ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness, Burden of Disease and Budget Impact of Inclisiran: Dynamic Cohort Modelling of a Real-World Population with Cardiovascular Disease

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Abstract

Objective We aimed to estimate the cost-effectiveness, burden of disease and budget impact of inclisiran added to standard-of-care lipid-lowering therapy in the real-world secondary cardiovascular prevention population in Switzerland.

Methods An open-cohort Markov model captured event risks by sex, age and low-density lipoprotein cholesterol based on epidemiological and real-world data. Low-density lipoprotein cholesterol reduction with add-on inclisiran was based on trial results and translated to meta-analysis-based relative risks of cardiovascular events. Unit costs for 2018 were based on publicly available sources, adopting a Swiss healthcare system perspective. Price assumptions of Swiss francs (CHF) 500 and CHF 3,000 per dose of inclisiran were evaluated, combined with uptake assumptions for burden of disease and budget impact. The assessment of cost-effectiveness used a discount rate of 3% per year. We performed deterministic and probabilistic sensitivity analyses, and extensive scenario analyses.

Results Patients treated with inclisiran gained a 0.291 qualityadjusted life-year at an incremental cost per QALY gained of CHF 21,107/228,040 (life-long time horizon, discount rate 3%) under the lower/higher price. Inclisiran prevented 1025 cardiovascular deaths, 3425 acute coronary syndrome episodes, and 1961 strokes in 48,823 patients ever treated during 10 years; the 5-year budget impact was CHF 49.3/573.4 million under the lower/higher price. Estimates were sensitive to calibration targets and treatment eligibility; burden of disease/budget impact results also to uptake. Limitations included uncertainties about model assumptions and the size and characteristics of the population modelled.

Conclusions Inclisiran may be cost-effective at a willingness to pay of CHF 30,000 if priced at CHF 500; a threshold upwards of CHF 250,000 will be required if priced at CHF 3000. Inclisiran could enable important reductions in cardiovascular burden particularly under broader eligibility with a budget impact range from moderate to high depending on price.

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1 Introduction

Prevention and management of cardiovascular disease (CVD) are a key public health priority in Switzerland. In 2017 alone, there were over 21,000 CVD-related deaths (31% of all deaths) [1] and nearly 50,000 CVD-related hospitalisations of which over 22,000 were due to acute coronary syndrome (ACS) and about 25,000 due to stroke [2]. These conditions jointly accounted for nearly 16% of the total healthcare expenditures [3]. Clinical guidelines on CVD concentrate strongly on risk factors; lowering low-density lipoprotein cholesterol (LDL-C) with statins or statins in combination with ezetimibe are among the primary strategies [4–6]. While these therapies are effective [7, 8], multiple factors contribute to nearly 30% of patients stopping statins within the first year [9–13]. Among the very high and high cardiovascular risk patients, over 80% fail to achieve the guideline-recommended LDL-C target [14].

Key Points for Decision Makers

Conventional lipid-lowering therapy may fail to reduce low-density lipoprotein cholesterol levels to target, leaving patients at risk of cardiovascular morbidity despite maximally tolerated dosing.

We developed a dynamic open-cohort model structure that enables, in one coherent framework, estimation of cost-effectiveness, burden of disease and budget impact under real-world assumptions.

Inclisiran added to standard-of-care lipid-lowering therapy in secondary cardiovascular prevention patients may be cost-effective from the perspective of the Swiss healthcare system at a willingness-to-pay threshold of Swiss francs (CHF) 30,000 if priced at CHF 500 per dose; a willingness to pay upwards of CHF 250,000 would be required if inclisiran was priced at CHF 3000.

Inclisiran could enable important reductions in cardiovascular burden at the population level, particularly under broader eligibility with a budget impact range from modest to high, depending on price.

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) entered the arena of lipid-lowering drugs several years ago [15]. The PCSK9i available on the market, evolocumab and alirocumab, are human monoclonal antibodies. Their high clinical efficacy and favourable safety profile come at a high cost compared to statins that are largely available as generics [15–17]. Under the current reimbursement of PCSK9i in Switzerland, their use is restricted to the most at-risk patients and requires initiation by a specialist and a prior cost authorisation [18]. Reimbursement eligibility for secondary prevention requires an LDL-C above 2.6 mmol/L, leaving many patients without therapeutic options.

Inclisiran is a first-in-class, small-interfering ribonucleic acid molecule inhibiting PCSK9 protein synthesis in liver cells, administered as a subcutaneous injection. It received marketing approval in the European Union [19] and Switzerland [20] based on the ORION clinical trials that showed strong LDL-C lowering and provided a good, albeit not final, understanding of the efficacy and safety of the drug [21]. The need for additional LDL-C lowering not met in many patients raises the question of whether, compared to current PCSK9i policies, broader access is warranted for inclisiran. In England, the National Institute for Health and Care Excellence (NICE) has recently recommended the use of inclisiran in patients with prior CVD events and LDL-C ≥2.6 mmol/L, implying such a broadening of access [22]. Related decision making requires evidence on the likely cost-effectiveness,

impact on burden of disease and budget impact. The classical clinical trial-based approach to the cost-effectiveness analysis may not fully reflect the use of the new therapy in the real world. Heterogeneity in patient, clinical management and health system characteristics limits the transferability of trial evidence between settings and from trials to policy [23]. Drawing on a primary care database, we characterise the real-world secondary cardiovascular prevention population in Switzerland and estimate the likely impact of inclisiran in these patients using a newly developed decision-analytic model.

2 Methods

We developed a dynamic open-cohort Markov model [24] suitable to consistently perform cost-effectiveness, burden of disease and budget impact analyses for real-world populations (Electronic Supplementary Material [ESM]). Outcomes included non-fatal and fatal cardiovascular events, death from other causes, life-years, quality-adjusted life-years (QALYs), costs in total and by category, and incremental cost-effectiveness ratios (ICERs). Costs were assessed from the Swiss statutory health insurance perspective. In the base-case and uncertainty analyses, lifelong, 10-year, and 5-year time horizons were adopted for cost-effectiveness, burden of disease, and budget impact, respectively. In the assessment of cost-effectiveness, costs and effects were discounted by 3%.

