ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2020) **00**, 1–8
doi:10.1093/ehjqcco/qcaa072

Original Article

Cost-effectiveness of proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab in patients with a history of myocardial infarction in Sweden

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Received 19 May 2020; revised 27 July 2020; editorial decision 31 August 2020; accepted 30 September 2020; online publish-ahead-of-print 16 October 2020

Aims To assess the cost-effectiveness of proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab added to standard-of-care lipid-lowering treatment [maximum tolerated dose (MTD) of statin and ezetimibe] in Swedish patients with a history of myocardial infarction (MI).

Methods and results Cost-effectiveness was evaluated using a Markov model based on Swedish observational data on cardiovascular event rates and efficacy from the FOURIER trial. Three risk profiles were considered: *recent MI* in the previous year; history of *MI with a risk factor*; and history of *MI with a second event* within 2 years. For each population, three minimum baseline low-density lipoprotein cholesterol (LDL-C) levels were considered: 2.5 mmol/L (≈100 mg/dL), based on the current reimbursement recommendation in Sweden; 1.8 mmol/L (≈70 mg/dL), based on 2016 ESC/EAS guidelines; and 1.4 mmol/L (≈55 mg/dL), or 1.0 mmol/L (≈40 mg/dL) for *MI with a second event*, based on 2019 ESC/EAS guidelines. Proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab was associated with increased quality-adjusted life-years and costs vs. standard-of-care therapy. Incremental cost-effectiveness ratios (ICERs) were below SEK700 000 (∼€66 500), the generally accepted willingness-to-pay threshold in Sweden, for minimum LDL-C levels of 2.3 (*recent MI*), 1.7 (*MI with a risk factor*), and 1.7 mmol/L (*MI with a second event*). Sensitivity analyses demonstrated that base-case results were robust to changes in model parameters.

Conclusion Proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab added to MTD of statin and ezetimibe may be considered cost-effective at its list price for minimum LDL-C levels of 1.7–2.3 mmol/L, depending on risk profile, with ICERs below the accepted willingness-to-pay threshold in Sweden.

Keywords Cost-effectiveness • Evolocumab • Low-density lipoprotein cholesterol • Myocardial infarction • PCSK9 inhibitors • Statins

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Introduction

Standard-of-care (SoC) therapy for patients with elevated low-density lipoprotein cholesterol (LDL-C) levels includes a statin and ezetimibe.[1] In recent years, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) alirocumab and evolocumab have become available for the management of patients with atherosclerotic cardiovascular disease or familial hypercholesterolaemia with elevated LDL-C levels despite SoC treatment.[2] This analysis focuses on evolocumab, a fully human monoclonal antibody against PCSK9 that has been shown in clinical trials to reduce LDL-C levels by ~60%.[3–6] Furthermore, the FOURIER cardiovascular (CV) outcomes trial showed that the addition of evolocumab to an optimized regimen of lipid-lowering therapy (LLT; moderate- to high-intensity statin therapy, with or without ezetimibe) in patients with established atherosclerotic CV disease (ASCVD) resulted in a 20% reduction in the key secondary endpoint of major CV events [MACE; i.e. a composite of myocardial infarction (MI), ischaemic stroke (IS), or CV death].[7]

A 2018 consensus statement from the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommended PCSK9i for high-risk patients with persistently high LDL-C despite being treated with a maximum tolerated dose (MTD) of statin in combination with ezetimibe, or in patients with statin intolerance.[8] In Sweden, treatment with evolocumab is reimbursed in two patient populations: those with ASCVD and LDL-C ≥ 2.5 mmol/L while receiving MTD LLT; and those with heterozygous familial hypercholesterolaemia without ASCVD but with LDL-C ≥ 3.0 mmol/L while receiving MTD LLT.[9,10]

Updated guidelines published by the ESC/EAS in 2019 recommended the addition of a PCSK9i for secondary prevention patients who are at very high-CV risk and do not achieve their target LDL-C goal on a MTD of statin and ezetimibe (Class I, level A evidence).[1] Moreover, for patients who present with acute coronary syndrome (ACS) and whose LDL-C levels are not at goal—despite MTD of statin and ezetimibe—the addition of a PCSK9i should be considered early after the ACS event (during hospitalization for the event if possible; Class IIa, level C evidence).

