Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease

Manon C. Stam-Slob a,1, Yolanda van der Graaf b,1, Anthonius de Boer c,2, Jacoba P. Greving b,1, Frank L.J. Visseren a,1

A R T I C L E  I N F O

Article history:
Received 3 October 2016
Received in revised form 4 October 2017
Accepted 19 October 2017

Keywords:
Cost-effectiveness
PCSK9 inhibition
Lifetime benefit
(Quality-adjusted) life years
Vascular disease

A B S T R A C T

Background: As proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies are entering the market, we assessed the cost-effectiveness of PCSK9 inhibition added to standard lipid-lowering therapy in patient groups at high risk for major adverse cardiovascular events (MACE).

Methods: A lifetime Markov Model was designed to estimate healthcare costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for PCSK9 inhibition added to standard therapy in patients with Familial Hypercholesterolemia (FH), patients with vascular disease at high MACE recurrence risk, and patients with vascular disease with diabetes mellitus. The balance between costs and health outcomes was established for a broad range of potential relative risk reductions and drug costs.

Results: The expected QALY gain per patient and ICER in the main scenario were 1.4 QALYs for €78,485/QALY gained in patients with FH, 0.22 QALYs for €176,735/QALY gained in those with vascular disease and a predicted risk of MACE ≥30% in 10 years, and 0.22 QALYs for €295,543/QALY gained in those with vascular disease and diabetes. Results were sensitive to assumptions on PCSK9 inhibitor treatment efficacy, and vascular event risks.

Conclusion: The costs and effects of PCSK9 inhibition added to standard lipid-lowering treatment in patient groups at high risk for MACE can be estimated and adapted to a specific clinical setting. PCSK9 inhibition could be cost-effective in patients with FH. In patients with vascular disease PCSK9 inhibition is less cost-effective, however, a price development may change clinical practice. This model may aid treatment and reimbursement decisions regarding PCSK9 inhibitors.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

The burden of cardiovascular disease has decreased significantly in the past decades by the introduction of drugs that lower low-density lipoprotein cholesterol (LDL-c) [1]. Statins effectively lower LDL-c and risk of major adverse cardiovascular events (MACE), and addition of ezetimibe to a statin regimen may further reduce LDL-c and MACE risk [2]. However, some patients remain at high vascular risk because of uncontrolled LDL-c levels despite maximal lipid-lowering therapy [3]. Recently, monoclonal antibodies that bind to proprotein convertase subtilisin-kexin type 9 (PCSK9) have shown to lower LDL-c serum levels with 57% (95% confidence interval [CI] 54%–60%) compared to placebo in patients with hypercholesterolemia when added to standard lipid-lowering treatment [4]. A recent large randomized trial revealed a 15% reduction with PCSK9 monoclonal antibodies on top of statin therapy on the incidence of MACE during a median follow-up duration of 2 years [5]. Combined secondary analyses on MACE of small clinical trials primarily evaluating the lipid-lowering effect of PCSK9 monoclonal antibodies revealed a relative risk reduction of 46% (95%CI 23%–62%) compared to standard lipid-lowering therapy [4,6,7]. PCSK9 monoclonal antibodies have been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of hypercholesterolemia and are entering the market. Compared to other lipid-lowering drugs the price of PCSK9 monoclonal antibodies will be high which raises questions on cost-effectiveness [8]. In the present study we evaluated the cost-effectiveness of PCSK9 monoclonal antibodies for the treatment of hypercholesterolemia in addition to maximal lipid-lowering therapy in patients defined by the international guidelines being at (very) high risk for vascular disease, namely patients with Familial Hypercholesterolemia (FH) or clinically manifest vascular disease with or without diabetes [9,10]. In sensitivity analyses,
effectiveness in terms of vascular risk reduction and drug costs are varied. The long-term effect of PCSK9 inhibitors on vascular events is still uncertain, and drug costs may differ between countries, between compounds and may change over time.

