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Bern, 1. Dezember 2023

Gesuch um Zugang zu amtlichen Dokumenten gemäss Bundesgesetz über das Öffentlichkeitsprinzip der Verwaltung (BGÖ; SR 152.3) – teilweise Gewährung des Zugangs

Sehr geehrter Herr Dr. Romanens

Wir beziehen uns auf Ihr per E-Mail zugestelltes Schreiben vom 30. August 2023 betreffend die Limitierung des Arzneimittels LEQVIO in der Spezialitätenliste. Mit diesem Schreiben ersuchen Sie uns unter anderem, «die Begründung für die Limitatio offen zu legen, insbesondere die Grundlagen und Resultate einer eventuell durchgeführten Budget Impact Analysis».

Vorab informieren wir Sie, dass uns die Zulassungsinhaberin Novartis sowohl die unveröffentlichte Studie «Health economic implications of secondary prevention inclisiran use in Switzerland» vom 17. März 2021 als auch die publizierte Version der vorgenannten Studie hat zukommen lassen. Die publizierte Studie «Cost-Effectiveness, Burden of Disease and Budget Impact of Inclisiran: Dynamic Cohort Modelling of a Real-World Population with Cardiovascular Disease» vom 20. Juni 2022 übersenden wir Ihnen ebenfalls in der Beilage.

Nach Prüfung Ihres Gesuches können wir Ihnen den Zugang zur Studie «Health economic implications of secondary prevention inclisiran use in Switzerland» vom 17. März 2021 wie folgt eingeschränkt gewähren.

I. Personendaten (Seite 1 der Studie)

Die Namen sowie andere Hinweise der Studienautoren bzw. Studienbeteiligten auf Seite 1 wurden standardmässig anonymisiert, da es sich um Informationen handelt, die sich auf identifizierbare Personen beziehen. Diese Informationen unterliegen dem Schutz von Personendaten nach Art. 7 Abs. 2 und

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Art. 9 Abs. 1 BGÖ.

II. Ausführungen bezüglich Budget Impact (Seite 9 ff. der Studie)

Es wurden alle Angaben bezüglich Budget Impact anonymisiert, da diese Angaben nicht öffentlich zugänglich sind und gemäss Art. 7 Abs. 1 Bst. g BGÖ zum Schutz von Geschäftsgeheimnissen zu schwärzen sind. Zudem sind diese Angaben auch durch Art. 7 Abs. 1 Bst. b BGÖ zum Schutz der zielkonformen Durchführung konkreter behördlicher Massnahmen nicht zu edieren.

III. Gebühren

Der Zugang zu amtlichen Dokumenten ist nach Art. 17 BGÖ seit 1. November 2023 grundsätzlich nicht mehr gebührenpflichtig. Da Ihr Zugangsgesuch keine besonders aufwändige Bearbeitung erforderte, erheben wir vorliegend keine Gebühren.

Hiermit betrachten wir Ihr vorliegendes Gesuch um Zugang zu amtlichen Dokumenten gemäss BGÖ als erledigt.

Da Ihnen der Zugang teilweise verweigert wird, steht Ihnen entsprechend Artikel 13 BGÖ das Recht zu, beim Eidgenössischen Datenschutz- und Öffentlichkeitsbeauftragten (Feldeggweg 1, 3003 Bern: www.edoeb.admin.ch) innert 20 Tagen nach Empfang dieser Mitteilung schriftlich einen Schlichtungsantrag zu stellen.

Freundliche Grüsse

Abteilung Leistungen Krankenversicherung
Sektion Leistungsrecht
Die Co-Leiterin

Sarah Leiendecker

Beilagen:

- Studie «Health economic implications of secondary prevention inclisiran use in Switzerland» vom 17. März 2021 (unveröffentlicht)
- Studie «Cost-Effectiveness, Burden of Disease and Budget Impact of Inclisiran: Dynamic Cohort Modelling of a Real-World Population with Cardiovascular Disease» vom 20. Juni 2022 (publiziert)

Health economic implications of secondary prevention inclisiran use in Switzerland

[redacted]

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Abbreviations

ACS	Acute coronary syndrome
AdViSHE	Assessment of the Validation Status of Health-Economic decision models
CABG	Coronary Artery Bypass Graft
CHF	Swiss Francs
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
FIRE	Family Medicine ICPC-Research using Electronic Medical Records)
GBD	Global Burden of Disease
HeHF	Heterozygous familial hypercholesterolaemia
HSUV	Health state utility values
HS	haemorrhagic stroke
ICD	International classification od diseases
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
IS	Ischaemic stroke
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDL	Low-density lipoprotein
LDL-c	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapy
MedStat	Medical Statistics of Hospitals
MI	Myocardial infarction
NSTEMI	Non-ST-elevation MI
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PSA	Probabilistic sensitivity analysis
PTCAs	Percutaneous transluminal coronary angioplasty
SFSO	Swiss Federal Statistical Office
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
STEMI	ST-elevation MI
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischaemic attack
UA	Unstable angina

Acknowledgements

We thank Patrick Schwab and Gian-Paolo Klinke from the Swiss Federal Statistical Office for providing aggregate data from the Swiss Medical Statistics of Hospitals data, Rahel Meier and Yael Rachamin for providing aggregate data from the FIRE database, André Höpli for providing aggregate data from the AMIS-plus registry, and Christina Tzogiou from Zürcher Hochschule für angewandte Wissenschaften Winterthur for supporting the collection of unit cost data. They are not in any way responsible for the content of this report. The responsibility for the content is with the authors.

Executive Summary

Background

Novartis is currently pursuing and completing the clinical development of inclisiran - a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor of the novel small interfering RNA molecule type. To define a medically and economically sensible positioning of the new treatment option in Switzerland, Novartis has an interest in understanding the potential impact of inclisiran on the burden of cardiovascular disease (CVD) in the country, and implications for cost-effectiveness and budget impact, to inform reimbursement decisions on this new therapy by the Swiss statutory health insurance. Toward these aims the report details the health economic model for inclisiran we have developed to evaluate the health economic properties of inclisiran and presents the modelled estimates of the implications of inclisiran in the real-world Swiss secondary cardiovascular prevention population with a prior ischaemic cardiac or cerebrovascular event (henceforward: Swiss secondary prevention population). Approximate cost-effectiveness results for very high risk patients that have not yet had a cardiovascular event, and for patients with heterozygous familial hypercholesterolaemia (HeFH) are also covered.

Objective and decision problem

The overall objectives of this study are:

- For the real-world Swiss secondary prevention population, to estimate the impact on burden of CVD in terms of life years, quality-adjusted life years, cardiovascular events and cardiovascular deaths;
- For the real-world Swiss secondary prevention population, to estimate the cost-effectiveness and budget impact of inclisiran in Switzerland, from the perspective of the Swiss statutory health insurance for different price points;
- For other relevant populations, including very high risk patients that have not yet had a cardiovascular event, patients with peripheral artery disease (PAD), and patients with HeFH, to approximate the cost-effectiveness of inclisiran in Switzerland.

The primary population of interest is defined as patients aged 40 years and above in the Swiss secondary prevention population. In the absence of data on the low-density lipoprotein cholesterol (LDL-c) levels of untreated patients, we used LDL-c levels under background lipid-lowering therapy (LLT) to determine eligibility for inclisiran treatment. In the base case analyses, we assumed patients with an LDL-c of above 1.8 mmol/L under background lipid-lowering treatment would be eligible for inclisiran treatment. This assumption was varied in scenario analyses.

Life years, cardiovascular events (revascularizations, episodes of non-fatal unstable angina myocardial infarction and stroke, and cardiovascular death), and quality-adjusted life years (QALYs) in the target population were compared between the inclisiran ('world with inclisiran') and standard of care ('world without inclisiran') strategies. The evaluation was conducted from the perspective of the Swiss statutory health insurance.

Methods of cost-effectiveness, burden of disease and budget impact analysis

A dynamic population model, essentially based on the principles of a cohort cost-effectiveness model with a flexible time horizon, was developed to generate evidence toward all health

economic objectives. The model relies on the Markovian principle of transitions between health states, with time modelled in discrete cycles of a fixed length (i.e., 1 year). Deviating from a single cohort model, the model distinguishes population subgroups characterised by age group, sex and LDL-c category, that are treated as separate sub-cohorts: These are co-modelled and combined to population-level estimates as necessary. In addition, persons newly meeting the eligibility criteria of the population of interest (incident patients) can enter the model in each cycle.

In order to ensure comparability with the results of other cost-effectiveness analysis, cost-effectiveness analyses pursue the approach to model a Swiss real-world population, but as a closed cohort and life-long. This is achieved by setting the number of persons entering the model after the first cycle, to zero. Patients are followed and costs and cardiovascular events are recorded for 100 years or until the patient dies. Full treatment uptake is assumed in the eligible population. Both costs and effects are discounted by 3% per year (except in scenarios assuming 0% discount rate).

For the burden of disease analysis, the model follows a Swiss real-world population for a defined number of years, pursuing the dynamic cohort approach with new, incident patients entering the model in each year while patients that entered earlier may die. The treatment uptake of prevalent patients can be spread over several years (assumption: 5 years). On this basis, cardiovascular events are counted in the 'world with inclisiran' and 'world without inclisiran'. The resulting differences in event numbers are interpreted as the burden of disease/public health impact of inclisiran. Real-world impact is estimated reflecting treatment uptake assumptions projected by Novartis. Impact estimates are reported undiscounted. A time horizon of 10 years is used.

Enabled by the model structure adopted, cost results from the cost-effectiveness model inform the budget impact analysis. The dynamic cohort approach is used as described above for the burden of disease analysis. This enables a realistic capturing of inclisiran costs but also costs influenced by inclisiran treatment, which may modify the overall budget impact (e.g. cardiovascular event costs). Treatment uptake assumptions are the same as for the burden of disease analysis. For budget impact analysis, the model is run without discounting, for a time horizon of 5 years.

Approach to health economic modelling

Overall structure

The dynamic population model captures characteristics of a real-world population with a total of 88 sub-Markov models corresponding to combinations of sex (women and men) age (5-year age groups starting at age 40-44 years and age 90 years or older), and 4 LDL-c categories (<1.4 mmol/L, ≥1.4 to <1.8 mmol/L, ≥1.8 to <2.6 mmol/L, ≥2.6 mmol/L). Results are combined using summation nodes. Based on input parameter tables, different characteristics can be assigned to each sub-population, namely average age at entry, LDL-c level and distribution of background LLT. LDL-c levels at entry are interpreted as LDL-c levels under background LLT. The correct behaviour of the model is ensured by formulae using indicator variables.