We defined the information needs for the model and evaluated potentially relevant Swiss and international data sources, determined based on the prior knowledge and experience of the research team and considering sources accepted by NICE in relevant technology appraisals [22, 25]. Model inputs characterising population size and numbers of CVD events in Switzerland were drawn from the Global Burden of Disease project [26], World Health Organization Mortality Database [27], and Swiss national statistics [2, 28] (see Tables 2 and 3 of the ESM). Patient characteristics came from a database of routine medical data by Swiss primary care physicians (Family medicine research using Electronic medical records (FIRE)) [29]. Transition probabilities from the British Clinical Practice Research Datalink [22] were adjusted to reflect Swiss event occurrence and LDL-C levels. The LDL-C changes achieved with inclisiran were based on the ORION-10 trial [31] and the relationship between LDL-C and event risks on a published meta-analysis [8]. Health-state utilities were based on published UK and Swiss data [32, 33] and unit costs on published Swiss studies and national sources [18, 34–39]. With the future public price of inclisiran in Switzerland yet unknown, inclisiran cost assumptions were based on two hypothetical price points:

reflecting, at the lower end, the yearly treatment cost of ezetimibe (Ezetrol®) resulting from the public list price at the launch, Swiss Francs (CHF) 971 [40], and at the upper end, the yearly cost resulting from the public list price of the PCSK9i monoclonal antibodies currently marketed in Switzerland, CHF 6067 [18]. Market uptake assumptions were provided by the manufacturer of inclisiran. Further details are provided below; base-case parameter values and distributional assumptions are presented in Table 1.

2.1 Population and Medical Strategies

The primary population of interest was defined as Swiss patients aged 40 years or above with a prior ischaemic cardiac or cerebrovascular event (secondary prevention population). In scenario analyses, we also approximated an alternative wider population of interest including very high-risk patients without a prior event, as defined by current European guidelines (very high-risk population) [6]. In the absence of data on LDL-C levels of untreated Swiss patients, the inclisiran strategy assumed eligibility for inclisiran treatment (284 mg/1.5 mL at days 0 and 90, then every half year) as an add-on for patients with LDL-C ≥1.8 mmol/L under any standard-of-care lipid-lowering treatment (SOC LLT). Alternative SOC LLT requirements and thresholds of ≥1.4 mmol/L (including all patients not reaching the current European treatment target [6]) and ≥2.6 mmol/L (reflecting the current Swiss reimbursement limitation for PCSK9i [18]) were considered in scenario analyses. The comparator strategy was current SOC LLT as observed in FIRE [29] (see Results and the ESM).

2.2 Model Structure

Inspired by Nghiem et al. [41], the model is a Markov cohort model with a 1-year cycle length that distinguishes 88 sub-cohorts characterised by age, sex and LDL-C group (<1.4 mmol/L, ≥1.4 to <1.8 mmol/L, ≥1.8 to <2.6 mmol/L, ≥2.6 mmol/L). Each sub-cohort is assigned its average age at entry, average LDL-C level and distribution of SOC LLT. Within each sub-cohort and as a function of these characteristics, patients transition through a series of CVD-related health states (see Fig. 1). The distribution of patients between health states does not reflect fractions of the sub-cohort but absolute patient numbers. The sub-cohorts are combined to the total modelled population using summation nodes.

The model distinguishes prevalent patients forming part of the population of interest at model start (the treatment uptake of these patients can be spread over several years) and incident patients. Incident patients can enter the model in each cycle, in appropriate health states, with tunnel states

allowing correct tracking of patient age. These functionalities are used for burden of disease and budget impact analyses, i.e. in these analyses, new-incident patients enter the model in each cycle. In contrast, cost-effectiveness analyses only consider prevalent patients and cycle 1 incident patients and assume full treatment uptake and immediate treatment start for eligible patients. To achieve a manageable reduction in real-world complexity, additional assumptions were required (ESM). Technical details on the implementation of the model in TreeAge software [42] are also provided in the ESM.

2.3 Epidemiological Data

The size of the prevalent secondary prevention population was approximated by multiplying the prevalence of ischaemic heart disease and ischaemic stroke by age and sex from the Global Burden of Disease project [26] with population counts by the Swiss Federal Statistical Office [28]. The size of the incident population by age and sex, defined here as patients who survived a first-time ischaemic heart disease or ischaemic stroke event in the reference year, was estimated from the Swiss statistics of inpatient episodes (MedStat) [2]. The size of the incident population was projected forward for 5 years and 10 years using the average annual growth rate of the incident secondary prevention population calculated from the Global Burden of Disease project [26].

The results of these calculations together with the LDL-C distribution from FIRE [14] determined the person numbers entering the sub-cohorts of the model. FIRE also provided the average LDL-C within each sex-age-LDL-C sub-cohort, the proportion receiving any SOC LLT, and the types of drugs under SOC LLT. For further details on the data sources, case definitions and secondary prevention population characteristics, see the ESM.

2.4 Event Risks and Clinical Effectiveness

Transition probabilities in the comparator strategy were based on values generated by the manufacturer of inclisiran using data from the Clinical Practice Research Datalink [22]. We adjusted these to the LDL-C levels of each of the 88 sub-cohorts using probability-rate-probability conversions and assuming a log-linear relationship between LDL-C change and event rates [22, 25]. Rate ratios per 1-mmol/L LDL-C change were based on the 2019 meta-analysis by the Cholesterol Treatment Trialists Collaboration [8]. Additional factors based on MedStat [2] were applied to ensure a plausible distribution of event risks across age groups, separately by sex, without affecting the overall event occurrence in the modelled population. The model was further calibrated to the expected event numbers in the Swiss secondary prevention population according to MedStat [2] for non-fatal events

Table 1 Base-case model inputs

Input parameter(s)	Base-case value (95% CI)	Variation in DSA	Distribution type in PSA (mean, SE)	Sources and approaches
Epidemiological parameters				
Number of prevalent and incident cases at model start	Tables; see ESM, Table 4	Not varied[a]		[2, 26, 28]
Average annual growth rate for incident cohort by sub-cohort	Tables; see ESM, Table 4	Not varied[a]		[26]
Sub-cohort characteristics	Tables; see ESM, Table 5	Not varied[a]		[29]
Health states[b] at model entry		Not varied[a]		[26] and assumptions
Prevalent patients				
Revasc post	0			
ACS 0–1	0			
ACS post	0.73			
Stroke 0–1	0			
Stroke post	0.27			
Incident patients				
Revasc post	0			
ACS 0–1	0.57			
ACS post	0			
Stroke 0–1	0.43			
Stroke post	0			
Factors to ensure plausible age distribution of event risks	Table; see ESM, Table 14	Varied in scenario analyses (alternative approach to estimation, see ESM, Tables 23–24)		[2, 49]
Calibration targets	Tables; see ESM	Varied in scenario analyses by ±30%, see ESM, Tables 23–24		[2, 28, 49, 50]
Non-CV mortality	Tables; see ESM, Table 17	Not varied[a]		[27]

Table 1 (continued)

