyses compared ICERs to an assumed willingness-to-pay per QALY. Given the estimation of opportunity cost in the UK (24) and the more recent translation of those results to other jurisdictions by Woods and colleagues (25), the assumed WTPs are probably too high, given that a WTP should be based on the opportunity cost. For the US, analyses used $100,000 or $150,000 per QALY, while Woods and colleagues report that an estimate of opportunity cost in the US could be in the range of $24,000 to $40,000 per QALY. Similarly for Spain a range of €30,000 to €45,000 was used in analyses, while Woods and colleagues calculated that it should be in the range of €10,000 to €12,000. For Norway, the analyses indicated a WTP of approximately €67,000, which is actually within the range calculated by Woods (€30,000-€70,000). Based on the calculations of opportunity cost made by Woods and colleagues, the only analyses that may show that introducing PCSK9 inhibitors produce more health than it displaces, was the Norwegian study.

There are limitations to our analysis. First, we can never be certain that our search strategy finds all relevant articles and reports that are published. Secondly, we only searched through Medline and Embase, which may not cover all relevant publications. That said, reports from several health technology assessment agencies, which previously were regarded as "grey literature" and difficult to locate, have now been made available on Medline.

## 4.1 The way forward for PCSK9 inhibitors

At present, PCSK9 inhibitors are expensive and utilized modestly. Patients with the highest risk of CVD are likely those who will get the drugs first, such as those analysed in the economic evaluations summarized here. Particularly patients who cannot achieve acceptable LDL-C levels with other drugs and have FH, established CVD, or both. In the short-run the number of patients for whom PCSK9 inhibitors are considered cost effective will likely remain small. These numbers are not likely to expand unless prices are lowered considerably. With two PCSK9 inhibitors available at the moment and more in the pipeline, reduced price is a likely scenario in the coming years. The introduction of small interference molecules such as icilsaran could also have an effect on market prices, as they are purported to be cheaper than and just as effective as PCSK9 inhibitors, and require only biannual injections (26). Whether prices will decline due to competition alone, however, is not certain, as can been seen from the oral anticoagulants which were introduced a few years ago. Although dabigatran, rivaroxaban and apixaban were all introduced about 10 years ago, prices have remained relatively unchanged. When comparing current prices to those gathered for an economic evaluation 5 years ago (25), prices of two oral anticoagulants have gone down 5 % and 6% in Norway, while the third has increased its price (www.legemiddelverket.no).  Similar small changes have been seen for newer insulins, where degludec, glargin and detemir have all seen either an increase in prices or a maximum of 1% reduction in Norway since their introduction ([www.legemiddelverket.no](www.legemiddelverket.no)). Given the slow price reductions of other drugs, large price reductions for PCSK9 inhibitors may not be likely. If the prices are not reduced, PCSK9 inhibitors may have limited use until patent protection expires. Given that up to 10% of the population of many countries are currently on statins, the potential market for PCSK9 inhibitors may be tens or even hundreds of millions of people globally. The extent to which these drugs are widely adopted will depend in part on the market effect of patent protection, assuming no severe side effects are identified. However, because PCSK9 inhibitors require injections, it unlikely that they will achieve as large market share as statins.

Some side effects have been observed with PCSK9 inhibitors. The development of bococizumab was discontinued in part because of side effects (28). Given the limited experience with PCSK9 inhibitors in routine clinical practice, it is important to follow up closely with post-licensing research, such as "phase IV studies". Using established registries and cohorts, or establishing new ones, could be imperative for the future practice in cardiovascular care with PCSK9 inhibitors.

Performing health economic evaluations of new drugs when there are already other drugs currently available requires thorough consideration regarding which comparators to include in the analyses. In a recent article, Woods and colleagues stress that assessments of PCSK9 inhibitors will face similar challenges as those that are experienced with direct-acting antivirals for treatment of hepatitis C (29). An example is the choice of comparator; PCSK9 inhibitors may be compared to statins, ezetimibe or the combination of these two. In addition, there may be a disagreement about which statin and dose is the most relevant comparator. There are also other, less widely used comparators, such as bile acid binding resins, that could be considered. A second example, as mentioned by Woods and colleagues, is sequence of treatments; should PCSK9 inhibitors be given as first line treatment in combination with statins and ezetimibe to select patients with very high risk, e.g. young patients in their 20's or 30's who are diagnosed with FH shortly after an AMI?  Or young patients with advanced atherosclerotic disease and recurrent events despite maximal doses of statins and ezetimibe? Time is important in young patients, as the rapid progression of atherosclerosis indicates an aggressive process. Bearing in mind the strong force of LDL cholesterol in atherosclerosis, an effective reduction is a targeted treatment. Time will tell what future guidelines will present. In the meantime most patients will typically receive statins as first line treatment, ezetimibe as second line, and finally PCSK9 inhibitors or potentially bile acid binding resins as third line in selected cases.