Dynamic population features

The distribution of each modelled sub-population between health states reflects absolute numbers of patients, totalling to the modelled target population and representing its characteristics. In the first cycle, i.e. first year of the model, prevalent and incident patients can enter and are assigned to the different sub-populations. If the dynamic cohort functionality is turned on, the incident patients of future years can additionally enter the model and are assigned to the different sub-populations. Using tunnel health states, the model ensures that correct transition probabilities are assigned to all patients.

Modelling of inclisiran uptake and use

The use of inclisiran in the 'world with inclisiran' strategy can be restricted to patients above a certain LDL-c level, based on the above LDL-c categories (e.g. to patients with LDL-c ≥1.8 mmol/L) and to patients with certain types of background LLT. In addition, the treatment uptake can be modelled specific for each sub-population defined by age, sex and LDL-c category. Treatment uptake assumptions can also be made separately for the prevalent patients and for the incident patients of each model year. The treatment uptake of prevalent patients can be spread over several years.

Health states and events

Patients can transition between several health states in each cycle; these refer to acute and stable states (e.g. acute coronary syndrome (ACS) or a state following an ACS event in which no other CVD event occurs) representative of the clinical pathways of patients in the target population. Patients' transitions between health states depend on the prior health state and the event occurring. Patients can have multiple events, also of the same type.

Modelling of utilities, QALYs and costs

The utility for any given CVD-related health state is calculated by determining the expected age- and sex-specific utility in persons free from CVD and by applying a multiplication factor for the relevant health state. In health states where patients have had events of different types the strongest of the available effects on utility is assumed. When patients have an acute event, and have already had an earlier event of the same or a different type, the cost of the acute event is assumed (e.g. the cost of a non-fatal ACS event, irrespective of whether there was a prior ACS event, stroke, or no prior event). The ongoing long-term costs of CVD events that occurred before the model entry of patients are counted in addition to the costs of new events. For the secondary prevention population, the model considers disease costs of myocardial infarction (MI), unstable angina (UA) and stroke (distinguishing fatal event costs, non-fatal event costs in the first year and non-fatal event costs in subsequent years), costs for revascularizations (Percutaneous Transluminal Coronary Angioplasty (PTCA) and Coronary Artery Bypass Graft (CABG), to the extent these treatments are not performed for the acute treatment of ACS events), background LLT costs including costs of statins and ezetimibe, and the costs of inclisiran including drug administration costs. [redacted]

Data sources and model input parameter values

Model inputs related to the epidemiology of CVD in Switzerland were primarily sourced from the Global Burden of Disease (GBD) project, FIRE database, Medical Statistics of Hospitals (MedStat) and the WHO Mortality Database (see Table 3 in the main part of the document). FIRE and MedStat data were particularly useful in defining and characterizing the secondary prevention population.

To model the transition probabilities from one state to another in the 'world without inclisiran', we used values generated by Novartis based on data from the Clinical Practice Research Datalink (CPRD). These were adjusted to the characteristics of the Swiss secondary prevention population with respect to the average age, LDL-c level, and presence of diabetes. Age adjustment was used to achieve a plausible age distribution of events. The effectiveness of inclisiran was obtained from the ORION randomised clinical trial programme, and implemented via the achieved LDL-c reduction.

Background health state utility values were represented by the background utility of the population free from CVD. The respective Swiss values were derived by combining Swiss general population utilities with a UK-based adjustment factor for people free from CVD. Utility multipliers for the initial CVD health states and subsequent CVD events were also UK-based. We did not consider a utility impact of treatment-emergent adverse events.

[redacted]

Calibration

The model was calibrated to the expected numbers of events in the Swiss secondary prevention population. Specifically, calibration factors were derived by dividing the number of events generated with Swiss age adjusted transition probabilities over event totals for each of the outcomes from SFSO, MedStat, and WHO mortality databases. The scaling factors were then applied to transition probabilities to ensure that event counts generated by the model result aligned with Swiss numbers of events.

Validation

Multiple validation steps were performed. The vast majority of validation steps showed fully satisfactory results. As a single exception, our model may moderately over-estimate life expectancy/age at death. However, this is 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.

Results: cost-effectiveness

For the primary population of interest, that covers the Swiss secondary cardiovascular prevention population and assuming eligibility defined with respect to LDL-c level ≥1.8 mmol/L

and any prior LLT [redacted]

The ICER was shown to be fairly robust to assumptions on costs of cardiovascular events, utilities and LDL-c reduction achieved with inclisiran, ranging ± CHF 5'000 when varied in deterministic sensitivity analysis. Of the scenarios evaluated, assumptions on the price of inclisiran and those that impacted the number of persons treated (mainly due to varied assumptions on LDL-c thresholds or background LLT), treatment uptake, and event counts (critically with respect to cardiovascular deaths) resulted in the broadest ICER ranges, particularly when interacted. [redacted]

[redacted]

Results: burden of disease

At population level, under partial treatment uptake assumptions as used for the budget impact analysis and considering the LDL-c threshold of ≥1.8 mmol/L (leading to treatment of roughly 10% of the secondary prevention population), the new therapy was estimated to gain a total of 2'854 undiscounted QALYs or an additional 0.058 QALYs per person treated with inclisiran and avert 3'425 non-fatal ACS events, 1'961 strokes, and 1'025 CVD deaths over the first 10 years following introduction.

Results: budget impact

[redacted]

Discussion

The strength of the modelling approach presented lies in the scope of the model that in one structure offers capabilities to generate predictions at cohort and population levels, thus facilitating coherence across the health-economic outcomes. It supports decision making on the adoption of new health technologies. Limitations were addressed with extensive uncertainty analyses.

The key challenge for the analysis was the difficulty of identifying and describing the size and structure of the Swiss secondary prevention population, and event occurrence in this population, in any available data source. We had to combine Swiss data sources, international data sources reporting or modelling Swiss data (namely, the GBD project and WHO Mortality Database), and data from other industrial countries (namely, the UK) to determine related estimates. The resulting set of data sources was unavoidably partially incoherent in terms of

populations covered/studied, methods of data generation and definitions used. Hence, it was not possible to generate a fully consistent set of input parameter values. We addressed this by generating the best possible estimates. 'Middle-of-the-road' and, in cases of doubt, conservative estimates were preferred over extreme ones.

Further notable limitations include the need to make assumptions on the long-term effectiveness of inclisiran, the absence of information on the reasons behind selecting background LLT for Swiss secondary prevention patients, and the need for simplifying assumptions on the utility values and costs for some health states. Data sources for the full very high risk population including secondary prevention patients and patients that have not yet had a CVD event, and for patients with HeFH, were even more sparse and also less of a priority given the very tight time horizon of the project. We had no data basis to estimate results for PAD patients. Finally, we also had no data basis for amending the adopted Swiss statutory health insurance perspective with a societal perspective considering the population level loss of productivity due to CVD.

Conclusion

The analysis demonstrated that adding inclisiran to the current standard of care LLT in Switzerland would enable additional benefits in terms of burden and mortality reduction in the secondary prevention CVD population and related very high risk populations. [redacted] Sensitivity analyses confirmed these results while scenario analyses reflected relevant uncertainty, mostly due to limitations of the available data sources. Based on treatment uptake assumptions provided by Novartis (leading to treatment of roughly 10% of the secondary prevention population), [redacted] Using the same uptake assumptions, the burden of disease analysis predicted that the introduction of inclisiran on the market would reduce CVD deaths by 1'025 cases in ten years. The reduction of non-fatal ACS events and strokes would be 3'425 and 1'961 cases, respectively.

1. Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors entered the arena of lipid-lowering drugs for the prevention of cardiovascular events several years ago. The PCSK9 inhibitor products available on the market so far are human monoclonal antibodies. Their high clinical efficacy and favourable safety profile come at a high cost in comparison with long-established drugs largely available as generics (most importantly, statins). Hence, their use so far has largely been restricted to patients with severe, often inherited, forms of hypercholesterolemia.

Novartis is currently pursuing and completing the clinical development of inclisiran, a PCSK9 inhibitor of the novel small interfering RNA molecule type [1]. The series of clinical trials forming the ongoing ORION Clinical Development Program are showing favourable results and already provide a good, albeit not final, understanding of the clinical efficacy and safety of inclisiran [2, 3]. In parallel to and after seeking marketing approval for inclisiran, Novartis will submit reimbursement applications in a variety of jurisdictions, including to the Swiss statutory health insurance. To define a medically and economically sensible positioning of the new treatment option in Switzerland, Novartis has an interest in understanding its potential impact on the burden of cardiovascular disease (CVD) in the country, and implications for cost-effectiveness and budget impact.

This report details the health economic model for inclisiran we have developed to estimate the cost-effectiveness, budget impact and burden of disease implications of inclisiran in the real-world Swiss secondary cardiovascular prevention population with a prior ischaemic cardiac or cerebrovascular event (henceforward: Swiss secondary prevention population). Approximate cost-effectiveness results for very high risk patients that have not yet had a cardiovascular event, and for patients with heterozygous familial hypercholesterolaemia (HeFH) are also covered.

2. Objectives

The overall objectives of this study are:

- For the real-world Swiss secondary prevention population, to estimate the impact on burden of CVD in terms of life years, quality-adjusted life years, cardiovascular events and cardiovascular deaths;
- For the real-world Swiss secondary prevention population, to estimate the cost-effectiveness and budget impact of inclisiran in Switzerland, from the perspective of the Swiss statutory health insurance for different price points;
- For other relevant populations, including very high risk patients that have not yet had a cardiovascular event, patients with peripheral artery disease (PAD), and patients with HeFH, to approximate the cost-effectiveness of inclisiran in Switzerland.

3. Decision problem

The primary population of interest is defined as patients aged 40 years and above in the Swiss secondary prevention population. Additional analyses were planned, to the extent feasible, for populations with very high cardiovascular risk that have not yet had a cardiovascular event, patients with PAD, and patients with heterozygous familial hypercholesterolaemia (HeFH). (In this document, we use the term 'primary prevention' for patients who have major risk factors but have not yet had a major clinical event. The term 'secondary prevention is used for patients who have already had a major event, such as acute coronary syndrome (ACS) event or stroke. This follows the terminology used in much of the cardiovascular literature, although it is not consistent with the definition of levels of prevention used in the public health literature [4].)