Input parameter(s)	Base-case value (95% CI)	Variation in DSA	Distribution type in PSA (mean, SE)	Sources and approaches
Transition probabilities				
SOC LLT strategy	Table; see ESM, Table 11	Not varied, as uncertainty covered by variation of calibration targets; see section on uncertainty analyses		[22] adjusted to diabetes prevalence, sex, age, LDL-C distribution in Swiss secondary prevention patients
Clinical effectiveness				
Event rate ratio per 1 mmol/L LDL-C change		CI based,	Lognormal	[8]
Revasc	0.75	0.72–0.78	−0.288; 0.017	
UA	0.73	0.70–0.76	−0.315; 0.021	
MI	0.73	0.70–0.76	−0.315; 0.021	
Stroke	0.79	0.77–0.81	−0.236; 0.013	
CVD death	0.84	0.80–0.88	−0.174; 0.024	
LDL-C reduction achieved with inclisiran	52%	CI based, 49–56%	Normal 52%; 2%	[31], observed at day 510
Utilities				
Utility multipliers for events[b]		±30%	1-base case value multiplied with normal (0; 0.153)	[33]
ACS 0–1	0.77			
ACS post	0.92			
Stroke 0–1	0.78			
Stroke post	0.82			
ACS 0–1 stroke post	0.77			
ACS post stroke 0–1	0.78			
ACS post stroke post	0.88			

Table 1 (continued)

Input parameter(s)	Base-case value (95% CI)	Variation in DSA	Distribution type in PSA (mean, SE)	Sources and approaches
Age-specific and sex-specific population utility	Tables; see ESM	±30%	1-base case value multiplied with normal (0; 0.153)	[32]
Correction factor to adjust general population utility to utility of population without CVD	1.06	Varied in scenario analyses (correction factor removed), see ESM, Tables 23–24		[33]
Unit costs				
Cardiovascular events		± 30%	Base-case value multiplied with normal (1; 0.153)	[34, 35][b,c]
MI, fatal	9067			
MI, non-fatal, first year	35,275			
MI, non-fatal, subsequent years	2910			
UA, fatal event	3873			
UA, non-fatal, first year	23,732			
UA, non-fatal, subsequent years	2490			
Stroke, fatal	11,613			
Stroke, non-fatal acute, first year	36,251			
Stroke non-fatal, subsequent years	12,899			
Revasc	17,358			[36]; Weighted average of PCI and CABG surgery[c]
Background LLT		± 30%	Base-case value multiplied with normal (1; 0.153)	[37]; for statins, costs represent an average over treatments of different intensity
Statin	240			
Ezetimibe	453			

Table 1 (continued)

Input parameter(s)	Base-case value (95% CI)	Variation in DSA	Distribution type in PSA (mean, SE)	Sources and approaches
Inclisiran therapy and administration				Administered at day 0, day 90, then every half year
Administration	23	± 30%	Base-case value multiplied with normal (1; 0.153)	[38, 39]
Inclisiran price per dose low	500	Not varied		Assumption based on ezetimibe [40]
Inclisiran price per dose high	3000	Not varied		Assumption based on PCSK9i antibodies [18]
Uptake assumptions				
Uptake	Table; see ESM, Table 19	Varied in scenario analyses of cost-effectiveness and burden of disease results, see ESM, Tables 23–25		Assumptions

ACS acute coronary syndrome, *CABG* coronary artery bypass surgery, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *DSA* deterministic sensitivity analysis, *LLT* lipid-lowering therapy, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *PCSK9i* Proprotein convertase subtilisin/kexin type 9 inhibitors, *PSA* probabilistic sensitivity analysis, *Revasc* revascularization, *SE* standard error, *UA* unstable angina

[a]Estimated characteristics of the Swiss secondary prevention population (apart from the key parameter values representing absolute event numbers in the start year of the model) were not varied

[b]Refer to Fig. 1 for event descriptions

[c]Adapted to 2018 using development of healthcare expenditures per capital[43]

and the World Health Organization Mortality database for deaths [27] (see ESM for details and examples).

The impact of inclisiran was modelled based on its impact on LDL-C observed in the ORION-10 trial [31]. ORION-10 was preferred on grounds of similarity of the trial population with our secondary prevention population. Transition probabilities were adjusted based on the induced absolute LDL-C difference, by applying the same log-linear relationship as above. Implied were the assumptions that the relationship between LDL-C reduction and CVD event occurrence reported by Cholesterol Treatment Trialists holds for inclisiran, and that the effectiveness of inclisiran does not change over time. For further details, see the ESM.

2.5 Resource Use and Unit Costs

We considered the direct costs of non-fatal unstable angina/myocardial infarction and stroke events, fatal CVD events, revascularisation, background treatment with statins and ezetimibe, and costs of inclisiran including drug administration, as detailed in Table 1. Literature-based event cost-estimates covered drugs, diagnosis, in-patient and outpatient treatments, maintenance and follow-up care including for long-term sequelae. They were time adjusted using the increase in Swiss healthcare expenditure per capita [43]. The two hypothetical assumptions on the price per dose of inclisiran were CHF 500 (lower price, ezetimibe based) and CHF 3000 (higher price, PCSK9i monoclonal antibody based), to reflect twice-yearly maintenance dosing. All costs were expressed in 2018 CHF, the latest year for which consistent unit costs could be generated.

2.6 Utilities

Health-state utility values for the Swiss population without a prior CVD event were estimated based on age-specific and sex-specific Swiss utility values for the general population [32], which were separately calculated for each sub-cohort and updated in each model cycle. These were adjusted with a scaling factor from a UK study by Ara and Brazier [33] (ESM). Utility multipliers for the initial health states and subsequent events were also taken from Ara and Brazier [33]. As adverse events related to inclisiran were well balanced between the study arms [31], these were not considered in the analysis. Adverse events associated with SOC LLT were similarly excluded.

2.7 Inclisiran Uptake

While the cost-effectiveness analyses assumed a full uptake of inclisiran in eligible patients, the burden of disease and budget impact analyses required assumptions on uptake in the real world. As a starting point, the manufacturer of inclisiran provided an exemplary assumption based on its most recent launch in the area of CVD: the worldwide average uptake of sacubitril/valsartan (Entresto®) ranged from about 10% to 36% during the first 5 years after the launch. Because of a different formulation and because only a fraction of secondary prevention patients would qualify for inclisiran treatment, we selected assumptions such that about 10% of this population would ever be treated during 5-year and 10-year model time horizons. For the prevalent patient group, this led to uptake assumptions of 13% and 22% in the LDL-C ≥1.8 mmol/L to <2.6 mmol/L and LDL-C ≥2.6 mmol/L groups, respectively, equally spread over 5 years. The uptake in incident patients was assumed to increase over the first 5 years to 24% and 30% in the aforementioned LDL-C groups. Uptake after 5 years was assumed to remain stable; see ESM for details.

2.8 Validation

Model validation addressed face validation, internal validation, cross-validation, and external validation [44]. The validation steps showed satisfactory results. As a single exception, the model may moderately overestimate life expectancy. This was identified to be a consequence of the necessary calibration to plausible fatal CVD event numbers in the Swiss secondary prevention population, which has conservative implications for the cost-effectiveness of inclisiran.