For the first time, we assessed the cost-effectiveness of PCSK9 inhibition added to SoC maximally tolerated LLT (i.e. MTD of statin and ezetimibe) in Swedish patients with a history of MI, based on risk profiles adapted from the 2019 ESC/EAS guidelines. For comparison, we also evaluated similar risk profiles based on the 2016 ESC/ESA guidelines and the current reimbursement conditions in Sweden.

Methods

Model structure

A Markov cohort-state transition model was used for the analysis, as used in all previous cost-effectiveness models for PCSK9i identified in a recent systematic literature review.[11] The model was updated from previously published models[12–18] and based on findings from Swedish observational data on baseline CV event rates[18] and efficacy data from the FOURIER trial.[7] The model was developed using Microsoft Excel (2019) and comprised six main health states (Supplementary material online, *Figure S1*): non-fatal MI; non-fatal IS; post-MI; post-IS; CV death; and non-CV death. The states for non-fatal MI and IS covered the first 1-year period after the respective event, with the post-event health states covering subsequent years. Coronary revascularisation was included in the model as a procedure (i.e. a cost) rather than a health state. The model also included composite health states that were a combination of two event health states. These were created to retain memory of previous CV events in patients who experienced more than one event, and to better model the increased risk, lower health-related quality of life, and higher costs associated with a history of multiple CV events. Further details of the model are presented in the Supplementary material online and in previous publications.[12–18]

Patient profiles

For this assessment of the cost-effectiveness of PCSK9 inhibition with evolocumab added to SoC LLT (i.e. MTD of statin and ezetimibe) in Sweden, three risk profiles were considered: (i) patients with an MI in the previous year (*Recent MI*); (ii) patients with a history of MI with a risk factor, illustrated by patients with diabetes and target organ damage (*MI with a risk factor*); and (iii) patients with a second CV event within 2 years, illustrated by a population with a second MI (*MI with a second event*). For each of the three risk profiles, three baseline LDL-C levels (while receiving SoC LLT) were considered: (i) 2.5 mmol/L (≈100 mg/dL), the minimum LDL-C level specified in the current reimbursement recommendation for evolocumab in Sweden; (ii) 1.8 mmol/L (≈70 mg/dL), the minimum LDL-C level specified in the 2016 ESC/EAS guidelines[19]; and (iii) 1.4 mmol/L (≈55 mg/dL), or 1.0 mmol/L (≈40 mg/dL) for patients with a second event within 2 years, the minimum LDL-C level specified in the 2019 ESC/EAS guidelines.[1]

Baseline patient characteristics

Baseline patient characteristics and CV event rates were derived from a retrospective study that included a cohort of patients meeting the inclusion criteria of the FOURIER trial,[7] based on nationwide, linked Swedish population registry data.[18] A summary of the inclusion criteria is included in the Supplementary material online. Patients were 72, 69, and 72 years old for the *Recent MI, MI with a risk factor,* and *MI with a second event* risk profiles, respectively. Cardiovascular event rates were calculated by dividing the number of first MACE observed since the index date by the number of patient-years of follow-up until censoring and expressed as MACE per 100 patient-years.[18] Post-event rates of MACE per 100 patient-years at baseline were 6.2, 10.7, and 10.7 for the *Recent MI*, *MI with a risk factor*, and *MI with a second event* risk profiles, respectively. Throughout the simulation, baseline CV event rates were adjusted for age, LDL-C level, and CV event history using published standard methods.[20]

Treatment efficacy

In the FOURIER trial, the mean percentage reduction in LDL-C levels with evolocumab vs. placebo was 59% (intention-to-treat analysis)[7] and a constant reduction over a lifetime treatment duration, consistent with long-term follow-up data,[21] was assumed. Event-specific rate ratios used in our model were based on meta-analyses conducted by the Cholesterol Treatment Trialists' Collaboration (CTTC), which are shown in *Table 1*.[22] Cardiovascular event rates after treatment were calculated using the following formula:

$$r_{tx} = r_0 \times \mathrm{RR}^{\Delta\mathrm{LDL-C}}$$

where r_{tx}, rate after treatment; r_0, rate before treatment; RR, rate ratio per 1 mmol/L of LDL-C reduction; and ΔLDL-C, absolute LDL-C reduction.