2. Methods

2.1. Model structure

A Markov model was designed to estimate costs, life years and quality-adjusted life years (QALYs) gained for PCSK9 inhibition in addition to standard lipid-lowering therapy for various patient groups at high risk for vascular disease (Fig. 1) [9,10]. These high risk groups were: 1) patients with familial hypercholesterolemia (FH) without a history of vascular disease, 2) patients with stable vascular disease and a 10-year recurrence MACE risk of ≥20% or ≤30%, and 3) stable vascular disease and type 2 diabetes. These groups partly overlap as patients with vascular disease and diabetes have a high recurrence MACE risk. Cost-effectiveness in patients with diabetes was assessed separately to account for diabetes treatment costs and the health impairment caused by diabetes. All patients started in the stable health phase at the left of the diagram. Each year a patient could transit to another state. After a vascular event the patient transited to the corresponding post-event state (myocardial infarction, stroke, revascularization or unstable angina). Multiple vascular events could occur during a lifetime. If patients died of any cause, they transited to the terminal ‘death’ health state.

2.2. Model input

2.2.1. Event risks

Model assumptions were made from a healthcare perspective in the Netherlands. Annual vascular event risks are presented in Supplementary Table 1. Event probabilities for patients with FH were based on observational Dutch multi-center studies [11–13]. These high risk groups were: 1) patients with familial hypercholesterolemia (FH) without a history of vascular disease, 2) patients with stable vascular disease and a 10-year recurrence MACE risk of ≥20% or ≤30%, and 3) stable vascular disease and type 2 diabetes. These groups partly overlap as patients with vascular disease and diabetes have a high recurrence MACE risk. Cost-effectiveness in patients with diabetes was assessed separately to account for diabetes treatment costs and the health impairment caused by diabetes. All patients started in the stable health phase at the left of the diagram. Each year a patient could transit to another state. After a vascular event the patient transited to the corresponding post-event state (myocardial infarction, stroke, revascularization or unstable angina). Multiple vascular events could occur during a lifetime. If patients died of any cause, they transited to the terminal ‘death’ health state.

2.2.2. PCSK9 treatment effect

The expected PCSK9 inhibitor relative treatment effect was based on the mean decrease in absolute LDL-c levels in trial populations [4,10,24]. Mean baseline LDL-c was 3.15 mmol/l, which was lowered with 48% (1.5 mmol/l) when PCSK9 inhibition was added to the combination of a statin and ezetimibe [4]. Assuming a hazard ratio (HR) for MACE of 0.79 per mmol/l absolute LDL-c reduction, the relative MACE risk reduction with PCSK9 inhibition added to statin and ezetimibe would be 30% (HR = 0.79^1.5 = 0.70) [1]. In additional scenario analyses, we modelled the PCSK9 inhibitor treatment effect for a lower or higher baseline LDL-c. For patients with vascular disease (and diabetes) we derived event risks from SMART patients in the lowest and the highest quartile of baseline LDL-c. The PCSK9 treatment effect for these patients was estimated as shown in the example above. Moreover, we estimated cost-effectiveness ratios based on the results from a recent clinical trial on the effect of PCSK9 inhibition on cardiovascular
outcomes [5]. Thereafter, the balance between costs and health outcomes was established for a broad range of potential PCSK9 inhibitor relative treatment effects.

2.2.3. Costs

The annual cost of standard lipid-lowering therapy was the mean cost in euros of the generic usual-dose statins plus ezetimibe once daily (Supplementary Table 3) [25]. Annual cost of PCSK9 inhibition was €6000 in the base case analysis based on estimated drug costs in different European countries [25,26]. These drug costs vary between countries and therefore the balance between costs and health outcomes was studied for a wide range of potential drug costs from €500 to €11,000 per year. Vascular event costs and post-event costs were obtained from observational studies and nationwide registries [27–31]. The cost of a revascularization procedure was a weighted mean for a percutaneous coronary intervention and a coronary artery bypass graft [32]. Annual costs for diabetes care were based on a recently performed cluster randomized trial in the Netherlands [33]. Annual pharmacy costs, laboratory costs for a lipid profile and one doctor’s visit per year were included [34,35]. Costs were updated to 2014 with Dutch consumer price indices [36].