Patients, payers and society in general need valid estimates of the cost-effectiveness of PCSK9 inhibitors. As more data from the large clinical trials are reported, we will have better foundation for reliable ICERs. However, the modelling approaches also seem to have considerable impact on the results. It seems to be prudent for cost-effectiveness modellers to come together and explore the reasons why they come to different results and how to improve future modelling. We have given some insight into these issues, but future analyses would gain from analysing with different sets of assumptions, which could give more direct evidence of the impact of different assumptions.

## 5. Conclusion

With some exceptions, PCSK9 inhibitors seems not to be cost-effective at the standard list prices, but price discounts are found to change cost-effectiveness results considerably.

## Funding

*Table 1 Description of each study analysed in the review*

| Study/citation | Country | Research question/ intervention | Update? | Time horizon | Perspective | Patient population | Health Outcomes | PSA? (include other forms of sensitivity analysis? E.g. varying the price or effect on individual health outcomes? | Discount rate |
|---|---|---|---|---|---|---|---|---|---|
| Arrieta 1, 2017 (21) | USA | CEA of PCSK9, vs. STA | N | Lifetime | Health system and private payer | Reflects evolocumab RCT population | LY, QALY | PSA | 3% for costs and outcomes |
| Arrieta 2, 2017 (22) | USA | CEA of PCSK9, vs. STA | Y | Lifetime | Health system and private payer | Reflects FOURIER population | LY, QALY | PSA | 3% for costs and outcomes |
| Fonarow, 2017 (12) | USA | CEA of PCSK9, vs. STA, STA + EZE | N | Lifetime | Societal (payer in scenario) | ASCVD, mean age 66, mean LDL 2.7 mmol/l | QALY | PSA, but only reports value based price | 3% for costs and outcomes |
| Gandra, 2016 (13) | USA | CEA of PCSK9, vs. STA | N | Lifetime | Payer | HeFH, ASCVD, ASCVD&SI; mean ages 51, 62 and 64, respectively | LY, QALY | PSA | 3% for costs and outcomes |
| ICER 1, 2015 (20) | USA | CEA of PCSK9, vs. STA, STA + EZE | N | Lifetime | Health system | HeFH, ASCVD, ASCVD&SI, 35-74 yrs | LY, QALY | PSA | 3% for costs and outcomes |
| ICER 2, 2016 (18) | USA | CEA of PCSK9, vs. STA, STA + EZE | N | Lifetime | Health system | HeFH, ASCVD, ASCVD&SI, 35-74 yrs | LY, QALY | PSA | 3% for costs and outcomes |
| ICER 3, 2017 (17) | USA | CEA of PCSK9, vs. STA + EZE | Y | Lifetime | Health system | ASCVD, LDL 1.81 mmol/L, 40-84 yrs | LY, QALY | Deterministic only (this is an update, was not seen as necessary to undertake PSA again) | 3% for costs and outcomes |
| ICER 4, 2017 (19) | USA | CEA of PCSK9, vs. STA | Y | Lifetime | Health system | ASCVD, LDL 1.81 mmol/L, 40-84 yrs | QALY | Deterministic only (this is an update, was not seen as necessary to undertake PSA again) | 3% for costs and outcomes |

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|---|---|---|---|---|---|---|---|---|---|---|
| Korman, 2017 (16) | Norway | CEA of PCSK9, vs. STA, STA + EZE | N | Lifetime | Health system | HeFH, Diabetic, ASCVD, SI | LY, QALY | PSA | | 4% for costs and outcomes |
| Villa, 2017 (14) | Spain | CEA of PCSK9, vs. STA | N | Lifetime | Health system | HeFH, ASCVD | LY, QALY | PSA | | 3% for costs and outcomes |

PSA = Probabilistic sensitivity analysis

CEA = Cost-effectiveness analysis

PCSK9 = proprotein convertase subtilisin/kexin type 9 inhibitor

STA = Statin

LY = Life year

QALY = Quality-adjusted life-year

FOURIER = the FOURIER trial (6)