The rate ratios per mmol/L of LDL-C reduction observed in the FOURIER trial (after accounting for study duration) were aligned with those from the CTTC meta-analysis. It has been well documented that it takes time for the benefit of LLT to become evident.[23–26] To account for

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Table 1 Rate ratios of CV events per mmol/L of LDL-C reduction, utility values, and costs for CV events and procedures

	RR per mmol/L (≈39 mg/dL) LDL-C reduction	Utility values		Direct costs, SEK[a]		Indirect costs, SEK[a]
		First year	Subsequent years	First year	Subsequent years	First year
Non-fatal MI	0.73	0.672	0.824	86 014	23 406	32 447
Non-fatal IS	0.77	0.327	0.524	86 158	18 557	63 519
CV death	0.86	0.000	–	12 994	–	–
Revascularization	0.75	–	–	77 138	–	–

Exchange rate: 1 SEK ≈ 0.095 EUR.
CV, cardiovascular; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RR, rate ratio; SEK, Swedish Kronor.
[a]Costs were inflated to 2019 SEK using the consumer price index for health set by Statistics Sweden.

this delayed treatment effect, prespecified landmark analyses were performed in FOURIER, in which patients who were alive and included in follow-up at the end of the first year formed the group at risk to estimate the effect of evolocumab on outcomes beyond the first year. These analyses showed that the magnitude of the relative risk reduction with regard to MACE grew over time, from 16% during the first year to 25% beyond the first year. Compared with the statin-based CTTC meta-analysis, treatment with evolocumab had very similar effects on the risk of MACE per 1 mmol/L of LDL-C reduction, as illustrated separately for years 0 to 1 and years 1 to 2.[7] Furthermore, the results from the FOURIER trial are consistent with the results of a recent Mendelian randomization study showing that variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (the target of statins) were associated with nearly identical effects on the risk of CV events per unit decrease of LDL-C.[27] In addition, a meta-analysis of 49 studies comparing the effects of statins and eight non-statin LLTs (including PCSK9i) demonstrated that lowering LDL-C level was associated with a consistent proportional improvement in CV outcomes.[28] Importantly, the reduction in risk of MACE observed in the FOURIER trial, when adjusted for duration of follow-up, is superimposable with that of statins based on the CTTC meta-analysis.[29] The treatment effect in our model was, therefore, based on the CTTC relationship between LDL-C reduction and reduced rates of CV events.

Utility values and costs

Cardiovascular disease health state utilities (*Table 1*) were derived from a time trade-off study based on a general population sample in the UK,[30] as used in a previous submission to the Swedish Dental Care and Medicines Benefit Agency (TLV) that led to the current recommendation of evolocumab in Sweden. Costs associated with medication and ASCVD were also considered following the guidelines of the TLV.[31] Annual medication costs based on list prices (before commercial discounts) were SEK48 759 for evolocumab 140 mg every 2 weeks, SEK206 for atorvastatin 20 or 40 mg/day and SEK454 for ezetimibe 10 mg (1 SEK = 0.095 EUR). An atorvastatin dose of 20 mg or 40 mg was used to reflect clinical practice in Sweden, where atorvastatin is the most prescribed statin in these intensity classifications. The assumptions used to generate medication costs are shown in Supplementary material online, *Table S1*. Therapy persistence for evolocumab, as observed in the FOURIER trial, was included in the model to adjust the cost of evolocumab over the modelled time horizon. Cardiovascular event and procedure costs were based on recent, retrospective studies from Swedish registries, including data from primary care, pharmaceutical prescriptions, inpatient care, and cause of death registries.[32,33]

In clinical trials of evolocumab in patients with hypercholesterolaemia, most reported adverse events were mild to moderate in severity, with infrequent reports of serious adverse events or adverse events leading to treatment discontinuation.[34] For this reason, no disutility, cost, or increased CV event risk for adverse events were modelled.

Economic analysis

In line with TLV requirements[31] and, as all patients in the present analysis were above retirement age, only costs associated with medication and ASCVD were considered. The analysis assumed a lifetime horizon, appropriate for evaluating the impact of an intervention on a chronic condition. The primary measure of health benefit was the quality-adjusted life-year (QALY), with the incremental cost-effectiveness ratio (ICER) calculated as the incremental cost per QALY gained. For transparency, the 10-year risk of MACE was also calculated using the model. In the base-case analyses, both costs and outcomes were discounted at an annual rate of 3.0%.