2.9 Uncertainty Analyses

Uncertainty analyses in the cost-effectiveness part included univariate deterministic and multivariate probabilistic sensitivity analyses with 1000 iterations. Ranges of variation in the univariate deterministic sensitivity analysis were based on upper and lower 95% confidence limits. Where not available, parameter values (e.g. those representing unit costs) were varied by ± 30%. In the case of utilities and utility multipliers, the difference from 1 was varied by ± 30%. The probabilistic sensitivity analysis used distributions reflecting these ranges of variation (lognormal for rate ratios and normal for all other parameters to ensure consistency with results of the deterministic analysis). Scenario analyses assessed the impact of varying assumptions on SOC LLT and LDL-C requirements for inclisiran treatment eligibility, inclisiran uptake and effect, cardiovascular event costs and discount rate. We also tested alternative approaches to the consideration of incident patients, including an open-cohort approach as used for the burden of disease and budget impact parts. The uncertainty in the occurrence of clinical events in the comparator strategy was solely addressed in
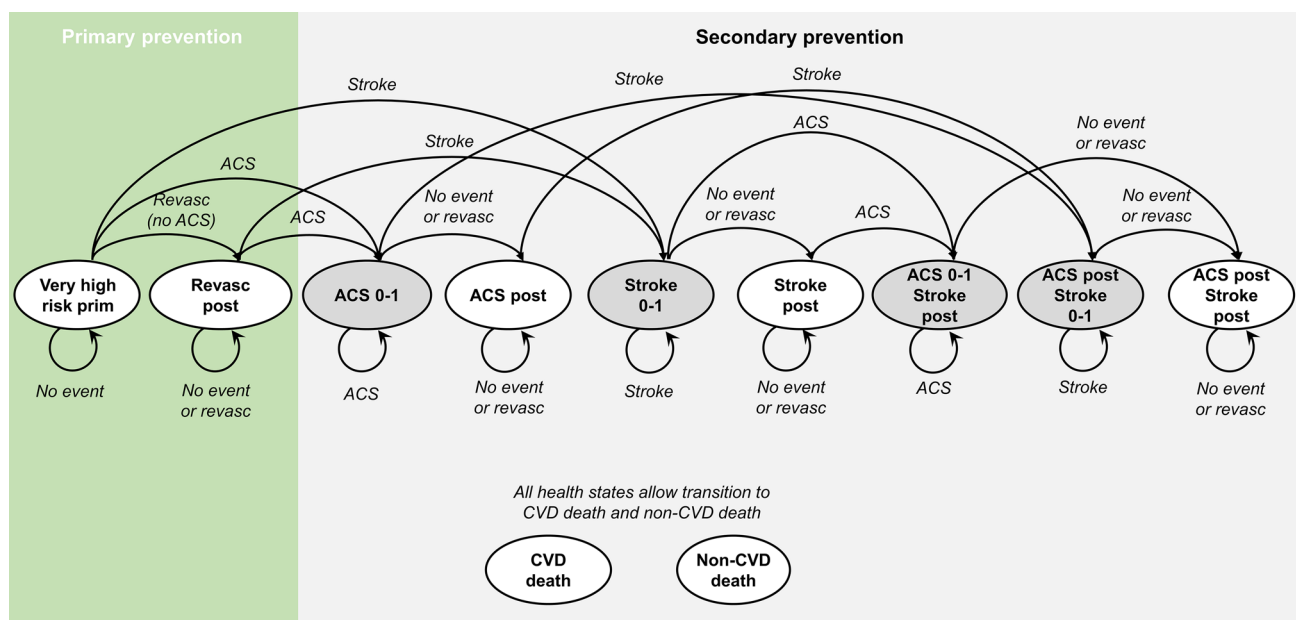
Fig. 1 Markov health state structure. Health states were defined as follows: "Very high risk prim" was used for very high risk patients who have not yet had a prior ischaemic cardiac or cerebrovascular event; "Revasc post" was used for very high risk patients who have not yet had a prior ischaemic cardiac or cerebrovascular event but had already undergone a cardiac revascularization (revasc) procedure that was not an immediate short-term treatment of an acute coronary syndrome (ACS) episode; "ACS 0–1" represented the first year after an ACS (i.e. unstable angina [UA] or myocardial infarction [MI]) event; "ACS post" represented subsequent years after an ACS (i.e. UA or MI) event; "Stroke 0–1" represented the first year after an acute cerebrovascular (i.e. ischaemic stroke) event; "Stroke post" represented subsequent years after an acute cerebrovascular (i.e. ischaemic stroke) event; "Stroke post and ACS 0–1" represented the first year after an ACS (i.e. UA or MI) event in patients who have already had at least one acute cerebrovascular (i.e. ischaemic stroke) event; "Stroke 0–1 and ACS post" represented the first year after an acute cerebrovascular (i.e. ischaemic stroke) event in patients who have already had at least one ACS (i.e. UA or MI) event; "Stroke post and ACS post" represented subsequent years (i.e. not the first year) after the last ACS or acute cerebrovascular event, in patients who have already had both types of events. "CVD death" and "Non-CVD death" are absorbing states entered at patient death due to either cardiovascular disease (CVD) or other causes. Health states "Very high risk prim" and "Revasc post" are not used for the modelling of the secondary prevention population, only for the very high risk population modelled in scenario analyses. "Revasc post" implies the patient has had a cardiac revascularization procedure that was not for the immediate short-term treatment of an ACS event. Further details on health state and event definitions are provided in the ESM

scenario analyses, given multiple transition probabilities and a strong influence of calibration. Other estimated characteristics of the Swiss secondary prevention population were not varied. Additional scenario analyses were used to approximate results for the very high-risk population. For the burden of disease and budget impact analyses, a suitable subset of the scenario analyses performed in the cost-effectiveness part was implemented. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [45].

3 Results

The size of the Swiss secondary prevention population was estimated at 302,738 patients (as of 2018). The number of incident patients was 17,024 and increased slightly in subsequent years (ESM). The average age of secondary prevention patients was 71 years, over 60% of these patients were male. Based on FIRE, the prevalence of diabetes mellitus was 27%

[29]. The average LDL-C under SOC LLT was 2.3 mmol/L. Patients with LDL-C ≥1.8 mmol/L accounted for about 80% of the prevalent and incident cohorts (239,214 and 13,442 patients, respectively). In this sub-population, LDL-C averaged 2.7 mmol/L. With respect to background SOC LLT, 69% of patients were taking statins, of which more than half (63%) received high-intensity statins, and 15% were taking ezetimibe. For details, see the ESM.

3.1 Cost-Effectiveness

Adding inclisiran to SOC LLT in eligible patients increased per-person life expectancy in the secondary prevention population by 0.199 years and yielded an additional 0.159 QALYs (based on gains of 0.364 years and 0.291 QALYs in those actually treated with inclisiran). The incremental cost was CHF 3354/36,233 per person under the lower/higher price assumption respectively (Table 2). The resulting

ICERs were CHF 21,107/228,040 per QALY gained under the lower/higher price.