2.2.4. Health outcomes

Health outcomes were measured in mean life years and quality-adjusted life years (QALYs) per patient with and without PCSK9 inhibition. The amount of time a patient is in a certain health state and the utility belonging to that health condition. A utility is a value that scales the quality of life between 1 (perfect health) and 0 (death). A patient that lives for 10 years with a disease that has a utility of 0.8 attributes 10 × 0.8 = 8 QALYs. Utilities for stable vascular disease, diabetes and post-event states were derived from the literature and adjusted for age (Supplementary Table 3) [37–39].

2.3. Analyses

A hypothetical cohort of 10,000 patients for each high risk group entered the Markov model. The model was run for the standard lipid-lowering treatment strategy and the strategy in which PCSK9 inhibition was added to the standard regimen. When starting in the stable health phase FH patients were on average 45 years of age, patients with stable vascular disease and ≥30% 10-year MACE risk 70 years of age, and those with diabetes and stable vascular disease were on average 63 years of age [11,12,15,23]. Furthermore, we performed a sensitivity analysis in patients with vascular disease aged ≥65 years. The model was run for a lifetime horizon, i.e. until all patients had died. Event and drug costs, life years and QALYs were calculated for the different groups and treatment strategies. Incremental cost-effectiveness ratios (ICERs) were estimated by dividing the difference in costs by the difference in QALYs with and without PCSK9 inhibition. A discount rate of 3% was applied for both costs and health outcomes [40]. The analysis was repeated for different event probabilities, drug costs, event costs, PCSK9 inhibitor treatment efficacy, discount rates and mortality multipliers, adjusting one model assumption at a time (lower and upper bound from Supplementary Tables 1 and 3). In a probabilistic sensitivity analysis with Monte Carlo simulations (1000 times), all model assumptions were varied at the same time choosing random values from the beta distribution for event probabilities and utilities, the gamma distribution for costs and mortality multipliers and the lognormal distribution for the hazard ratio of PCSK9 inhibition versus standard lipid-lowering therapy. The chance that PCSK9 inhibition would be a cost-effective therapy was presented in a graph for different thresholds in euros willing to pay for an additional QALY.

All model assumptions and calculations can be found in the supplementary Excel file for transparency and to enable the reader to adapt them to another clinical setting.

3. Results

3.1. Incremental costs and effects for PCSK9 inhibitors in FH patients

PCSK9 inhibition yields 2.3 life years and 1.4 QALYs per patient with FH without vascular disease at baseline (mean age of 45 years) when added to standard lipid-lowering therapy (Table 1). Expected lifetime costs for PCSK9 inhibition in addition to standard lipid-lowering treatment are €108,414 per FH patient, resulting in an ICER of €78,485 euros per QALY gained.

The expected costs for one QALY gained are below €80,000 if the relative risk reduction with PCSK9 inhibition is ≥30%, ≥23% or ≥15% for annual PCSK9 inhibitor treatment costs of €6000, €4500 or €3000 respectively (Fig. 2A–C). Assuming a relative risk reduction of 30%, the estimated costs for one QALY gained in patients with FH are below €80,000 for annual PCSK9 inhibitor drug costs ≥€6000, and below €20,000 for drug costs ≤€1500 (Fig. 3).

3.2. Incremental costs and effects for PCSK9 inhibitors in patients with vascular disease

For patients with vascular disease, 0.25 QALY may be saved with PCSK9 inhibition for those with ≥20% risk (mean age 67 years), and 0.22 QALY for those with ≥30% risk of MACE in 10 years (mean age 70 years). Expected incremental costs during a patient’s lifetime are €47,799 for those with ≥20% risk, and €39,411 for those with ≥30% risk of MACE in 10 years. ICERs in patients with vascular disease are €193,726 euros per QALY gained for those with ≥20% risk, and €176,736 euros per QALY gained for those with ≥30% risk of MACE in 10 years.

For patients with vascular disease and ≥30% risk of MACE in 10 years, the ICER falls below €100,000/QALY if the relative risk reduction with PCSK9 inhibition is ≥52%, ≥40% or ≥27% for annual PCSK9 inhibitor treatment costs of €6000, €4500 or €3000 respectively. Assuming a relative risk reduction of 30%, expected costs per QALY are below €100,000 if annual PCSK9 inhibitor treatment costs are ≤€3000, and ≤€3250 for patients with vascular disease and a 10-year MACE risk of ≥20%, and ≥30% respectively.