Sensitivity analyses

Univariate sensitivity analyses were conducted, in which one parameter was varied at a time relative to its base-case value. Efficacy parameters, baseline rates and their adjustment factors, health state utility values and costs were changed to the lower and upper bound of their 95% confidence interval. Probabilistic sensitivity analysis was also conducted to examine the combined effect of parameter uncertainty on the incremental cost per QALY gained. Appropriate probability distributions (Supplementary material online, *Table S2*) were assigned to model parameters based on their respective means and standard errors, and values for parameters were sampled by Monte-Carlo simulation with 1000 iterations in each loop. Cost-effectiveness acceptability curves were generated to illustrate the probability that evolocumab is cost-effective over a range of willingness-to-pay thresholds.

Results

Base-case analysis

PCSK9 inhibition with evolocumab added to SoC was associated with QALY gains and increased costs compared with SoC therapy (*Table 2*). At the list price of evolocumab, ICERs were below

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Table 2 Summary of cost-effectiveness results

	Recent MI		*MI with a risk factor*		*MI with a second event*	
	Evo + SoC	**SoC**	**Evo + SoC**	**SoC**	**Evo + SoC**	**SoC**
LDL-C of 2.5 mmol/L—minimum LDL-C level specified in the current reimbursement recommendation for evolocumab in Sweden						
10-year risk of first MACE (%)	37	44	48	54	49	54
Total cost (SEK)	663 562	283 814	590 650	246 137	566 430	252 830
Incremental cost (SEK)	379 748	—	344 513	—	313 601	—
Total QALY	7.06	6.45	6.31	5.56	5.67	4.98
QALY gained	0.61	—	0.75	—	0.68	—
ICER (SEK/QALY) [€/QALY]	623 367 [59 220]	—	460 241 [43 723]	—	458 380 [43 546]	—
LDL-C of 1.8 mmol/L—minimum LDL-C specified in the 2016 ESC/EAS guidelines						
10-year risk of first MACE (%)	36	41	47	51	47	52
Total cost (SEK)	679 934	289 919	611 491	254 233	585 841	260 509
Incremental cost (SEK)	390 014	—	357 258	—	325 332	—
Total QALY	7.27	6.86	6.56	6.03	5.91	5.42
QALY gained	0.42	—	0.54	—	0.49	—
ICER (SEK/QALY) [€/QALY]	933 748 [88 706]	—	667 456 [63 408]	—	668 512 [63 509]	—
LDL-C of 1.4 mmol/L for the *Recent MI* and *MI with a risk factor* profiles groups; LDL-C ≥1.0 mmol/L for the MI with a second event group—minimum LDL-C specified in the 2019 ESC/EAS guidelines						
10-year risk of first MACE (%)	35	39	46	50	46	48
Total cost (SEK)	688 958	293 178	623 366	258 841	607 770	269 061
Incremental cost (SEK)	395 781	—	364 525	—	338 709	—
Total QALY	7.39	7.08	6.71	6.30	6.18	5.92
QALY gained	0.31	—	0.41	—	0.26	—
ICER (SEK/QALY) [€/QALY]	1 257 578 [119 470]	—	882 265 [83 815]	—	1 283 860 [121 967]	—

Evo, evolocumab; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major cardiovascular event; MI, myocardial infarction; QALY, quality-adjusted life-year; SEK, Swedish Kronor; SoC, standard of care.

SEK700 000 (~€66 500) per QALY gained, the generally accepted willingness-to-pay threshold in Sweden,[35] for minimum LDL-C levels of 2.3 (*recent MI*), 1.7 (*MI with a risk factor*), and 1.7 mmol/L (*MI with a second event*). Cost-effectiveness results improved for patients with high LDL-C levels and high 10-year risk of MACE (*Figure 1*).

Sensitivity analyses

All univariate and probabilistic sensitivity analyses were conducted using the *Recent MI* risk profile (baseline LDL-C of 2.5 mmol/L) as an illustration. Univariate sensitivity analyses demonstrated that base-case results were generally robust to changes in model input parameters. Only three parameters affected the base-case ICER (SEK623 367) by more than 5% when varied: the rate ratio (per 1 mmol/L LDL-C reduction) for CV death[22] (SEK530 187 to SEK763 600); the rate ratio for IS[22] (SEK584 109 to SEK676 572); and the hazard ratio for patients with a history of both MI and IS[20] (SEK591 596 to SEK660 870).