The 2019 ESC/EAS guideline for the management of dyslipidaemias [1] defines cardiovascular risk categories as a basis for recommendations on lipid-lowering therapy (LLT). All patients with established arteriosclerotic CVD, by definition, fall into the highest risk category ("very high risk"). For both the secondary and primary prevention of CVD events in very high risk patients, the guideline recommends a low-density lipoprotein cholesterol (LDL-c) reduction by at least 50% of the untreated LDL-c value and an LDL-c goal of <1.4 mmol/L. Recommendations for pharmacological lowering of LDL-c start by treatment with a high-intensity statin (up to the highest tolerated dose), subsequently adding ezetimibe and a PCSK9 inhibitor for patients not achieving their goal.

In the absence of data on the LDL-c levels of untreated patients in Switzerland, we used LDL-c levels under real-world LLT to determine eligibility for inclisiran treatment. In the base case analyses, the eligibility threshold was set at ≥1.8 mmol/L. This value higher than the target value of the European treatment guideline was chosen given the strong LDL-c reduction achievable with inclisiran. Alternative thresholds of ≥1.4 mmol/L and ≥2.6 mmol/l were additionally considered in scenario analyses. The scenario with a cut-off of 1.4 mmol/L strictly includes all patients not effectively treated to target, while the cut-off of 2.6 mmol/L considers a scenario equal to the current reimbursement limitation for PCSK9-inhibitors in Switzerland [5].

According to the Swiss marketing approvals for evolocumab and alirocumab [6], PCSK9 inhibitor treatment is indicated if patients are already on their maximum tolerated standard therapy, consisting of the maximally tolerated statin dose with or without other LLTs. However, related, specific information is unavailable for real-world patients. We therefore interpreted the therapy reported in real-world data sources as maximum tolerated therapy. The obvious limitations of this approach were remedied by considering different levels of background LLT: any, treatment with a high intensity statin ± ezetimibe, treatment with a high intensity statin and ezetimibe. In accordance with both the marketing approvals and the current reimbursement limitations [5] of PCSK9 inhibitors in Switzerland, the use of ezetimibe was not assumed to be a mandatory pre-treatment requirement for the use of inclisiran except in some scenario analyses.

Outcomes in the target population were compared between the inclisiran ('world with inclisiran') and standard of care ('world without inclisiran') strategies. To inform reimbursement decisions on inclisiran, the evaluation was conducted from the perspective of the Swiss statutory health insurance. Other perspectives were not considered due data limitations. In the cost-effectiveness analyses, both costs and effects of inclisiran and standard of care

strategies were discounted at 3%, other discount rates were evaluated in scenario analyses. The burden of disease and budget impact analyses did not use discounting.

The decision problem is further specified in Table 1.

Table 1. Decision problem

Population	Primary population of interest: Swiss secondary cardiovascular prevention population with a prior ischaemic cardiac or cerebrovascular event (Swiss secondary prevention population) Secondary populations of interest: very high risk patients that have not yet had a cardiovascular event; patients with PAD; and patients with HeFH without or with a prior ischaemic cardiac or cerebrovascular event
Intervention	Inclisiran, modelled as 'world with inclisiran' where different subsets of the population on interest may be treated
Comparators	Standard of care ('world without inclisiran') reflecting routine practice conditions
Outcomes	Cardiovascular events including deaths, life-years, quality-adjusted life-years, total costs, costs by category, incremental cost-effectiveness
Setting	Switzerland
Perspective	Swiss statutory health insurance perspective
Time horizon	Cost-effectiveness: lifetime (allowing for a maximum age of 100 years) Burden of disease: 10 years Budget impact: 5 years
Discount rate	Cost effectiveness: 3% for costs and effects (varied in scenario analysis) Burden of disease: no discounting Budget impact: no discounting

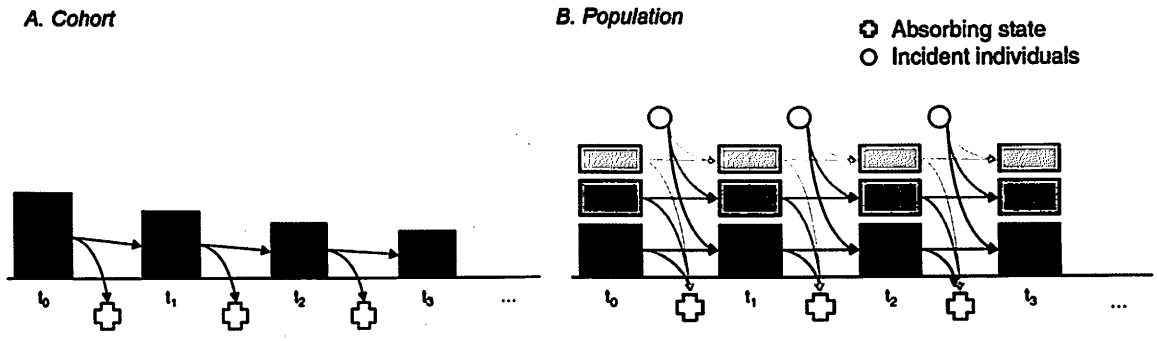
Key: HeFH, Heterozygous familial hypercholesterolemia; PAD, perpipheral artery disease

4. Methods

In order to generate evidence on the incremental cost-effectiveness, impact on population health/burden of disease, and budget impact of inclisiran versus standard of care in Switzerland in a consistent modelling framework, we have developed a dynamic population model – equivalent to an '(open and heterogeneous) population model' in the terminology of Ethgen and Standaert, represented in the left part of Figure 1 [7].

The model structure is in essence equivalent to that of a cohort cost-effectiveness model with a flexible time horizon. It uses the Markovian principle of transitions between health states, with time modelled in discrete cycles of a fixed length. One major deviation from the standard approach is that the model allows to distinguish population subgroups with distinct characteristics, e.g. different age or LDL-c level at entry into the model, that are treated as separate sub-cohorts. In addition, persons newly meeting the eligibility criteria of the population of interest (incident patients) can enter the model in each cycle. These features make it possible to generate cost-effectiveness, burden of disease and budget impact results within the same, coherent model. The impact of inclisiran can thus be estimated at the level of an entire target population if sufficient details of the epidemiology of the condition of interest (e.g. numbers of prevalent and incident secondary prevention patients) and characteristics of the target population are available. Further details are provided in the following sections of this report.

Figure 1. Differences between cohort (A) and population (B) models



Source: Ethgen and Standaert *Pharmacoeconomics* 2012 [7]

4.1 Methods of cost-effectiveness analysis

In most cases, cost-effectiveness models are cohort models following a closed group of individuals over a defined period of time [7]. The members of the cohort will age and ultimately die, but there will be no new members entering over time. This approach is particularly suitable for clinical trial-based cost-effectiveness analyses, where modelling the average characteristics of a trial population is often sufficient. However, the cost-effectiveness of drugs in real-world populations may not be adequately captured, particularly where target populations are subject to substantial heterogeneity. In our dynamic population model, such diverse target population characteristics can be captured by co-modelling of a number of sub-populations and combining the results.

In order to ensure comparability with the results of other cost-effectiveness analysis, we model a Swiss real-world population, but as a closed cohort and life-long. This is simply achieved by setting the number of persons entering the model after the first cycle, to zero. Alternatively, cost-effectiveness could be estimated over a variable time horizon representing calendar time, with incident members of the population entering in each cycle. In order to achieve this, the dynamic population approach would be 'turned on'. Obviously, in such an analysis, the modelled cohort could not be followed until all members of the cohort have died, and results would not be directly comparable with those of closed-cohort analyses. As a third option, the model allows to model the cost-effectiveness of a single cohort with average characteristics, an approach suitable to generate a basis for comparison with immediately trial-based analyses. Discounting is always used in cost-effectiveness analysis (except in scenarios assuming 0% discount rate).

4.2 Methods of burden of disease analysis

Here, the model is run to follow a Swiss real-world population for a defined number of years, pursuing the dynamic cohort approach with new, incident patients entering the model in each year. On this basis, cardiovascular events (revascularizations, episodes of unstable angina (UA) and myocardial infarction (MI), stroke and cardiovascular death) can be counted in the 'world with inclisiran' and in the 'world without inclisiran'. The resulting differences in event numbers are interpreted as the burden of disease/public health impact of inclisiran. If full

inclisiran uptake (100% market penetration) in patients eligible for inclisiran treatment is assumed, the results represent a theoretical potential. On the basis of more limited treatment uptake assumptions, real-world impact can be estimated. This is obviously subject to the inherent uncertainties of treatment uptake assumptions (and other uncertainties resulting from limitations of the available data basis, as addressed elsewhere in this report). Discounting of effects in terms of life years and quality-adjusted life years (QALYs) lived is typically not applied; event numbers are always reported undiscounted. A time horizon of 10 years is primarily used, but may be modified.

4.3 Methods of budget impact analysis

Budget impact models evaluate the financial implications, i.e. budgetary requirements and/or achievable savings, associated with the adoption of different medical strategies by healthcare financing systems. Many budget impact models are rather rudimentary and limited in their coverage of costs, often considering drug and drug administration costs only. Clinical events may be covered but not usually at a high level of granularity. More refined budget impact models often use undiscounted, yearly cost data extracted from companion cost-effectiveness models. They can potentially cover population-level cost implications of medical strategy decisions. Time horizons are typically no longer than 3-5 years.

In the present case, the approach of using cost results from a cost-effectiveness model to inform budget impact analysis, is pursued in an enhanced form that becomes possible due to the use of a single model structure. As when used for burden of disease analysis, new, incident patients enter the model in each year while patients that entered earlier may die. This enables a realistic capturing of inclisiran costs but also costs influenced by inclisiran treatment, which may modify the overall budget impact (e.g. cardiovascular event costs). Treatment uptake assumptions are again required. For budget impact analysis, the model is run without discounting, for a time horizon of 5 years.

4.4 Characteristics and structure of health economic model

Overall structure

The dynamic population model generally follows the principles of a cohort-based Markov state transition model with a cycle length of 1 year. In order to enable the modelling of the characteristics of a real-world population, a number of sub-models distinguish 11 age groups (5-year age groups starting at age 40-44 years and age 90 years or higher), women and men, and 4 LDL-c categories (<1.4 mmol/L, ≥1.4 to <1.8 mmol/L, ≥1.8 to <2.6 mmol/L, ≥2.6 mmol/L). This results in 88 sub-Markov models representing sub-populations, per strategy. Results are combined using summation nodes. Based on input parameter tables, different characteristics can be assigned to each sub-population, namely average age at entry, LDL-c level and distribution of background LLTs. LDL-c levels at entry are interpreted as LDL-c levels under background LLT. The approach to use a series of sub-models was inspired by the work of Nghiem et al. [8].