3.3. Incremental costs and effects for PCSK9 inhibitors in patients with diabetes

An estimated 0.22 QALY is saved with PCSK9 inhibitor treatment per patient with vascular disease and diabetes (mean age of 63 years). Predicted lifetime costs for PCSK9 inhibitor therapy are €63,489 per patient, resulting in an ICER of €295,543 per QALY gained.

For patients with vascular disease and diabetes, an ICER below €100,000/QALY would be achieved with a relative risk reduction ≥85%, ≥66% or 47% for annual PCSK9 inhibitor treatment costs of €6000, €4500 or €3000 respectively. Assuming a relative risk reduction of 30%, annual PCSK9 inhibitor treatment costs ≤€1750 result in an ICER below €100,000/QALY.

3.4. Incremental costs and effects for PCSK9 inhibitors in patients with vascular disease aged ≥65 years

For patients aged ≥65 years, PCSK9 inhibition yields 0.53 QALY in those at ≥20% risk for MACE in 10 years (mean age 58 years), and 0.61 QALY per patient for those at ≥30% risk for MACE in 10 years (mean age 59 years). Estimated incremental costs during a patient’s lifetime are €74,022 for those with ≥20% risk, and €71,859 for those with ≥30% risk of MACE in 10 years. ICERs in patients with vascular disease are €139,020 euros per QALY gained for those with ≥20% risk, and €117,288 euros per QALY gained for those with ≥30% risk of MACE in 10 years.

3.5. Scenario analyses

ICERs are most sensitive to assumptions on PCSK9 inhibitor treatment efficacy (Supplementary Fig. 1), which closely relates to the absolute LDL-c reduction. Assuming a 15% relative risk reduction in the incidence of MACE [5], 0.66 QALY is gained per patient with FH for €161,676/QALY, 0.11 QALY is gained per patient with vascular disease at ≥30% MACE recurrence risk for €359,778/QALY, and 0.11 QALY is gained per patient with vascular disease and diabetes for €600,038/QALY. Event probabilities and the annual costs of PCSK9 inhibitor treatment affect the results as well. In a scenario analysis with 50% lower vascular event probabilities, PCSK9 inhibition gains 1.6 life years and 0.9 QALY per FH patient, resulting in an ICER of €135,012 euros per QALY gained. If the mean age of patients with FH is increased to 60 years, approaching the mean age of patients with vascular disease, a mean of 1.0 QALY is gained per patient with PCSK9 inhibition for €80,782.
The Markov Model in this study was robust and representative for clinical practice. This is the first study to assess costs and health outcomes for patients in a European health care setting, and to select patients according to their predicted MACE risk. Moreover, extensive scenario analyses were performed, in particular for costs and effects of PCSK9 inhibitor treatment. There are several considerations that need to be addressed when interpreting the model results. The long-term relative effect of PCSK9 inhibition on MACE is unknown. Event probabilities in FH patients were mainly derived from older studies and might be favorable cost-effectiveness ratio for European FH patients, which is to a great extent explained by lower mean drug costs in Europe (a scenario analysis with USA drug costs increased the ICER to €200,000/QALY).

Furthermore, event risks in the present study were higher as we also took revascularization procedures and angina pectoris into account. Another report written from a USA payer perspective concludes that PCSK9 inhibition in patients with FH or vascular disease may be cost-effective, with lower costs per QALY gained in patients with FH than in patients with vascular disease. Recently, a cost-effectiveness analysis for the Norwegian situation found that PCSK9 inhibition would only be cost-effective for patients aged ≥65 years at very high risk and a history of myocardial infarction. The Markov Model included pre- and post-health states for myocardial infarction and stroke. Revascularization procedures and heart failure were not modelled. The cost-effectiveness of secondary prevention was only modelled for patients with a history of myocardial infarction. The differing conclusion from the Norwegian study and the present study may be due to the differences in the Markov Model as revascularization, heart failure and stroke are costly events which concur a higher risk of both vascular death and death due to other causes. The authors from the Norwegian study note that with lower drug prices, PCSK9 inhibition may be more attractive for younger patients at high risk. This is in line with the present study which focuses on the European health care setting with many scenario analyses on possible treatment effects and costs of PCSK9 inhibitor treatment. There is quite some difference in cost-effectiveness between patient groups. Patients with FH have the highest QALY gain and the lowest costs per QALY gained. This could be partly, but not entirely due to the lower mean age of patients with FH compared to patients with clinically manifest vascular disease, with more potential life years to be saved in patients with FH. Their high overall QALY gain may further be explained by high LDL-c serum levels, even when treated with statins in combination with ezetimibe. Therefore, a larger LDL-c reduction can be achieved in FH patients. In patients with clinically manifest vascular disease with or without diabetes, the recurrent vascular risk is caused by various risk factors including LDL-c. Consequently, patients with clinically manifest vascular disease have a higher risk of death due to other causes than MACE which limits the health gain with PCSK9 inhibition.