For the probabilistic sensitivity analysis, *Figure 2A* shows the cost-effectiveness acceptability curves for PCSK9 inhibition with evolocumab added to SoC therapy compared with background LLT. The individual iterations plotted on the cost-effectiveness plane (*Figure 2B*) indicate that all incremental cost-QALY gained pairs are in the north-east quadrant, and thus adding evolocumab to MTD of statin with ezetimibe in the *Recent MI* risk profile (baseline LDL-C of 2.5 mmol/L) is both costlier and more effective than treatment without evolocumab. Overall, the probability that PCSK9 inhibition with evolocumab at its list price added to MTD of statin with ezetimibe is cost-effective at the generally accepted willingness-to-pay threshold of SEK700 000 (~€66 500) per QALY gained was 82.5%. At this willingness-to-pay threshold and price of evolocumab, this probability becomes 0% for the *Recent MI* risk profile with baseline LDL-C of 1.8 mmol/L (Supplementary material online, *Figure S2*).

Discussion

To our knowledge, our study is the first cost-effectiveness analysis of PCSK9 inhibition in the context of the 2019 ESC/EAS dyslipidaemia guidelines.[1] In addition, we assessed the cost-

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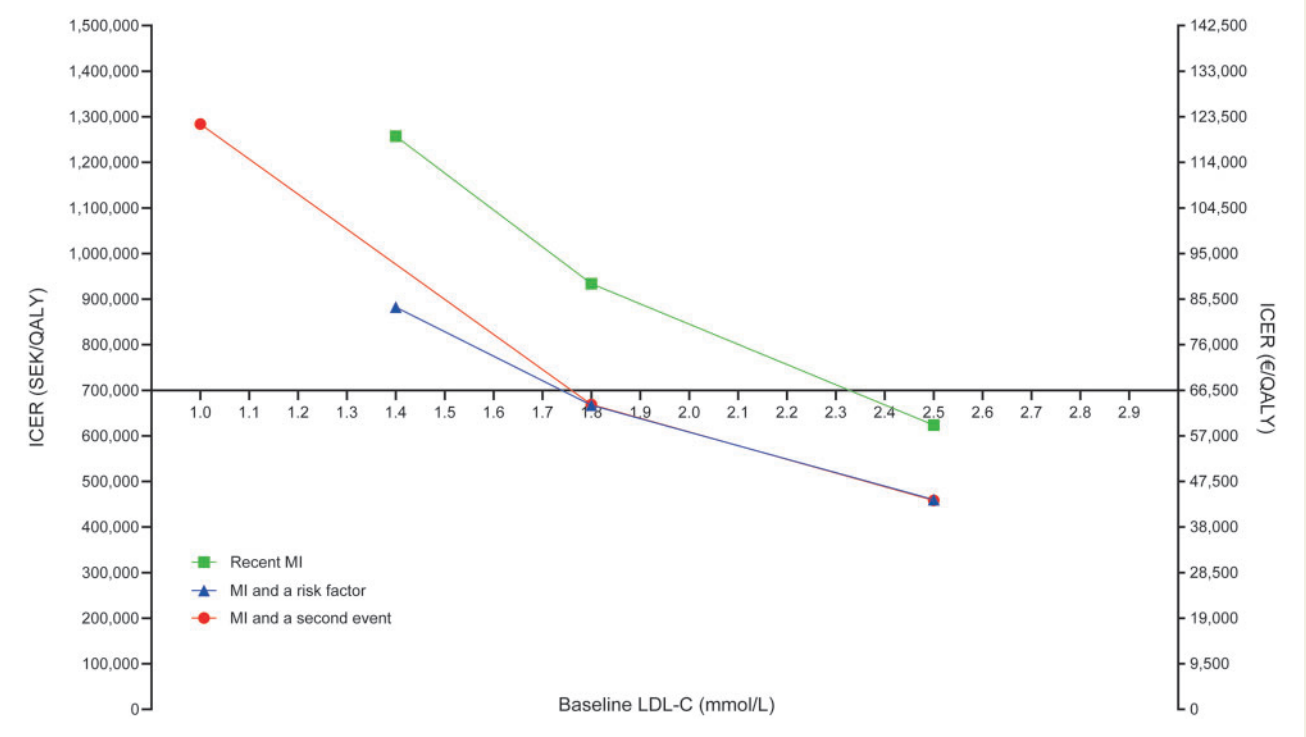