In the univariate sensitivity analysis (Fig. 2), parameters related to costs of clinical events led to proportionally greater changes in ICER under the lower inclisiran price assumption, whereas parameters related to utilities were more impactful under the higher price. The impacts of inclisiran on LDL-C and background utility were in the top five most impactful parameters. Across inputs and ranges assessed, ICERs remained bounded within a relatively narrow range around the main result of ±CHF 5000 under the lower price and ±CHF 20,000 under the higher price.

In scenario analyses (Tables 23–24 of the ESM), ICERs were most sensitive to calibration targets for non-fatal events (scenarios 15–18). Particularly large changes were observed when calibration targets for non-fatal and fatal events were varied jointly (scenario 18). Scenarios exploring alternative eligibility criteria, uptake, and effectiveness of inclisiran resulted in at most a ±20% change over the base case (scenarios 1–5). Alternative assumptions on the target population (i.e. secondary prevention population [base case] vs very high-risk population), baseline utilities, and age-adjustment of transition probabilities had a similar impact (scenarios 9, 10, 19). Other features related to the real-world use of inclisiran including persistence and maximum age at treatment start (scenarios 6–8) had only a limited impact on the predicted cost-effectiveness. Alternative approaches to the consideration of incident patients were not influential (scenarios 21 and 22).

In the probabilistic sensitivity analysis, the 2.5th and 97.5th ICER percentiles were CHF 14,557 and CHF 28,497 per QALY gained under the lower price assumption and CHF 195,042 and CHF 278,316 under the higher price assumption. Figure 3 presents a cost-effectiveness scatterplot and cost-effectiveness acceptability curves. The probability inclisiran is cost-effective if priced at CHF 500 per dose was estimated at 99% under a willingness-to-pay (WTP) threshold of CHF 30,000 per QALY gained. If priced at CHF 3000, the probability of cost-effectiveness was <1% up to a WTP of CHF 200,000, and 97% at a WTP of CHF 250,000 per QALY gained.

3.2 Burden of Disease

Under the base-case eligibility and uptake assumptions, about 10% of the secondary prevention population would be treated with inclisiran over 10 years (Table 3). The greatest relative reduction in the number of events due to inclisiran was estimated for revascularisations and non-fatal ACS (about 4%), followed by stroke and CVD deaths (2–3%). With 788 deaths averted, all-cause mortality was least impacted by inclisiran because of competing risks (<0.1% reduction relative to the comparator strategy). Population

gains in life expectancy and QALYs were both less than 0.1%, translating to 0.064 life-years and 0.058 QALYs gained per person relative to the comparator strategy.

The burden of disease estimates were most sensitive to assumptions that varied the number of patients treated (i.e. uptake, treatment eligibility; see Table 25 of the ESM). Scenarios assuming full uptake (i.e. inclisiran administered in all secondary prevention patients meeting the set LDL-C threshold and SOC LLT requirement) resulted in an over five-fold increase in the number of eligible patients with proportionate reductions in burden. Restricting treatment eligibility to patients taking high-intensity statins and ezetimibe resulted in the lowest impact in all outcomes (531 non-fatal ACS, 141 CV deaths averted, and 416 QALYs gained over 10 years). Similarly, introducing an age cut-off for starting inclisiran treatment, while fairly marginal when considering changes to the predicted ICER, reduced deaths avoided and QALYs gained by about 30%. Calibration targets for cardiovascular events remained a sensitive parameter.

3.3 Budget Impact

Under the base-case treatment eligibility and uptake assumptions, 33,398 patients would be treated with inclisiran over 5 years (Table 4). The net budget impact of the new therapy would be CHF 49.3/573.4 million under the lower/higher inclisiran price, increasing the current cost of CVD management in this population by about 0.4/4%. Cost reductions achieved through reduced CVD morbidity enabled by inclisiran would offset 55%/10% of the lower price/higher price inclisiran costs, respectively.

Aside from the price of inclisiran, budget impact estimates were most sensitive to assumptions on treatment eligibility (Tables 26–27 of the ESM). Restricting inclisiran eligibility to patients already treated with high-intensity statins led to a 45% decrease in the budget impact (CHF 67.7 million). Restricting eligibility to those treated with high-intensity statins and ezetimibe reduced the budget impact further (CHF 21.2 million). Increasing the LDL-C threshold eligibility to ≥2.6 mmol/L reduced the budget impact by 56% (to CHF 52.8 million). Scenarios unrelated to treatment eligibility and price resulted in an at most 5% change in the budget impact.

4 Discussion

We modelled the likely impacts of adding inclisiran to SOC LLT in Swiss secondary cardiovascular prevention patients with LDL-C ≥1.8 mmol/L. The new therapy was estimated to enable an additional 0.291 QALYs per person treated at an ICER of CHF 21,107/228,040 per QALY gained under an

assumed price of CHF 500/3000 per dose of inclisiran. The estimated ICERs were fairly robust in the deterministic sensitivity analysis. Scenario analyses provided broader ICER ranges reflecting uncertainty about the size and characteristics of the target population. Changes in calibration targets, reflecting substantial uncertainty around true event rates in the target population, were particularly influential. Features related to the real-world use of inclisiran including persistence and maximum age at treatment start had only a limited impact on the predicted cost-effectiveness. In the very high-risk prevention patients, the benefits and the value for money were broadly comparable to the base-case estimates. Under base-case eligibility and uptake assumptions, inclisiran was shown to lead to important reductions in CVD mortality and morbidity. The budget impact in the first 5 years was 0.4% or 4% of the current cardiovascular treatment costs in the target population, depending on price.

To date, only one published study by Kam and colleagues [46] considered the economic properties of inclisiran in a wider population currently not eligible for PCSK9i. The authors developed a Markov model populated with UK-based transition probabilities that described a narrow set of health states (myocardial infarction, revascularisation, CVD, and non-CVD deaths) in a population modelled after the ORION-10 trial [31]. From the perspective of the Australian health system and at an assumed annual inclisiran cost of AUD 6334 (similar to the higher price evaluated in our base-case analysis), the authors