ASCVD = Atherosclerotic cardiovascular disease

HeFH = Heterozygous Familial Hypercholeterolemia

LDL = Low-density lipoprotein

SI = Statin intolerant

EZE = ezetimibe

ICER = Institute for clinical and economic review

Update = Analysis re-performed with FOURIER data, based on original analyses published prior to FOURIER

*Table 2 Key cost-effectiveness results of each study in the review*

| Study/citation | | Health states* | Effectiveness modeled | ASCVD patients | | | HeFH patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | ICER, per QALY | Probability cost effective (PSA) ($100,000/QALY threshold and market price) | Price reduction to achieve cost effectiveness (% from original)(if applicable/reported) | ICER, per QALY | Probability cost effective (PSA) ($100,000/QALY threshold) | Price reduction to achieve cost effectiveness (%) |
| Arrieta 1, 2017 (21) | CEA of PCSK9, vs. STA | AMI (1 year), post AMI, stroke (1 year), post stroke, other CVD (1 year), post other CVD | Framingham + observed evolocumab RCT (OSLER, 1 year) Effect on MI, angina, stroke, CV death | $348,807 | 0% | ca. 70% (system persp.) ca. 95% (payer persp.) | n/a | n/a | n/a |
| Arrieta 2, 2017 (22) | CEA of PCSK9, vs. STA | As for Arrieta 1 | Observed FOURIER data (3 year) + Framingham extrapolation | $337,728 | <1% | 62% (system persp.) 83% (payer persp.) | n/a | n/a | n/a |
| Fonarow, 2017 (12) | CEA of PCSK9, vs. STA, STA + EZE | ASCVD, AMI (1 year), IS (1 year), post-AMI, post-stroke | Through LDL reduction, but based on data with hard clinical endpoints: FOURIER, adjusted to fit US population (hence smaller effect in model than trial) Effect on mortality only after 5 years | $268,637 | 0% | 33% | n/a | n/a | n/a |
| Gandra, 2016 (13) | CEA of PCSK9, vs. STA | ECVD, ACS, IS (1 year), HF, post-HF, post-ACS, post-stroke | Through LDL reduction on ECVD, ACS, IS, HF, revasc. and CHD death (Amgen document and GAUSS-2 combined with CTTC) | $141,699 | 0% | n/a | $75,863 | 97% | n/a |

| Study | | Health states* | Effect mechanism | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ICER 1, 2015 (20) | CEA of PCSK9, vs. STA, STA + EZE | post angina, post AMI, post revascularization, post AMI + revascularization, post stroke, post stroke + post AMI | Through LDL reduction on stroke, AMI and CHD mortality (PCSK9 meta-analysis + CTTC) | $302,000 | 0% | 63% | $290,000 | 0% | 60% |
| ICER 2, 2016 (18) | CEA of PCSK9, vs. STA, STA + EZE | As for ICER 1 | As for ICER 1 | $414,000 | 0% | 68% | $503,000 | 0% | 68% |
| ICER 3, 2017 (17) | CEA of PCSK9, vs. STA + EZE | As for ICER 1 | FOURIER, extrapolation to all CHD, including death | $450,000 | assumed 0% | 71% | n/a | n/a | n/a |
| ICER 4, 2017 (19) | CEA of PCSK9, vs. STA | As for ICER 1 | FOURIER, restricted mortality effect in line with FOURIER | $1,336,221 | assumed 0% | 88% | n/a | n/a | n/a |
| Korman, 2017 (16) | CEA of PCSK9, vs. STA, STA + EZE | post MI, post IS | Through LDL reduction on MI, IS and CVD death (PCSK9 meta-analysis + CTTC) | € 128,191 (threshold: € 67,165) (age: 65 yrs at treatment) | 0% | 50% | € 101,351 (threshold: € 67,165) (age: 65 yrs at treatment) | 0% | 50% |
| Villa, 2017 (14) | CEA of PCSK9, vs. STA | 24 different, of which 13 are composite | Through LDL reduction on ECVD, ACS, IS, HF, revasc. and CHD death (RUTHERFORD-2, LAPLACE-2 AND GAUSS-2, combined with CTTC) | € 45,340 (threshold: € 45,000) | 43% | Already approximately cost-effective | € 30,893 (threshold: € 45,000) | 97% | Already cost-effective |

*We have here included only health states that are assumed to last for more than one month

PSA = Probabilistic sensitivity analysis

CEA = Cost-effectiveness analysis

PCSK9 = proprotein convertase subtilisin/kexin type 9 inhibitor

STA = Statin

QALY = Quality-adjusted life-year

AMI = Acute myocardial infarction

FOURIER = the FOURIER trial (6)