Figure 1 Incremental cost-effectiveness ratios as a function of 10-year risk while receiving standard-of-care lipid-lowering therapy. *≥1.0 mmol/L for the *MI with a second event* risk profile. ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major cardiovascular events; MI, myocardial infarction; SEK, Swedish Kronor; SoC, standard of care.

effectiveness of PCSK9 inhibition added to SoC LLT in Swedish patients with a history of MI based on selected risk profiles adapted from the 2016 ESC/EAS dyslipidaemia guidelines[19] and the current reimbursement conditions in Sweden. The addition of evolocumab to SoC was associated with QALY gains and increased costs compared with SoC LLT. Moreover, ICERs were below the generally accepted willingness-to-pay threshold in Sweden for minimum LDL-C levels of 2.3 (*recent MI*), 1.7 (*MI with a risk factor*), and 1.7 mmol/L (*MI with a second event*).

Consistent with the 2019 ESC/EAS guidelines, the cost-effectiveness of PCSK9 inhibition was improved in selected patients with high LDL-C levels and a history of MI with increased risk.[1] Our results were also consistent with a recent cost-effectiveness analysis in the US context.[17] Considering a list price similar to the one used in our analysis, Fonarow *et al.*[17] showed that PCSK9 inhibition with evolocumab may be cost-effective in very high-risk patients with ASCVD as defined by the 2018 guidelines from the American College of Cardiology and American Heart Association.[36] In Europe, Villa *et al.*[14] had previously found that PCSK9 inhibition with evolocumab may be considered cost-effective in patients with ASCVD eligible for reimbursement in Spain. Other previously published European cost-effectiveness analyses in Germany,[37] the Netherlands,[38] and Norway[39] considered higher PCSK9i base-case prices that are no longer relevant.

The results of our analysis can be extended to other lipid-lowering therapies with similar efficacy, safety, and price, and these data can be used to inform future European guidelines, which until now have mostly relied on US cost-effectiveness data.[1,20] Our results should, however, be interpreted in the context of the data and modelling assumptions used. For example, the predictions of the model were based on extrapolation beyond the duration of the FOURIER trial. Furthermore, if levels of compliance with, and adherence to, evolocumab therapy and the components of SoC differed from those modelled based on the FOURIER trial, outcomes, and costs might be affected. It should also be noted that the analyses were conducted using the list price of evolocumab in Sweden. In practice, however, reimbursement agreements, including those in Sweden, usually involve payment of a confidential net price that is lower than the list price. Using such a net price in the model would have further improved the cost-effectiveness of treatment. Finally, it is important to note that cost-effectiveness results obtained in one country cannot necessarily be extrapolated to other countries.[1] In the future, it will be informative to examine the cost-effectiveness of PCSK9 inhibition in other healthcare systems, and in other patient populations with similar, or even higher, risk profiles than those with a history of MI included in the current analysis.

In conclusion, our results indicate that the addition of PCSK9 inhibition with evolocumab to SoC treatment may be considered cost-effective at its list price for minimum LDL-C levels ranging from 1.7 mmol/L to 2.3 mmol/L, depending on the risk profile. The results may also be considered to be valid for other patient populations with similar or higher CV risk or LDL-C levels.