The Markov structures for all 88 sub-populations in both strategies are identical. The correct behaviour of the model is ensured by formulae using indicator variables. For example, in the 'world without inclisiran' strategy, an indicator variable *ind_strat* precludes any inclisiran use.

Dynamic population features

Other than in a 'classical' cohort Markov model, the distribution of each modelled sub-population between health states is not interpreted as fractions of a cohort but rather reflects absolute numbers of patients. As a result, all sub-populations together amount to the modelled target population and represent its characteristics.

In the first cycle, i.e. first year of the model, prevalent and incident patients can enter and are assigned to the different sub-populations. In the standard implementation for a secondary prevention population that has survived an ischaemic cardiac or cerebrovascular event, prevalent patients would be interpreted as patients that have survived such an event in a previous year. Incident patients would be interpreted as patients who survive such an event in the first year of the model and hence become secondary prevention patients. If the dynamic cohort functionality is applied, the incident patients of future years can additionally enter the model and are assigned to the different sub-populations. This implies that patients entering the model, e.g., in the 40-44 year age group, will in fact be heterogeneous in terms of their age in a given model cycle, as model cycles represent calendar time. Using tunnel health states, the model ensures that correct transition probabilities, e.g. based on age-specific mortality, can still be assigned to all patients.

Modelling of inclisiran uptake and use

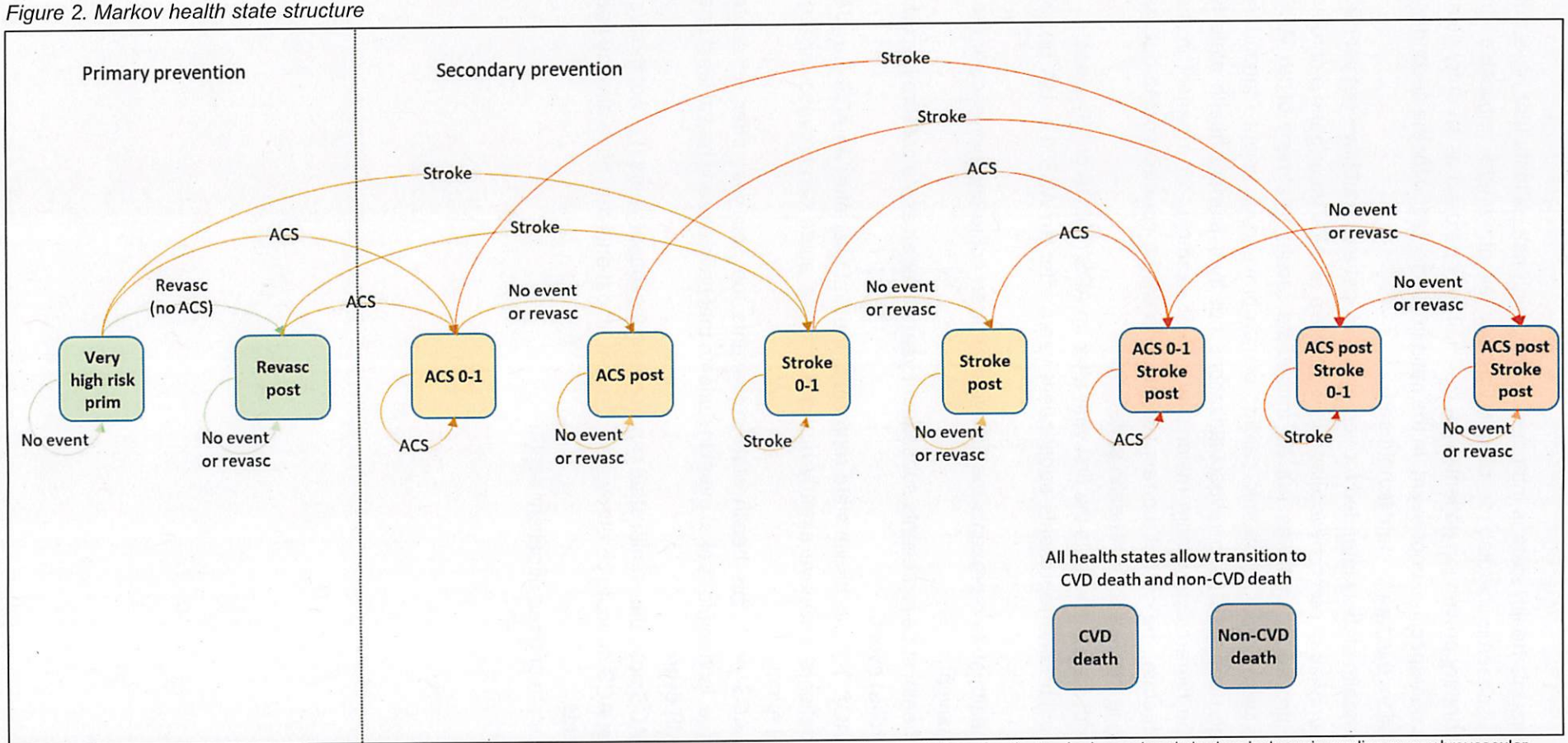
The use of inclisiran in the 'world with inclisiran' strategy can be restricted to patients above a certain LDL-c level, based on the above LDL-c categories (e.g. to patients with LDL-c ≥1.8 mmol/L) and to patients with certain types of background LLT. In addition, the treatment uptake can be modelled specific for each sub-population defined by age, sex and LDL-c category. Treatment uptake assumption can also be made separately for the prevalent patients and for the incident patients of each model year. The total treatment uptake of the prevalent patients, but not of the incident patients, can be spread over several years in principally equal steps, such that the start of inclisiran treatment occurs distributed over time. Such spreading will lead to a slightly smaller number of patients actually starting inclisiran treatment, because a fraction of patients will die while 'waiting' for their treatment start. Also, for technical reasons, the spreading of the start of inclisiran treatment cannot be combined with two other features of the model, namely the option to model a lower/higher effect of inclisiran treatment in the first/subsequent years of treatment or a limited persistence of inclisiran treatment depending on time since treatment start (see sub-section *Model settings* for additional details).

Health states and events

Due to the occurrence of clinical events, patients can transition between health states in each cycle, i.e. year. The heath states used may take slightly different meanings depending on the specific population modelled. Where not otherwise indicated, specifications given below refer to the population of main interest of this analysis, namely the Swiss secondary prevention population. The health states are the following (Figure 2):

- *Very high risk prim*: this health state is intended for very high risk patients that have not yet had a prior ischaemic cardiac or cerebrovascular event, where applicable. In modellings of secondary prevention patients with HeFH, it may be used as an entry point for patients with a non-specified prior event. In the main implementation for the secondary prevention population, this health state is not used.
- *Revasc post*: this health state is intended for very high risk patients that have not yet had a prior ischaemic cardiac or cerebrovascular event but have already undergone a cardiac revascularization procedure that was not an immediate, acute treatment of an ACS episode. Patients with a prior ischaemic cardiac or cerebrovascular event (secondary prevention patients) can also have revascularizations but their primary health state is assigned based on hierarchically more major events. For example, for a patient in the *Stroke post* health state, the cost of the revascularization will be counted/costed but the patient will remain in the *Stroke post* health state.
- *ACS 0-1*: this health state represents the first year after an ACS (i.e. UA or MI) event.
- *ACS post*: this health state represents subsequent years after an ACS (i.e. UA or MI) event.
- *Stroke 0-1*: this health state represents the first year after an acute cerebrovascular (i.e. ischaemic stroke) event.
- *Stroke post*: this health state represents subsequent years after an acute cerebrovascular (i.e. ischaemic stroke) event.
- *Stroke post and ACS 0-1*: this health state represents the first year after an ACS (i.e. UA or MI) event in patients that have already had at least one acute cerebrovascular (i.e. ischaemic stroke) event.
- *Stroke 0-1 and ACS post*: this health state represents the first year after an acute cerebrovascular (i.e. ischaemic stroke) event in patients that have already had at least one ACS (i.e. UA or MI) event.
- *Stroke post and ACS post*: this health state represents subsequent years (i.e. not the first year) after the last ACS or acute cerebrovascular event, in patients that have already had both types of events.
- *Dead*: absorbing state entered at patient death.

Figure 2. Markov health state structure



Health states 'Very high risk prim' and 'Revasc post' are not used for the modelling of the Swiss secondary prevention population of patients who have already had an ischaemic cardiac or cerebrovascular event. They are only used for the modelling of populations that consist of or include patients with no prior event. 'Revasc post' implies the patient has had a cardiac revascularization procedure that is not for the immediate, acute treatment of an ACS event. Further details on health state and event definitions are provided in the text. In the actual model, all health states apart from the death states are duplicated to cover patients who start versus do not start inclisiran treatment. When the inclisiran treatment uptake of prevalent patients is spread over several cycles, jumps from non-inclisiran to inclisiran health states are enabled. The last-mentioned aspects are only relevant for the 'world with inclisiran' strategy.
Key: ACS, acute coronary syndrome; CVD, cardiovascular disease; Revasc, revascularization.

The possible clinical events used by the model are slightly different from the primary health states. They include:

- *Stable*: indicates no event
- *Revasc*: indicates a cardiac revascularization procedure that is not an immediate, acute treatment of an ACS episode.
- *UA*: indicates a non-fatal ACS episode that meets the definition of UA.
- *MI*: indicates a non-fatal ACS episode that meets the definition of MI.
- *Stroke*: indicates a non-fatal, acute cerebrovascular (i.e. ischaemic stroke) event.
- *Death cardiovasc*: death from a cardiovascular cause.
- *Death other*: death from a non-cardiovascular cause. The distinction between cardiovascular and non-cardiovascular causes of death is mainly for reporting purposes.

Patients' transitions between health states depend on the prior health state and the event occurring (Figure 2). For example, a patient who is in the *Revasc* health state and has no event (*Stable*) or a *Revasc* event remains in the *Revasc* health state. If such a patient has a *UA* or *MI* event, he/she transitions to the *ACS 0-1* health state. A patient in the *ACS 0-1* health state that has no event (*Stable*) transitions to the *ACS post* health state. In case of an additional *UA* or *MI* event, he/she remains in the *ACS 0-1* health state. In case of a *Stroke* event, he/she transitions to the *Stroke 0-1 and post ACS* health state, etc. Thus, all patients can have multiple events, also of the same type.