ECVD = Established CVD

CTTC = Cholesterol treatment trialists' collaboration (15)

ASCVD = Atherosclerotic cardiovascular disease

HeFH = Heterozygous Familial Hypercholeterolemia

LDL = Low-density lipoprotein

EZE = ezetimibe

ICER (column 1) = Institute for clinical and economic review

ICER (columns 5 and 8) = Incremental cost-effectiveness ratio

*Table 3 Incremental effect of PCSK9 inhibitor in each study*

| Study/citation | ASCVD patients | | | HeFH patients | | |
|---|---|---|---|---|---|---|
| | QALY gain* | Age** | Effect | QALY gain* | Age** | Effect |
| Arrieta 1, 2017 (21) | 0.66 | 58 | indirect | n/a | n/a | |
| Arrieta 2, 2017 (22) | 0.36 | 58 | direct | n/a | n/a | |
| Fonarow, 2017 (12) | 0.39 | 66 | direct | n/a | n/a | |
| Gandra, 2016 (13) | 1.12 | 62 | indirect | 2.02 | 51 | indirect |
| ICER 1, 2015 (20) | 0.86 | | indirect | 0.69 | | indirect |

| | | | | | | |
|---|---|---|---|---|---|---|
| ICER 2, 2016 (18) | 0.93 | 61 | indirect | 0.57 | 51 | indirect |
| ICER 3, 2017 (17) | 0.62 | 66 | direct | n/a | n/a | |
| ICER 4, 2017 (19) | 0.27 | 66 | direct | n/a | n/a | |
| Korman, 2017 (16) | 0.64 | 65 | indirect | 0.84 | 65 | indirect |
| Villa, 2017 (14) | 0.93 | 71 | indirect | 2.12 | 50 | indirect |
| *All QALY gains compared to statin+ezetimibe | | | | | | |
| **Age at start of simulation model or average age in population | | | | | | |

Figure 1 Flow of information through different phases of the review (*reasons for exclusion in appendix 2)
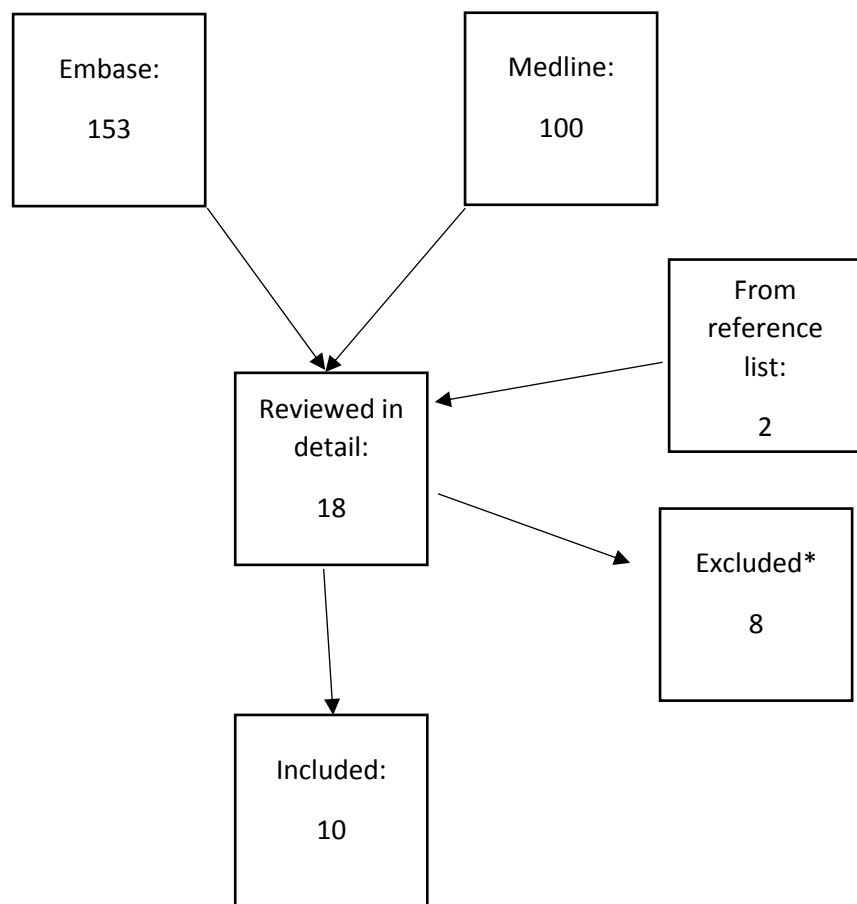
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