Fig. 2 Univariate sensitivity analysis of cost-effectiveness results by inclisiran price per dose. Panel **A** presents results of the univariate sensitivity analysis under inclisiran price per dose = Swiss francs (CHF) 500. Panel **B** presents results of the univariate analysis under inclisiran price per dose = CHF 3000. The length of the bar indicates the resulting incremental cost-effectiveness ratio (ICER) when the respective parameter is set to its lower (lighter shade) and upper (darker shade) bound values (see text for ranges); the diagram is centred on the base-case ICER, i.e. CHF 21,107/228,040 under the lower/higher inclisiran price assumption. Results in tabular format are reported in the ESM. *ACS* acute coronary syndrome, *CV* cardiovascular, *CVD* cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *UA* unstable angina

estimated an ICER slightly over AUD 125,000 per QALY gained, more favourable compared with our finding for the higher price. Differences are expected given different approaches to modelling (based on a single cohort aged 66 years in Kam et al. versus a population with a widespread age range ≥40 years and an average age of 71 years in our analysis). In addition, Swiss secondary prevention patients appeared somewhat healthier, displaying lower LDL-C levels, a lower incidence of diabetes, and, as a consequence, facing relatively lower cardiovascular risk which translated to relatively lower gains from inclisiran. Our findings are still broadly consistent with those of Kam et al., showing better value of inclisiran in populations with higher LDL-C.
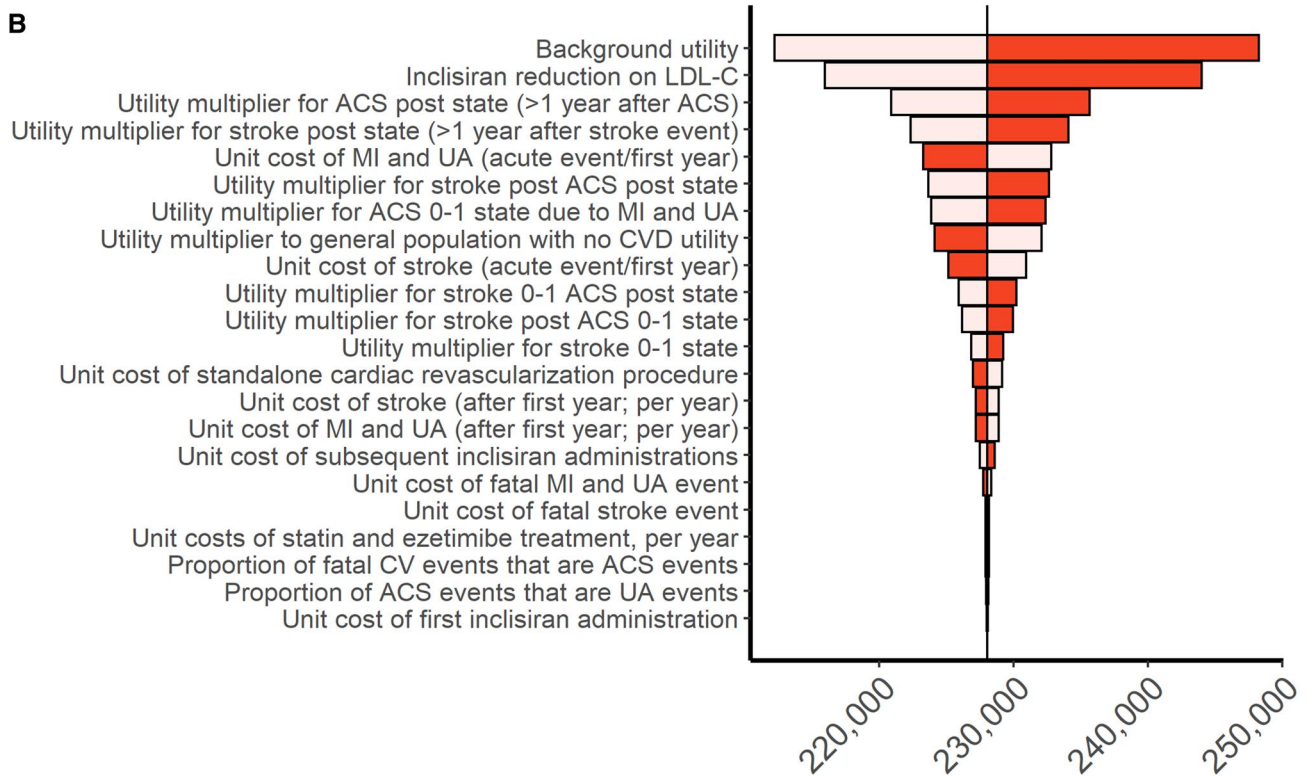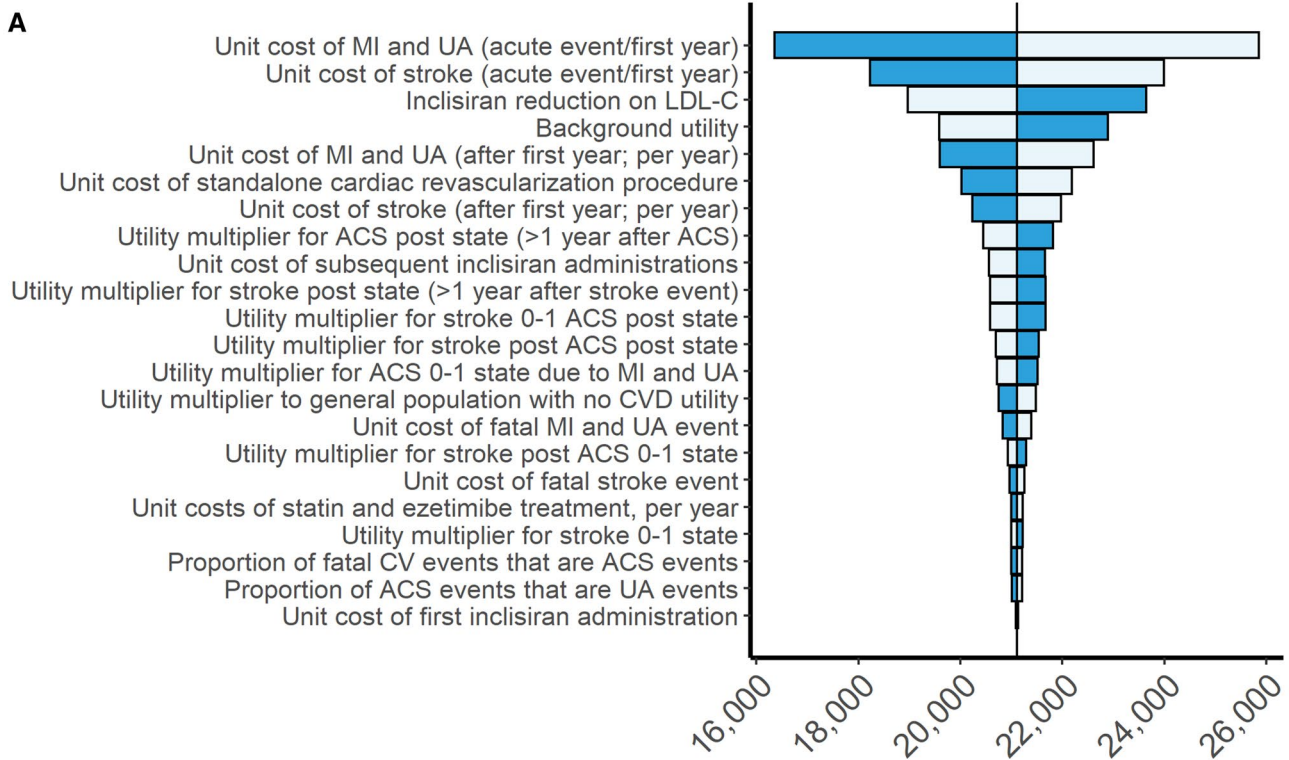
The present analysis is subject to limitations. Our key challenge was in identifying the size and structure of the