Vascular event probabilities were higher for patients with vascular disease at ≥30% risk of recurrent vascular risk and a history of myocardial infarction would only be cost-effective for patients aged ≥65 years at very high risk and a history of myocardial infarction. The ICER in these patients was still ≥€100,000 per extra QALY.

The Markov Model included pre- and post-health states for myocardial infarction and stroke. Revascularization procedures and heart failure were not modelled. The cost-effectiveness of secondary prevention was only modelled for patients with a history of myocardial infarction. The differing conclusion from the Norwegian study and the present study may be due to the differences in the Markov Model as revascularization, heart failure and stroke are costly events which concur a higher risk of both vascular death and death due to other causes. The authors from the Norwegian study note that with lower drug prices, PCSK9 inhibition may be more attractive for younger patients at high risk. This is in line with the present study which focuses on the European health care setting with many scenario analyses on possible treatment effects and costs of PCSK9 inhibitor treatment. There is quite some difference in cost-effectiveness between patient groups. Patients with FH have the highest QALY gain and the lowest costs per QALY gained. This could be partly, but not entirely due to the lower mean age of patients with FH compared to patients with clinically manifest vascular disease, with more potential life years to be saved in patients with FH. Their high overall QALY gain may further be explained by high LDL-c serum levels, even when treated with statins in combination with ezetimibe. Therefore, a larger LDL-c reduction can be achieved in FH patients. In patients with clinically manifest vascular disease with or without diabetes, the recurrent vascular risk is caused by various risk factors including LDL-c. Consequently, patients with clinically manifest vascular disease have a higher risk of death due to other causes than MACE which limits the health gain with PCSK9 inhibition.

Vascular event probabilities were higher for patients with vascular disease at ≥30% risk of recurrent vascular risk and a history of myocardial infarction would only be cost-effective for patients aged ≥65 years at very high risk and a history of myocardial infarction. The ICER in these patients was still ≥€100,000 per extra QALY.

The Markov Model in this study was robust and representative for clinical practice. This is the first study to assess costs and health outcomes for patients in a European health care setting, and to select patients according to their predicted MACE risk. Moreover, extensive scenario analyses were performed, in particular for costs and effects of PCSK9 inhibitor treatment. There are several considerations that need to be addressed when interpreting the model results. The long-term relative effect of PCSK9 inhibition on MACE is unknown. Event probabilities in FH patients were mainly derived from older studies and might be favorable cost-effectiveness ratio for European FH patients, which is to a great extent explained by lower mean drug costs in Europe (a scenario analysis with USA drug costs increased the ICER to €200,000/QALY).