Entry into the model is possible through several health states, namely *Very high risk prim*, *Revasc post*, *ACS 0-1*, *ACS post*, *Stroke 0-1* and *Stroke post*. Patients without a prior ischaemic cardiac or cerebrovascular event would enter in the two first-mentioned health states. Patients forming part of the prevalent population would typically enter in the *ACS post* or *Stroke post* health states, incident patients in the *ACS 0-1* or *Stroke 0-1* health states. Given an expectation of lack of granular data, we did not implement an option to directly enter the model in the health states representing both a current/recent ischaemic cardiac and cerebrovascular event. For the same reason, the distribution of health states at model entry is assumed to be the same for all prevalent, and the same for all incident patients, irrespective of age, sex or LDL-c category.

In the 'world with inclisiran' strategy, patients starting inclisiran treatment versus not need to be distinguished. Therefore, all health states apart from *Dead* are present in duplicate, representing patients who have started inclisiran treatment versus not. Of note, in some scenarios, inclisiran treatment may end due to limited persistence or age. In such situations, patients do not return to the health states indicating that inclisiran treatment has not started. Instead, the consequences of ending inclisiran treatment (for simplicity, we assume no costs any more and no effect any more) are implemented using formulae. To reduce complexity, the duplication of health states described here is not shown in Figure 2.

In most cases, it is decided at model entry whether a patient entering the 'world with inclisiran' strategy actually starts inclisiran treatment or not (depending on background LLT, LDL-c category, treatment uptake). However, as described above, the start of inclisiran treatment of

prevalent patients can be spread over several years. In order to achieve this, prevalent patients that have not started inclisiran treatment can jump to the set of health states representing that inclisiran treatment has started, as a function of assumed treatment uptake and number of years over which the uptake is spread. This is also not shown in Figure 2.

Within the described model, a standard approach to half-cycle correction could generate implausible results at least under some circumstances, namely when analyses are run over short time horizons for the purpose of burden of disease and budget impact analysis. In addition, the costs of inclisiran treatment are not distributed linearly over time, due to more dense dosing at treatment start (i.e., first dose at day 0, second dose at day 90, and then every half year). Tailored-to-purpose formulae were implemented to consider this and ensure correct behaviour of the model in the sense that events occur at mid-cycle on average and costs are accrued accordingly. The model also allows assuming either that all patients are at risk and take up treatment immediately at model entry (as would typically be assumed in a standard cost-effectiveness analysis), or that model entry and treatment uptake is spread over the patients' year of model entry, assuming model entry at mid-cycle on average.

Approach to transition probabilities in the 'world without inclisiran'

Event occurrence in the model is steered by transition probabilities. Given expected unavailability of transition probabilities directly valid for the Swiss target populations addressed, a nine-step approach was implemented to make transition probabilities from other sources usable. The first two steps are performed outside the dynamic population model, the subsequent ones directly in the model.

- *Step 1*: upon identification of a suitable set of transition probabilities TP_0, the average age, average LDL-c level, and proportion of diabetes patient of the underlying study population are identified. Some sources may provide separate sets of transition probabilities for patients with and without diabetes, in which case both sets are retrieved
- *Step 2*: in case separate sets of transition probabilities are available for patients with and without diabetes, weighted averages are calculated, using the proportion of diabetes patients in the target population of a given analysis (e.g. Swiss secondary prevention patients). This leads to the set of transition probabilities TP_1. (If there are no separate sets available, the proportion of diabetes patients in the originator population of the transition probabilities and in the target population of the analysis are compared and any related issues discussed.)
- *Step 3*: the transition probabilities are converted to rates as a basis for multiplication with hazard ratios in the next two steps.
- *Step 4*: the transition probabilities are adjusted to the LDL-c level in the target population of the analysis, based on published rate ratios per 1 mmol/L LDL-c change (see section 5.3) and by assuming a log-linear relationship [9, 10]. The formula is as follows:

$$R_{2i} = R_{1i} * RR_i^{LDL_1 - LDL_2}$$

where:

  - $\mathbf{LDL_1}$ is the LDL-c level (in mmol/L) in the source population from which the transition probabilities originate

- $\mathbf{LDL_2}$ is the LDL-c level (in mmol/L) in the Swiss target population
- $\mathbf{RR_i}$ is the rate ratio (RR) per unit change in LDL-c for event **i** based on [10]
- $\mathbf{R_{1i}}$ is the 1-year rate for experiencing event **i** at the LDL-c level $\mathbf{LDL_1}$ (resulting from the conversion of TP_1 into a rate)
- $\mathbf{R_{2i}}$ is the 1-year rate for experiencing event **i** at the LDL-c level $\mathbf{LDL_2}$

The described conversion is performed separately in each of the sub-populations covered by the dynamic population model

- *Step 5*: the rates are multiplied with factors interpreted as hazard ratios to adjust the event occurrence to what can be expected for the different age groups, i.e. to consider that the rate ratios calculated in the previous step cannot be uniformly applied to all age groups. Two alternative approaches to this are offered by the model, (a) the use of a table with the possibility to use a separate factor for each relevant event type and age-sex group (henceforward: Swiss age adjustment factors) and (b) the use of the hazard ratios per one year age difference reported by Wilson et al. [11]. In both approaches, the multiplication factors are centred around the average age of the source population of the transition probabilities, i.e. they are 1 for the respective age group. The reason to include approach (a) was that in our dynamic population model, a large number of patients may be included at the borders of the relevant age range (from age 40 to very old), whereas in a standard cohort-based cost-effectiveness model in the cardiovascular field, patients typically enter at an average age of around 60-70 years. We considered that the Wilson adjustment may become less reliable at the borders of the age range. (For further details and actual parameter values used, please see section 5.3.)
- *Step 6*: under the notion that the event rates adjusted in *step 5* represent a population average, *step 5* should not affect the overall occurrence of events in the modelled population. In light of this a first set of calibration factors is introduced to keep the overall event occurrence constant (i.e. when run over a year, this step ensures that the model produces the same number of events as if the rates resulting from *step 4* were directly used, albeit with an adjusted age distribution).
- *Step 7*: if the model is set to assume the model entry of patients at mid-cycle on average, the event rates are halved for patients newly entering the model.
- *Step 8*: the event rates resulting from the previous steps are converted back to set of transition probabilities TP_2.
- *Step 9*: the resulting event numbers per year are calibrated to event numbers expected in the Swiss target population of the analysis, by applying a second set of calibration factors. The need for this step arises because the use of transition probabilities/event rates from other geographies may not directly lead to suitable estimates of Swiss event numbers due to differences in epidemiology and medical practice (e.g. frequency of use of revascularization procedures). It leads to transition probabilities $TP_{2calibrated}$.

Treatment effect: approach to transition probabilities in the 'world with inclisiran'

The impact of inclisiran is modelled based on its impact on LDL-c. In patients on inclisiran, the relative LDL-c reduction observed in clinical trials (see section 5.4) is applied. Transition probabilities $TP_{2calibrated}$ are adjusted based on the resulting absolute LDL-c difference between

the LDL-c level under background LLT in the target population (above: $\mathbf{LDL_2}$) and the resulting LDL-c level under additional inclisiran treatment ($\mathbf{LDL_3}$). This is achieved by applying the same formula as above, that now takes the following form.

$$R_{3icalibrated} = R_{2icalibrated} * RR_i^{LDL_2-LDL_3}$$

As before, calculations are performed for each of the 88 sub-populations in the model, that may have different $\mathbf{LDL_2}$ values. Of course, conversion to rates and back-conversion to transition probabilities is again used. The resulting probabilities $TP_{3calibrated}$ are applied to all patients under inclisiran treatment. In the base case, the treatment effect is assumed to start with the start of the treatment, and end with the end of the treatment, where applicable (typically in scenario analyses). Alternative settings (typically used in scenario analyses) allow to reduce the $\mathbf{RR_i}$ (i.e. make them closer to 1) in the first year of treatment to reflect reduced treatment effectiveness early after treatment start, and to apply a counter-correction in subsequent years (as longer-term average effect estimates may be underestimated due to the inclusion of year 1). For further details, see section sub-section *Model settings* and section 5.4.

Modelling of utilities, QALYs and costs
Detailed information on the modelling of utilities, QALYs and costs is available from sections 5.5 and 5.6, describing input parameter values and sources. A few general principles need to be addressed here.

The utility for any given CVD-related health state is calculated by determining the expected age- and sex-specific utility in the general population and by applying a multiplication factor for the relevant health state. As the available multiplication factors may make reference to persons free from CVD, as opposed to the general population, an additional factor can be used to inflate general population utilities to the utility levels of persons free from CVD, before the CVD-related multiplication factors are applied. In health states where patients have had events of different types and where there is no specific utility multiplier for the relevant combination of events available, the strongest of the available effects on utility is assumed. Taking the example of patients who have had an ACS and a stroke, if stroke has a stronger impact on utility than ACS, the impact of stroke is assumed.

When patients have an acute event, and have already had an earlier event of the same or a different type, the cost of the acute event is assumed (e.g. the cost of a non-fatal ACS event, irrespective of whether there was a prior ACS event, stroke, or no prior event). In the *Stroke post and ACS post* health state, the higher of the *ACS post* and *Stroke post* unit costs is used; 50% are counted as ACS costs and 50% as stroke costs.

The ongoing long-term costs (i.e. costs of health states *ACS post* and *Stroke post*) of ACS events and stroke events that occurred before the model entry of patients are counted in addition to the costs of new events, from the time point of model entry onwards, consistent with the notion that decision-analytic models should consider all costs of the condition of interest [12].

Model outputs

The model generates the outputs listed in Table 2, which can either be used directly for reporting cost-effectiveness, burden of disease and budget impact results, or may require a limited degree of post-processing. In particular, given that the model uses absolute numbers of patients rather than fractions of patient cohorts, the reported cost, QALY etc. results are added up across all patients and do not immediately represent per-person values.