Table 2 Results of the cost-effectiveness analysis: base-case, lifelong time horizon

Outcome	Inclisiran	Comparator	Difference
Life-expectancy			
Life-years per person	11.416	11.217	0.199
Life-year difference per person treated with inclisiran	–	–	0.364
QALYs			
QALYs per person	8.485	8.326	0.159
QALY difference per person treated with inclisiran	–	–	0.291
Costs and ICER at inclisiran price CHF 500			
Cost per person (CHF)	97,731	94,377	3354
Cost difference per person treated with inclisiran (CHF)	–	–	6144
ICER (CHF per life-year gained)	–	–	16,875
ICER (CHF per QALY gained)	–	–	21,107
Costs and ICER at inclisiran price CHF 3000			
Cost per person (CHF)	130,610	94,377	36,233
Cost difference per person treated with inclisiran (CHF)	–	–	66,375
ICER (CHF per life-year gained)	–	–	182,318
ICER (CHF per QALY gained)	–	–	228,040

Modelled outcomes were cumulated starting from age 40 years through end of life for a cohort of real-world Swiss cardiovascular secondary prevention patients (including first-year prevalent cases and new incident cases from that year) representing 302,738 patients. In the inclisiran strategy, reflecting the assumed treatment eligibility criteria, 55% of the cohort were treated with inclisiran. QALYs and costs were discounted at 3%. See text and ESM for details on the model and calculations

CHF Swiss francs, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

A

Unit cost of MI and UA (acute event/first year)
Unit cost of stroke (acute event/first year)
Inclisiran reduction on LDL-C
Background utility
Unit cost of MI and UA (after first year; per year)
Unit cost of standalone cardiac revascularization procedure
Unit cost of stroke (after first year; per year)
Utility multiplier for ACS post state (>1 year after ACS)
Unit cost of subsequent inclisiran administrations
Utility multiplier for stroke post state (>1 year after stroke event)
Utility multiplier for stroke 0-1 ACS post state
Utility multiplier for stroke post ACS post state
Utility multiplier for ACS 0-1 state due to MI and UA
Utility multiplier to general population with no CVD utility
Unit cost of fatal MI and UA event
Utility multiplier for stroke post ACS 0-1 state
Unit cost of fatal stroke event
Unit costs of statin and ezetimibe treatment, per year
Utility multiplier for stroke 0-1 state
Proportion of fatal CV events that are ACS events
Proportion of ACS events that are UA events
Unit cost of first inclisiran administration

16,000   18,000   20,000   22,000   24,000   26,000

B

Background utility
Inclisiran reduction on LDL-C
Utility multiplier for ACS post state (>1 year after ACS)
Utility multiplier for stroke post state (>1 year after stroke event)
Unit cost of MI and UA (acute event/first year)
Utility multiplier for stroke post ACS post state
Utility multiplier for ACS 0-1 state due to MI and UA
Utility multiplier to general population with no CVD utility
Unit cost of stroke (acute event/first year)
Utility multiplier for stroke 0-1 ACS post state
Utility multiplier for stroke post ACS 0-1 state
Utility multiplier for stroke 0-1 state
Unit cost of standalone cardiac revascularization procedure
Unit cost of stroke (after first year; per year)
Unit cost of MI and UA (after first year; per year)
Unit cost of subsequent inclisiran administrations
Unit cost of fatal MI and UA event
Unit cost of fatal stroke event
Unit costs of statin and ezetimibe treatment, per year
Proportion of fatal CV events that are ACS events
Proportion of ACS events that are UA events
Unit cost of first inclisiran administration

220,000   230,000   240,000   250,000

Swiss secondary prevention population and the occurrence of events in these patients. To derive the relevant inputs, Swiss sources were combined with international databases covering data from Switzerland and other industrial countries. In the absence of suitable Swiss data, we used starting transition probabilities derived from the British Clinical

Table 3 Results of the burden of disease analysis: base-case, 10-year time horizon

Outcome	Inclisiran	Comparator	Difference
Clinical events			
Number of revascs	43,681	45,529	−1849
Number of ACS (non-fatal)	87,849	91,274	−3425
Number of strokes	68,918	70,880	−1961
Number of CV deaths	48,384	49,409	−1025
Number of all-case deaths	165,452	166,240	−788
Life expectancy			
Total life-years	3,009,397	3,006,279	3118
Life-years per person	6.238	6.232	0.006
Life-year difference per person treated with inclisiran	–	–	0.064
QALYs			
Total QALYs	2,246,587	2,243,733	2854
QALYs per person	4.657	4.651	0.006
QALY difference per person treated with inclisiran	–	–	0.058

Modelled outcomes were cumulated over a 10-year time horizon in a real-world Swiss cardiovascular secondary prevention population (including first-year prevalent cases and new incident cases emerging each year [aged 40 years and above]) representing 482,408 patients who ever entered the model. In the inclisiran strategy, reflecting the assumed treatment eligibility criteria and uptake, 48,823 patients or about 10% of the secondary prevention population were ever treated with inclisiran during 10 years. Nominal values refer to 2018 prices. See text and ESM for details on the model and calculations

ACS acute coronary syndrome, *CHF* Swiss francs, *CV* cardiovascular, *QALY* quality-adjusted life-year, *revascs* revascularizations

Table 4 Results of the budget impact analysis (in million CHF): base-case, 5-year time horizons

Outcome	Inclisiran	Comparator
Costs and budget impact at inclisiran price CHF 500		
Cost of inclisiran	109.6	0.0
Cost of lipid-lowering drugs	486.5	486.4
Costs of CVD events and deaths	13,446.1	13,506.6
Total costs	14,042.3	13,993.0
Budget impact	49.3	
Costs and budget impact at inclisiran price CHF 3000		
Cost of inclisiran	633.8	0.0
Cost of lipid-lowering drugs	486.5	486.4
Costs of CVD events and deaths	13,446.1	13,506.6
Total costs	14,566.4	13,993.0
Budget impact	573.4	

Modelled outcomes were cumulated over a 5-year time horizon in a real-world Swiss cardiovascular secondary prevention population (including first year prevalent cases and new incident cases emerging each year) representing 389,833 patients who ever entered the model. In the inclisiran strategy, reflecting the assumed treatment eligibility criteria and uptake, 33,268 patients or about 10% of the secondary prevention population who were ever treated with inclisiran during 5 years. See text and ESM for details on the model and calculations

CHF Swiss francs, *CVD* cardiovascular disease

Practice Research Datalink database [22], as also used in the NICE Single Technology Appraisal of inclisiran, which were subsequently adjusted to the age and LDL-C characteristics of our population of interest. This implied a separate calculation for each sub-cohort and in each model cycle, hindering variation in the standard sensitivity analysis. However, a potential lack of applicability was mitigated by introducing calibration factors that scaled the model outputs in the comparator strategy to the number of annual non-fatal and fatal cardiovascular events realistically expected in the Swiss secondary prevention population. These calibration factors were extensively varied in scenario analyses. We also used UK-based utility multipliers for cardiovascular events [33] and factors to convert utilities in the general population to the non-CVD population [33]. These were, however, applied to general population utility estimates for Switzerland [32], minimising potential bias.