Furthermore, event risks in the present study were higher as we also took revascularization procedures and angina pectoris into account. Another report written from a USA payer perspective concludes that PCSK9 inhibition in patients with FH or vascular disease may be cost-effective, with lower costs per QALY gained in patients with FH than in patients with vascular disease. Recently, a cost-effectiveness analysis for the Norwegian situation found that PCSK9 inhibition would only be cost-effective for patients aged ≥65 years at very high risk and a history of myocardial infarction. The Markov Model included pre- and post-health states for myocardial infarction and stroke. Revascularization procedures and heart failure were not modelled. The cost-effectiveness of secondary prevention was only modelled for patients with a history of myocardial infarction. The differing conclusion from the Norwegian study and the present study may be due to the differences in the Markov Model as revascularization, heart failure and stroke are costly events which concur a higher risk of both vascular death and death due to other causes. The authors from the Norwegian study note that with lower drug prices, PCSK9 inhibition may be more attractive for younger patients at high risk. This is in line with the present study which focuses on the European health care setting with many scenario analyses on possible treatment effects and costs of PCSK9 inhibitor treatment. There is quite some difference in cost-effectiveness between patient groups. Patients with FH have the highest QALY gain and the lowest costs per QALY gained. This could be partly, but not entirely due to the lower mean age of patients with FH compared to patients with clinically manifest vascular disease, with more potential life years to be saved in patients with FH. Their high overall QALY gain may further be explained by high LDL-c serum levels, even when treated with statins in combination with ezetimibe. Therefore, a larger LDL-c reduction can be achieved in FH patients. In patients with clinically manifest vascular disease with or without diabetes, the recurrent vascular risk is caused by various risk factors including LDL-c. Consequently, patients with clinically manifest vascular disease have a higher risk of death due to other causes than MACE which limits the health gain with PCSK9 inhibition.

Vascular event probabilities were higher for patients with vascular disease at ≥30% risk of recurrent vascular risk and a history of myocardial infarction would only be cost-effective for patients aged ≥65 years at very high risk and a history of myocardial infarction. The ICER in these patients was still ≥€100,000 per extra QALY.
lower in current times because of improved cardiovascular preventive strategies. Therefore, we performed a scenario analysis with 50% lower event probabilities, based on a recent study that assessed the effect of increased statin use on coronary artery disease and mortality in FH patients [45]. PCSK9 inhibitor treatment costs may decrease over time and are likely to drop after patent expiration. As we model lifelong treatment with PCSK9 inhibition, lower treatment costs in the future would decrease the costs per QALY gained. Also, costs may differ between countries. We have not included possible costs or health impairment by any side effects of PCSK9 inhibitor treatment as there are no results of blinded long term follow-up trials yet. Quality of life was not lowered for subcutaneous injections with PCSK9 inhibitors.

Fig. 2. Incremental cost-effectiveness ratios (ICERs) for PCSK9 inhibition versus standard lipid-lowering therapy for varying relative treatment effects of PCSK9 inhibitors. Annual costs of PCSK9 inhibition were assumed to be a) €6000 per patient, b) €4500 per patient or c) €3000 per patient. PCSK9i = PCSK9 inhibition.
Fig. 3. Incremental cost-effectiveness ratios (ICERs) for PCSK9 inhibition versus standard lipid-lowering therapy for varying annual costs of PCSK9 inhibition. The relative risk reduction with PCSK9 inhibition was assumed to be 30%. PCSK9 = PCSK9 inhibition.

currently administered every 2 to 4 weeks. We assumed that standard lipid-lowering treatment consisted of a usual-dose statin and ezetimibe, as optimal therapy in those with refractory hypercholesterolemia should be a combination of the maximally tolerated statin dose and another lipid-lowering therapy [46]. Although some patients are not treated as such in the PCSK9 inhibitor trials and in clinical practice, this will not greatly impact the results as statins and ezetimibe are less costly than PCSK9 inhibitors.

5. Conclusions

We derived a model to estimate the costs and health outcomes of PCSK9 inhibition in addition to standard lipid-lowering treatment in different patient groups at high risk of vascular disease. The balance between costs and health outcomes was best for patients with FH. Depending on the drug price, and the willingness to pay per additional QALY, PCSK9 inhibition may be cost-effective for patients with FH. The cost-effectiveness ratio of PCSK9 inhibition is less favorable in patients with vascular disease at high risk for MACE or patients with vascular disease and diabetes. With current drug prices, the cost-effectiveness ratio is above an acceptable willingness to pay threshold in these patients. This model may be helpful in making decisions as to which patient groups are treated with PCSK9 inhibition to reduce the risk of (recurrent) vascular events, and to negotiate on pricing and reimbursement of these drugs.

Funding

None.

Disclosures

The institution of Dr. Visseren received payments from Amgen, Pfizer and Sanofi for phase II and III clinical trials. These sponsors did not influence any aspect of this work. The other authors declare no other support, relationships or activities that could appear to have influenced the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.10.080.

References