Table 2. Model outputs[1]

Category	Population/inclisiran use	Costs	Effectiveness	Burden of disease
	Total number of patients entered	Total costs	QALYs	Number of revascularizations
	Total number of patients treated with inclisiran	Costs of inclisiran (including administration)	Life years	Number of non-fatal UAs, MIs
	Number of patients treated with inclisiran in a given cycle	Costs of background lipid-lowering treatment		Number of non-fatal strokes
	Total years of inclisiran treatment	Costs of revascularizations		Number of cardiovascular deaths
	Average age at model entry (for validation purposes)	Costs of non-fatal ACS		Number of deaths
	Average age at cardiovascular death (for validation purposes)	Costs of non-fatal stroke		
	Average age at death (for validation purposes)	Costs of fatal cardiovascular events		

1 Additional outputs could be made available for specific populations, e.g. costs of LDL apheresis.
Key: MI, myocardial infarction; QALYs, quality-adjusted life years; UA, unstable angina.

Besides deterministic sensitivity and scenario analysis, the model allows to perform probabilistic sensitivity analysis (PSA), with outputs in the form of cost-effectiveness scatterplots and cost-effectiveness acceptability curves. (Tornado diagrams depicting the results of deterministic sensitivity analysis are best prepared outside the main model.)

Model settings

The model allows to make the following settings using switch variables. The numbers in the variable names indicate the allowable integer values; descriptions directly in the model explain what each allowable value means. (TreeAge does not necessarily produce error messages if other values are used but the results cannot be assumed to be meaningful.) The most important switch variables are the following:

- *sw01_age_death*: impacts the reporting behaviour of the model: age at death is either assessed for all deaths or for cardiovascular deaths only
- *sw01_age_incl_max*: if set to 1, a maximum age of inclisiran administration can be set using variable *v_age_incl_max* (e.g. in scenario analyses)
- *sw01_corr_time*: if set to 1, a short-term downwards and long-term upwards correction of the effect of inclisiran can be set using variables *eff_incl_init* and *eff_incl_subs* (see description above; e.g. in scenario analyses). Should not be used in combination with *sw01_del_upt*
- *sw01_del_upt*: if set to 1, the inclisiran treatment uptake of prevalent patients can be spread over several years using variable *v_yrs_del_upt* (see description above; important

for burden of disease and budget impact analyses). Of note, this option cannot be reliably used when *sw01_corr_time* or *sw01_prop_pers* are set to 1. It also implies a need for some post-processing of model results outside TreeAge in order to achieve correct calculation of inclisiran costs in a given year (if *sw01_imm_start* is set to 1) and years of inclisiran treatment in a given year (if *sw01_imm_start* is set to 0)

- *sw01_full_upt*: a convenience function. If set to 1, all patients with an eligible background lipid-lowering therapy and LDL-c level are assumed to start inclisiran treatment, overruling treatment uptake assumptions. (The treatment uptake of prevalent patients can still be spread over several years using *sw01_del_upt*)
- *sw01_imm_start*: if set to 1, patients entering the model in a given cycle are not assumed to enter on average at mid-cycle, but immediately at the beginning of the cycle. This setting should usually be used when the model is run as a cost-effectiveness model. With respect to this, no difference is made between prevalent and incident patients, to avoid an additional layer of model complexity. Also see the entry on *sw01_del_upt, above*
- *sw01_PSA*: needs to be set to 1 before PSA is run
- *sw01_PSA_RRs*: if set to 1, includes variation of the rate ratios of event occurrence, per 1 mmol/L LDL-c change, in the PSA. If the approach to the age adjustment of the rate ratios of event occurrence based on Wilson et al. is used, the involved hazard ratios are also varied based on their confidence intervals (see section 5.3) [11]
- *sw01_trial_mim*: if set to 1, the model can be run such that a trial-based cost-effectiveness analysis with average cohort characteristics can be approximated, using the values entered in variables *v_trial_age*, *v_trial_fem* and *v_trial_LDLc*. This is mostly relevant for validation purposes
- *sw02_prop_pers*: if set to 1 or 2, allows to model limited persistence with inclisiran treatment, e.g. decreasing over time, in combination with table *t_prop_pers* (in scenario analyses; see section 4.6.2). Should not be used in combination with *sw01_del_upt*
- *sw05_incl_yrsnum*: if set to zero, total years of inclisiran treatment are reported. If set to an integer value above 1, the number of patients treated with inclisiran in the respective cycle/year is reported
- *sw13_anal_type*: switches between cost-effectiveness, burden of disease and budget impact analysis. If set to 3, implying budget impact analysis, discounting of costs and effects is automatically set to zero
- *sw13_cali_mode*: makes the final calibration step (see sub-section *Approach to transition probabilities in the 'world without inclisiran'*, above) variable-based or table-based (allowing for age- and sex-specific calibration factors), or turns it off
- *sw13_trial_ORION*: defines which ORION trial should be used as the basis for modelling LDL-c reduction under inclisiran treatment; the default value of 1 implies ORION 10. Also see section 5.4)
- *sw13_u_no_CVD*: switches inflation from general population average utility to general population with no CVD utility on (default value of 1), or turns if off for patients without a prior event, or totally
- *sw14_LDL_thr*: defines the LDL-c threshold under background lipid-lowering treatment above which patients are eligible for treatment with inclisiran: any, ≥1.4 mmol/L, ≥1.8 mmol/L, ≥2.6 mmol/L

- *sw15_age_type*: defines the type of age correction of event rates (based on a table with the possibility to use a separate factor for each relevant event type and age-sex group (with a correction to keep overall event rates stable); using hazard ratios per one year age difference reported by Wilson et al. [11] (with a correction to keep overall event rates stable); as before but without a correction to keep overall event rates stable, or turns it off
- *sw1910_LDLc_LLT*: defines the background lipid-lowering treatments for which eligibility for treatment with inclisiran is assumed

Model assumptions

The model reported here, as all decision-analytic models, is a simplification of reality. A series of assumptions needed to be made. Key assumptions are listed here.

- The characteristics (e.g. mean age and distribution of LDL-c categories within age-sex groups, proportion with diabetes) of patients entering the model remain stable over time
- In the absence of detailed information on background lipid-lowering treatments and the reasons behind selecting these, we had to implicitly assume that all patients receiving any background LLT, according to real-world data (see section 5.2), are on their maximum tolerated treatment. This assumption does not influence the actual model results but implies that no still unused, suitable treatment options are available for the patients. The impact of this relatively strong assumption was assessed by restricting the initiation of inclisiran treatment to patients with more intensive types of background lipid-lowering treatments (see sections 3 and 5.2)
- Events per model cycle (i.e. year) were restricted to one, under the assumption that this would affect the distribution of events across patients but not the overall numbers of events and resulting model outcomes. (This assumption is frequently made in Markov cohort models)
- The assumed relationship between LDL-c reduction and CVD event occurrence, based on the CTTC 2019 meta-analysis [10], holds for inclisiran.
- The effectiveness of inclisiran does not change over time (base case assumption); see sub-section *Treatment effect: approach to transition probabilities in the 'world with inclisiran'*, above, and section 5.4)
- After the initiation of inclisiran treatment, persistence is 100% (base case assumption)
- Patients are treated until death (base case assumption)
- After end of inclisiran treatment (applicable in scenario analyses) the costs and effects of inclisiran treatment end immediately
- Patients die at age 100 at the latest

Technical platform used, technical limitations and alternatives

The model structure has been implemented in the specialized decision-analytic software TreeAge [13], as we judged this be the most time-efficient solution and the only one feasible within the time horizon of the project. TreeAge has particular advantages in accommodating dynamic population features and conveniently offering tunnel health states to steer the behaviour of the model with respect to patients entering a health state at different points in time. Summation nodes allow to automatically combine the results of different sub-Markov models/sub-populations. Finally, the option to use clones copies of parts of the model made the working with the 88 sub-Markov models well feasible.

Given the implementation platform used and time constraints, the model has a few technical limitations that are noteworthy:

- Uptake of inclisiran treatment spread over several years is only possible for patients that are prevalent patients at the start of the model, not for patients entering the model in subsequent cycles/years. (For the sake of consistency, incident patient entering the model in the first year are treated as patients entering the model in subsequent years)
- The delayed treatment uptake of prevalent patients is only possible in equal steps. For example, if 25% of the prevalent population are assumed to initiate treatment with inclisiran, with a spread of 5 years, then 5% of the prevalent population will initiate treatment in each of years 1-5, minus the patients that die earlier, as patients are assumed to be immediately at risk when they enter the model
- The functionality to spread the treatment uptake of prevalent patients should not be combined with assumptions on changing treatment effectiveness over time (i.e., lower in the first year and higher later, see sub-section *Treatment effect: approach to transition probabilities in the 'world with inclisiran'*, above) or assumptions of decreasing persistence as a function of time since treatment initiation (see sub-section *Model settings*, above). Results might be not valid
- When the functionality to spread the treatment uptake of prevalent patients is used, some post-processing of model results outside TreeAge is required in order to achieve correct calculation of inclisiran costs in a given year (if *sw01_imm_start* is set to 1) and years of inclisiran treatment in a given year (if *sw01_imm_start* is set to 0). (Correct totals over the entire time horizon of any given model run are still generated within TreeAge as long as the treatment uptake of prevalent patients falls within that time horizon, in full)
- The output of the model is only easily accessible on a summary basis, i.e. across the time horizon used, not by sub-population and by cycle. This is particularly relevant for budget impact analysis where results are usually reported year-per-year. Here, the model needs to be run, e.g., for 1 to 5 years, separately, and the results for a given year are achieved by subtraction. For example, the results for year 3 are generated by subtracting the results from the run over 2 years from the results from the run over 3 years. (The number of patients treated in a given year is extracted separately, considering patients ending treatment due to death etc.)

For technical and performance reasons, we judge building an equivalent dynamic population model in Microsoft Excel® as not practically feasible. It would however make sense to co-program the model in a statistical software package (i.e., R or Stata). This would improve the model's accessibility, as TreeAge is not widely available. In addition, the increased flexibility of working with such packages would allow to overcome the above-described, remaining limitations in terms of model mechanics, flexibility of possible scenarios and by-cycle reporting of outcomes.

Implementation as a microsimulation model would have been an alternative with some advantages but also disadvantages. Our main reasons for deciding against a microsimulation approach were substantial processing (i.e. many individuals need to be run through the model, sequentially) and post-processing times and large number of reporting variables ('tracker variables') required to summarize and cumulate individual outcomes over time. In our

experience, these limitations can become particularly problematic where a large number of sensitivity and scenario analyses is required, and for the running of PSA.

4.5 Planned main analyses

4.5.1 Secondary prevention population

The key settings related to the implementation of base-case analyses covering cost-effectiveness, burden of disease and budget impact are summarized below.