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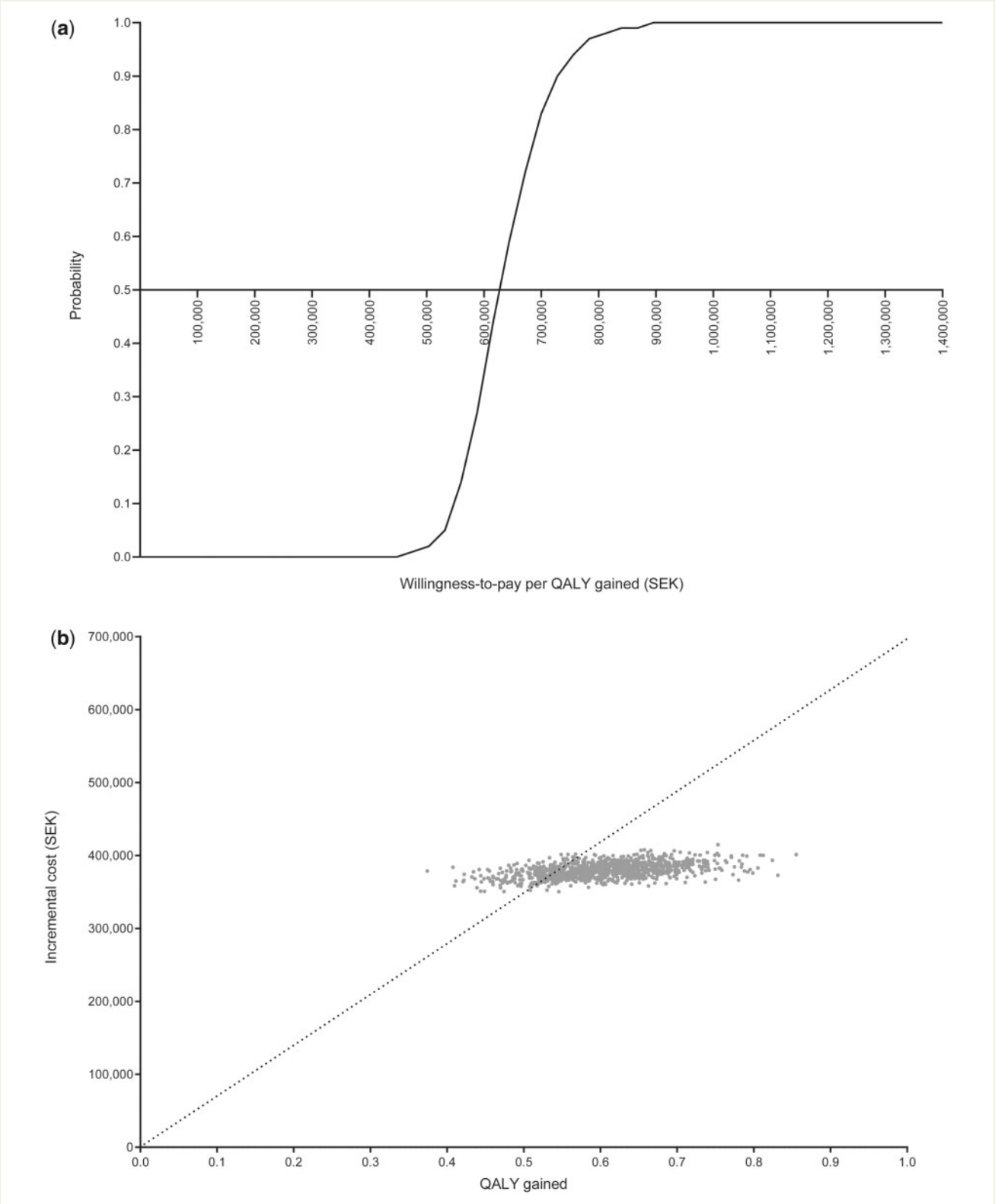

Figure 2 Probabilistic sensitivity analysis for the *Recent MI* risk profile (baseline low-density lipoprotein cholesterol of 2.5 mmol/L): (*A*) cost-effectiveness acceptability curves; (*B*) cost-effectiveness plane. The cost-effectiveness acceptability curves represent the probability that the addition of evolocumab is cost-effective over a range of willingness-to-pay thresholds. The cost-effectiveness plane represents each individual iteration (incremental cost–QALY gained pairs) from the probabilistic sensitivity analysis. LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; QALY, quality-adjusted life-year; SEK, Swedish Kronor; SoC, standard-of-care.

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Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

Funding

This work was supported by Amgen.

Conflict of interest: U.L. has received lecture and advisory fees from Amgen, Sanofi, Medicines Company and Novartis. P.L. received grants from Amgen, BMS, EFPIA Merck, Novo Nordisk, Pfizer, and Sanofi. E.H. acted as expert committee member for and received lecture fees and institutional research grants from Sanofi and Amgen, and lecture fees from AstraZeneca, Bayer, and Novo Nordisk. B.v.H. consulted for Amgen. G.V., P.P.-R., J.A., M.E.S., and M.S. were employees and stockholders of Amgen. G.C.F. consulted for Abbott, Amgen, Bayer, Janssen, and Novartis.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Acknowledgements

Medical writing assistance was provided by Dan Booth PhD (Bioscript Medical Ltd, Macclesfield, UK) and funded by Amgen.

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