Unavoidable inconsistencies in case definitions, methods of data generation, and populations covered across the data sources were also addressed in the uncertainty analyses, by comparing different approaches to the derivation

of parameters and evaluating alternative assumptions on parameter values. Generally, middle-of-the-road and conservative estimates were preferred over extreme values. To avoid additional layers of technical complexity, the presented results assumed the characteristics of the Swiss secondary prevention population were estimated correctly. Given uptake assumptions, the time horizon for the burden of disease analyses covered an initial period of dynamic development of the numbers of persons treated and relative stabilisation thereafter. Additional scenarios assumed immediate full treatment uptake of all eligible patients to facilitate interpretation. Because of a current lack of real-world adherence and persistence data for inclisiran, we assumed full adherence, and reduced persistence only in some cost-effectiveness scenarios. Research into these topics may be warranted after the introduction of inclisiran into the market. Given the low use of the currently available PCSK9i antibodies in the Swiss secondary prevention population (0.8% according to [27]), we did not consider the impact of these drugs in our analyses.

One major assumption of the model was that the meta-analysis-based relationship between LDL-C reduction and CVD event occurrence would hold for inclisiran. This was supported by review results from Ference et al. [5] that indicated the impact of lipid-lowering therapies on clinical outcomes is independent of the mechanism of action. Moreover, constrained by the data limited to within-trial observations of inclisiran-treated patients (1.4 years in ORION studies),

Fig. 3 Probabilistic sensitivity analysis-based cost-effectiveness plane and cost-effectiveness acceptability curves from 10,000 iterations by inclisiran price per dose. Panel **A** shows the cost and quality-adjusted life year (QALY) differences per person treated with inclisiran. *Dashed lines* represent thresholds of Swiss francs (CHF) 50,000, 100,000, 200,000, and 300,000 per QALY gained. The population size was 319,742 and the percentage treated was 0.54%. Panel **B** shows the corresponding cost-effectiveness acceptability curves for inclisiran price per dose = CHF 500. Panel **C** shows the corresponding cost-effectiveness acceptability curves for inclisiran price per dose = CHF 3000
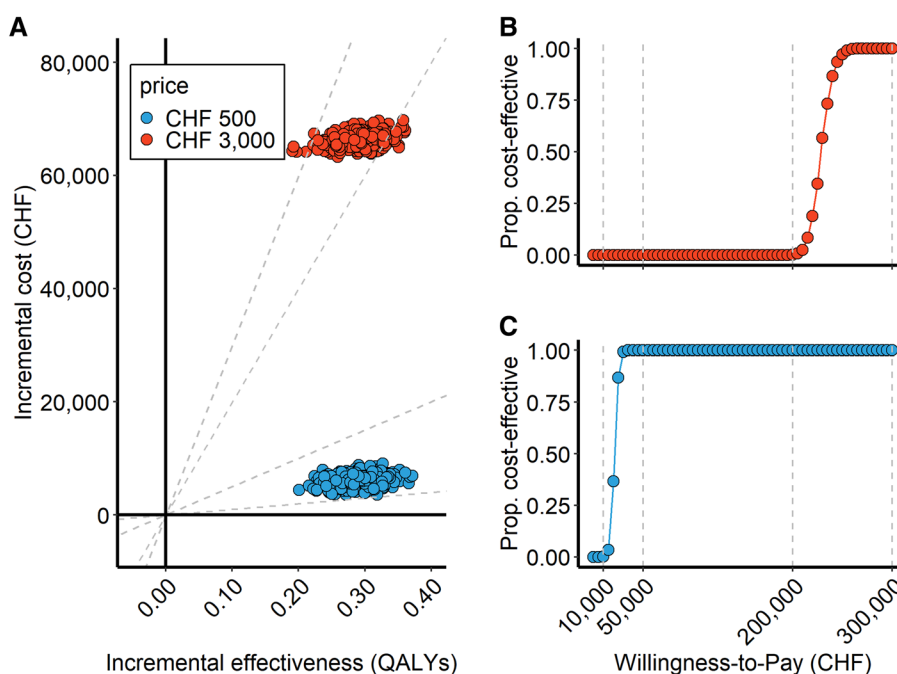
we assumed that there would be no change in the efficacy of inclisiran over time. Several trials are in progress to directly quantify the impact of inclisiran on cardiovascular events and mortality allowing for a longer follow-up [47, 48]; the results, once available, may be used to update our analysis. Noteworthy, similar assumptions were accepted in the NICE appraisal of inclisiran in light of the potential benefits of this new therapy, further strengthening the policy relevance of the modelled evidence presented here.

Compared with conventional approaches, our innovative dynamic open-cohort model supports the generation of highly consistent cost-effectiveness, burden of disease, and budget impact predictions at cohort and population levels. Heterogeneity in population features relevant to the risk of cardiovascular events (i.e. age, sex, LDL-C, SOC LLT, diabetes) is easily accommodated, facilitating applications to other countries or populations. Moreover, the flexibility of the modelling framework and the data collated support further evaluations of health interventions other than inclisiran in patients at risk of CVD, including primary prevention patients in Swiss and other settings. Performing the cost-effectiveness part with an open-cohort instead of a closed-cohort approach was not influential in the present case but might induce substantial ICER differences for other intervention types, for example treatments with high initial costs and no or very low subsequent costs. Policy-relevant scenarios with respect to adherence, longer term efficacy, uptake and pricing scenarios can easily be implemented to inform reimbursement and budgeting discussions.

5 Conclusions

From the perspective of the Swiss healthcare system, inclisiran may be cost-effective in secondary cardiovascular prevention patients at a WTP threshold of CHF 30,000 per QALY gained if priced at CHF 500 per dose. A threshold upwards of CHF 250,000 would be required if inclisiran was priced at CHF 3000. Similar value for money was estimated for a broader population at very high risk of CVD events. Inclisiran could enable important reductions in cardiovascular burden particularly under broader eligibility with a budget impact range from modest to high depending on price and actual uptake. These findings should be interpreted considering the uncertainty around the size and characteristics of the Swiss secondary prevention population and the stated limitations.

Declarations

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