Cost-effectiveness analysis

- Only prevalent patients and year 1 (= cycle 0) incident patients are modelled
- Patients are deemed eligible for inclisiran treatment if they have any background LLT and exceed the LDL-c cut-off of 1.8 mmol/L
- Full uptake is assumed for eligible patients
- For those initiating inclisiran treatment, immediate treatment start is assumed, i.e. at the beginning of year 1 (=cycle 0). Consistent with this, immediate at-risk status for cardiovascular events is assumed for all patients entering the model.
- Swiss age adjustment factors derived are applied for age adjustment of event rates
- [redacted]
- Life-long time horizon is implemented by running the model for 60 cycles and assuming/forcing death at age 100
- Costs and effects are discounted at 3%

Burden of disease analysis

- Subsequent-year incident patients enter the model in addition to prevalent patients and year 1 (= cycle 0) incident patients
- Eligibility for inclisiran treatment as in the cost-effectiveness base case
- Treatment uptake probabilities as in the budget impact base case (see below). For years 5 to 10, the year 5 values are carried forward
- For those initiating inclisiran treatment, treatment start is assumed to be at mid-year on average, in the year of treatment initiation. At-risk status for cardiovascular events is assumed to be at mid-year in the year of model entry, for all patients entering the model
- Run over 10 years
- Effects/impact on burden of disease is reported undiscounted

Budget impact analysis

- Subsequent-year incident patients enter the model in addition to prevalent patients and year 1 (= cycle 0) incident patients
- Eligibility for inclisiran treatment as in the cost-effectiveness base case
- Treatment uptake probabilities derived to match the patient number uptake projections provided by Novartis

- For those initiating inclisiran treatment, treatment start is assumed to be at mid-year on average, in the year of treatment initiation. At-risk status for cardiovascular events is assumed to be at mid-year in the year of model entry, for all patients entering the model
- Run over 5 years and reported as yearly and cumulative outcomes
- Budget impact is reported undiscounted

4.5.2 Other populations of interest

For other populations of interest, besides the secondary prevention population, data were sparse and data collection could not take the level of thoroughness used for the secondary prevention population. We performed approximate cost-effectiveness analyses as follows:

Full very high risk population
Cost-effectiveness in the full very high risk population, comprised of secondary prevention patients (including those with PAD that we did not consider in our main analysis) and very high risk patients that have not yet had a prior cardiovascular event, was approximated with the following settings:

- Patient numbers were inflated with the ratio of all very high risk to secondary prevention patients in the Family medicine ICPC Research using Electronic medical records (FIRE) database (see section 5.2)
- The characteristics of the full FIRE very high risk population were used
- The health state distribution at model entry was adapted to reflect the proportion of very high risk patients that have not yet had a prior cardiovascular event, from FIRE
- Transition probabilities were updated to reflect the proportion of patients with diabetes in the full FIRE very high risk population (45.2% as opposed to 26.6% in the secondary prevention population)

Peripheral artery disease
We had no sufficient data to perform an analysis of this population. Of note, the secondary prevention patients in FIRE comprised 13.2% of patients with a diagnosis of PAD (together with or without other cardiovascular diagnoses).

Heterozygous familial hypercholesterolaemia, primary prevention:
An approximate cost-effectiveness analysis was performed for a single cohort with a single average age and LDL-c level. Based on Clinical Practice Research Datalink (CPRD) data [14], we used weighted averages from 97.6% HeFH patients without diabetes and 2.4% with diabetes to estimate mean age 52.6 years, proportion of women 63.9% and LDL-c level under background LLT of 4.75 mmol/L. We assumed no low-density lipoprotein (LDL) apheresis use, consistent with CPRD population data. Comparison with PCSK9 inhibitors other than inclisiran was not considered. CPRD-based transition probabilities were adjusted for the above mentioned proportion of diabetes patients, and CPRD-based 'starting' transition probabilities (see section 5.3) for the primary prevention HeFH population were used to enter patients into the model through the *Very high risk prim* health state.

Heterozygous familial hypercholesterolaemia, secondary prevention:
The same approach and settings as above were used. Patients were entered into the model either using CPRD-based 'starting' transition probabilities for the secondary prevention HeFH population (see section 5.3) and the *Very high risk prim* health state, or through the *ACS post* health state, with the standard CPRD-based, diabetes adjusted transition probabilities for this health state. (In this case also, the LDL-c level of the HeFH population under background LLT is automatically considered and leads to higher event risks in the model.)

4.6 Approaches to uncertainty analyses

Uncertainty analyses were only performed for the main population of interest, i.e. secondary prevention population, not for the other population of interest given the very approximate character of these analyses. For the cost-effectiveness part, uncertainty analyses comprised univariate sensitivity analysis, a range of scenario analyses and PSA. Difficult to model uncertainty in the occurrence of clinical events in the 'word without inclisiran' strategy via standard sensitivity analysis (many transition probabilities; strong influence of calibration), we added related scenario analyses. In particular, scenario analyses using different calibration targets were additionally performed (see section 4.6.2). For the burden of disease and budget impact analyses, uncertainty analyses were restricted to scenario analyses, typically a suitable subset of those performed for the cost-effectiveness part.

4.6.1 Univariate sensitivity analysis

Univariate sensitivity analyses were performed to evaluate the potential impact of uncertainty around the major parameters on modelled estimates. Where the 95% confidence intervals were available, the base case parameter value was set to its upper and lower confidence limits. Where not available, suitable ranges of variation were defined as detailed below. Base case parameter values and ranges are reported in respective sections covering model inputs in section 5.

- Relative events rates per 1 mmol/L LDL-c change were varied by their confidence intervals
- The LDL-c reduction achieved with inclisiran was varied by its confidence interval
- In the case of base case utilities and utility multipliers reflecting the utility impact of cardiovascular events the difference from one was varied by ±30%. For example, 0.6 varied from 0.48-0.72

[redacted]

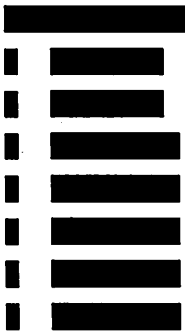
In some cases, it may be illustrative to (only or additionally) vary some parameters jointly. This will be stated in the results section. Results of the sensitivity analysis are presented in tabular format and as Tornado diagrams.

4.6.2 Scenario analyses

We performed a wide range of scenario analyses to capture the impact of structural assumptions and possibilities that could not be sufficiently captured in the univariate, deterministic sensitivity analysis and PSA. The burden of disease and budget impact analyses relied on scenario analyses only. The elements varied are listed below. All details, including the alternative assumptions on parameter values used, are available from Table 19, Table 20, Table 22 and Table 24 in the results section.

Cost-effectiveness analysis scenarios

We ran the model with different price points reflecting the price of one dose of inclisiran [redacted]



We considered different requirements regarding background LLT (versus any LLT treatment in the base case):

- High intensity statins
- High intensity statins plus ezetimibe

We assumed different LDL-c levels for eligibility (versus eligibility at LDL-c ≥1.8 mmol/L in the base case), in combination with all the price points:

- Eligibility if LDL-c level ≥1.4 mmol/L
- Eligibility if LDL-c level ≥2.6 mmol/L

We modelled a 'mixed' uptake of inclisiran by applying the treatment uptake assumptions provided by Novartis for the LDL-c level ≥1.8 to <2.6 mmol/L and LDL-c level ≥2.6 mmol/L groups.

We modified the use and effect of inclisiran, in the 'world with inclisiran' in several, additional ways:

- The effect of inclisiran in year 1 was reduced by 50% by appropriately increasing that rate ratios of events per 1 mmol/L LDL-c reduction [15]
- As before but the effect was counter-corrected by multiplying the rate ratios by 0.95, from the second year of treatment onwards [15]
- We assumed restricted persistence, i.e. that a certain proportion of patients would end inclisiran treatment after a certain time
- We assumed a maximum age (85 years) for inclisiran treatment

- As we had much better detail for the full FIRE very high risk population (including secondary prevention and high risk primary prevention patients) than for the secondary prevention population alone, we alternatively used the characteristics of the full very high risk population (comprising information an average age, distribution of LDL-c level groups, mean LDL-c level per group, LLT) instead of the characteristics of the secondary prevention population
- Utilities: the correction factor used to adapt background general population utilities to the utilities of persons with no CVD was alternatively removed

We modified event occurrence in the 'world without inclisiran' as follows:

- Calibration targets reflecting expected Swiss event number in the secondary prevention populations were varied by ±30%: all jointly; only revascularizations; only non-fatal events excluding revascularizations; only fatal events
- Instead of the Swiss age adjustment factors the adjustment hazard ratios by Wilson et al. were used (hazard ratio per 1 year age difference, 1.03 for non-fatal events and 1.05 for fatal events) [11]

Additional scenario analyses:

- As the model covers the costs of ischaemic cardiac and cerebrovascular events that occurred prior to entry into the model, we intended to gain an understanding of the impact of this feature, and halved the costs of the *ACS post* and *Stroke post* health states by half

Discounting

- The discounting of costs and effects was set to 0% and 5%

Burden of disease analysis scenarios

As in the cost-effectiveness analysis, we considered different requirements regarding background LLT (versus any LLT treatment in the base case):

- High intensity statins
- High intensity statins plus ezetimibe

We restricted the LDL-c level for eligibility to ≥2.6 mmol/L (versus eligibility at LDL-c ≥1.8 mmol/L in the base case).

In a plausible subset of the scenario analyses performed on the cost-effectiveness analysis, and with one addition, we modified the use and effect of inclisiran, in the 'world with inclisiran', in the following ways:

- We modified the treatment effect of inclisiran (reduction of LDL-c) based on the upper and lower confidence limit of the effect estimate. (In the uncertainty analyses of the cost-effectiveness results, this forms part of the sensitivity analyses)
- We assumed a maximum age (85 years) for inclisiran treatment

We modified event occurrence in the 'world without inclisiran' as follows:

- Calibration targets reflecting expected yearly Swiss event numbers in the secondary prevention population in the 'world without inclisiran' were varied by ±30%: all jointly; only revascularizations; only non-fatal events excluding revascularizations; only fatal events
- Instead of the Swiss age adjustment factors the adjustment hazard ratios by Wilson et al. were used (hazard ratio per 1 year age difference, 1.03 for non-fatal events and 1.05 for fatal events) [11]

In order to achieve an understanding of the theoretically possible, maximum impact of inclisiran, we assumed full uptake in a series of scenarios:

- Eligibility if LDL-c level ≥1.4 mmol/L
- Eligibility if LDL-c level ≥1.8 mmol/L
- Eligibility if LDL-c level ≥2.6 mmol/L

Budget impact analysis scenarios

We ran the model with different price points per inclisiran dose [redacted]

[redacted]

As in the cost-effectiveness analysis, we considered different requirements regarding background lipid-lowering therapy (versus any treatment in the base case):

- High intensity statins
- High intensity statins plus ezetimibe

We restricted the LDL-c level for eligibility to ≥2.6 mmol/L (versus eligibility at LDL-c ≥1.8 mmol/L in the base case).

As in the cost-effectiveness analysis, we modified event occurrence in the 'world without inclisiran' as follows:

- Calibration targets reflecting expected yearly Swiss event numbers in the secondary prevention population in the 'world without inclisiran' were varied by ±30%: all jointly; only revascularizations; only non-fatal events excluding revascularizations; only fatal events
- Instead of the Swiss age adjustment factors the adjustment hazard ratios by Wilson et al. were used (hazard ratio per 1 year age difference, 1.03 for non-fatal events and 1.05 for fatal events) [11]

4.6.3 Probabilistic sensitivity analysis

Joint parameter uncertainty was further explored in the PSA. In this analysis parameters varied in the univariate sensitivity analysis were assigned distributions from which parameter values were simultaneously sampled. The sampling was iterated 1'000 times. The resulting impact

and cost estimates from each iteration were recorded and plotted on the cost-effectiveness plane. These outputs were then used to generate the cost-effectiveness acceptability curve.

The relative event rates per 1 mmol/L LDL-c change influence events and outcomes in both the comparator and intervention strategies. The former is because these relative rates are not only used to model the inclisiran effect but also to adapt the health state transition probabilities to target population LDL-c levels. Hence two sets of PSA estimates were generated: first allowing the parameter to vary along with other model inputs and second - keeping the parameter fixed at its base case value while varying all other model inputs.

5. Model inputs

5.1 Overview of input parameter sources and assumptions

Section 5.1 details data requirements for the cost-effectiveness, burden of disease, and budget impact analyses covered by this report. Swiss data were available for many relevant model input parameters. Nonetheless, populating the model presented substantial challenges, particularly, with respect to distinguishing events occurring in the primary and the secondary prevention populations. In addition, we could not identify or generate Swiss rates, risks or transition probabilities for cardiovascular events, overall or in the secondary prevention population. Further details on the data challenges and ways in which these were mitigated are found in the subsequent sections.

Focusing on the primary population of interest, the following types of data were required for some or all of the analyses:

- Size and characteristics of the real-world Swiss secondary prevention population.
- Clinical event risks or rates in the "world without inclisiran" including CVD and non-CVD mortality
- Clinical event risks or rates in the "world with inclisiran" Utility-related
- Data on medical resource use
- Unit costs
- Assumptions on the future treatment use/treatment uptake of inclisiran

Details on the available data, sources used, and model input parameters finally used, are summarised in the next chapters.

5.2 Epidemiological data

Model inputs related to the epidemiology of CVD in Switzerland cover the size of the entering prevalent and incident cohorts, their distribution across the health states at model entry, and population characteristics related to sex, age, LDL-c levels, background LLT, and comorbidities. These data were primarily sourced from the Global Burden of Disease (GBD)

project [16], FIRE database [17], and Medical Statistics of Hospitals (MedStat) [18] (see Table 3 for a brief overview of these and other data that informed the epidemiological parameters). FIRE and MedStat data were particularly useful in defining and characterizing the secondary prevention population. Still, it was often necessary to combine data from multiple sources to derive the necessary metric. While we aimed to stay consistent in defining the target population and CVD outcomes, differences in case definitions between the data sources implied a risk of inconsistencies (Table 4). Uncertainties around true parameter values, including case definitions, were evaluated in the sensitivity analyses documented in section 7.1.3 of the report.

Table 3. Brief summary of epidemiological data sources used and description

Name full	Name abbreviated	Ref	Year	Description	Parameters sourced	Availability
The Global Burden of Disease project	GBD	[16]	2009-2018	A global study that draws on a systematic workflow integrating country and global data to generate modelled estimates of mortality, cause of death, incidence, prevalence and duration of illness/disability for 333 causes of global health relevance and multiple sequelae. Annual estimates are produced by country, age, and sex.	Incidence and prevalence of CVD events, population size	Available from the website
The Swiss Federal Statistical Office's Medical Statistics of Hospitals database	MedStat	[19]	2018	A database of hospital statistics covering most in-patient admissions in Switzerland. Allows linkage of individual records within the database. Covers causes, length and outcomes of hospitalizations along with some basic demographic information and hospital data.	Incidence of CVD events, cases, fraction of non-fatal events in secondary prevention population	Aggregate tabulations from the database provided on request to the project
The Family medicine ICPC Research using Electronic medical records database	FIRE	[17]	2018-2020[1]	A database of routine medical data with diagnoses recorded according to the International Classification of Primary Care.	Characteristics of secondary prevention and very-high risk populations with no prior CVD with respect to sex, age, LDL-c, LLT, diabetes	Aggregate tabulations from the database provided on request to the project
The World Health Organization Mortality database	WHO Mortality Database	[20]	2015-2016	A compilation of mortality data as reported annually by Member States from their civil registration systems. Yearly counts of deaths by ICD-10 code are given by country, age, and sex.	CVD and all cause mortality	Available from the website

The National Registry of Acute Myocardial Infarction in Switzerland	AMIS-plus	[21]	2015-2019	The registry collects and analyses data on patients with acute myocardial infarction in the pre-admission, hospital and follow-up phases.	CVD mortality	Aggregate tabulations from the database provided on request to the project
The Swiss Health Observatory	Obsan	[22]	2018	A project that collates available health information in Switzerland. Mortality data by cause of death from MedStat.	CVD mortality	Available from the website
The Swiss Federal Statistical Office	SFSO	[23]	2018	Swiss national competence centre for official statistics covering the status and development of the population, economy and other areas.	Population	Available from the website
Clinical Practice Research Datalink	CPRD	[14]	2009-2019	A database linking the Hospital Episode Statistics (HES) admitted patient care and Office of National Statistics (ONS) datasets in the UK.	Transition probabilities	Unpublished report

Table 4. Description and ICD-10 codes by CVD outcome and data source

Outcome	GBD	MedStat	FIRE	WHO	AMIS Plus	Obsan
CVD	IHD+Isc stroke I20, I20.0-9, I21, I21.0-9, I22, I22.0-9, I23, I23.0-9, I24, I24.0-9, I25, I25.0-9,	MI+UA+Isc stroke I21, I21.0-9, I22, I22.0-9, I20.0, I63, I63.0-9	CVD wide G45, G45.0-9, I20, I20.0-9, I21, I21.0-9, I22, I22.0-9, I23, I23.0-9, I24, I24.0-9, I25, I25.0-9, I63, I63.0-9, I64, I65, I65.0-9, I66, I66.0-9	MI+UA+Isc stroke G45.0-9, I20.0-9, I21.0-9, I22.0-9, I23.0-9, I24.0-9, I25.0-9, I63.0-9, I64, I65.0-9, I66.0-9	MI, UA, PCI, CABG, cerebrovascular insult with few or no residuals as well as patients with TIA	
ACS	IHD I20, I20.0-9, I21, I21.0-9, I22, I22.0-9, I23, I23.0-9, I24, I24.0-9, I25, I25.0-9	MI+UA I21, I21.0-9, I22, I22.0-9, I20.0		MI+UA I21, I21.0-9, I22, I22.0-9, I20.0		
MI		MI I21, I21.0-9, I22, I22.0-9		MI I20.0		
UA		UA I20.0		UA I20.0		
Stroke	Isc stroke I63, I63.0-9	Isc stroke I63, I63.0-9		Isc stroke I63.0, I63.1-9		Stroke I60-I64

1 Average over the observation period.
Key: GBD, Global Burden of Disease; MedStat, Medical Statistics of Hospitals; FIRE, Family medicine ICPC Research using Electronic medical records; WHO, World Health Organization Mortality database; AMIS Plus, National Registry of Acute Myocardial Infarction; CVD, cardiovascular Disease; IHD, ischaemic heart disease; Isc stroke, ischaemic stroke; ACS, Acute Coronary Syndrome; TIA, transient ischaemic attack.

Reflecting that the epidemiology of CVD is concentrated in the older ages the analysis was restricted to adults aged 40 and above. Details on the derivation of specific model inputs along with reference values used in the base-case and sensitivity analyses are provided below.

Size of the prevalent and incident populations

The size of the prevalent population was based on the 2018 modelled estimates of CVD-related conditions from the GBD project. To better align estimates to the Swiss official population statistics [23], the number of prevalent cases were not taken as reported by GBD. Instead, we extracted and added the prevalence (in percent) of IHD and ischaemic stroke for each sex-age group and then applied these percentages to the Swiss sex-age population from the Swiss Federal Statistical Office (SFSO) [23]. It is one disadvantage of this strategy that it may over-estimate the true size of the secondary prevention population in Switzerland as prevalent patients might experience both IHD and stroke events and thus contribute to prevalence estimates for both conditions. The possible error in the estimated size of the prevalent cohort, which affects BI and BU results but not CE, was further covered by varying Swiss calibration targets by ±30% in the scenario analysis (see section 7.1.3.2).

The size of the incident population, defined here as patients with no prior CVD event that experienced either an MI or UA or an ischaemic stroke in the reference year (i.e. were new entries into the secondary prevention population), by sex and age (5-year age groups) was sourced from the MedStat data. Specifically, the number of incident cases was calculated by subtracting from the total number of people that experienced a CVD event in the reference year, (a) the number of people that had already had a prior CVD event and (b) the number of in-hospital CVD deaths among those with a prior CVD event. The occurrence of in-hospital death among those with a prior CVD event was approximated by assuming the same risk of in-hospital death in people with and without a prior CVD event, in the absence of more granular information.

For burden of disease and budget impact analyses the size of the incident population was projected forward for 10 years and 5 years, respectively, using the average annual growth rate of the incident CVD population estimated from GBD.

Table 5. Epidemiological parameters

Input Parameter(s)	Source	Derivation/assumption	Heterogeneity	Expected value and UI	Distribution
The number of prevalent cases in the secondary prevention	GBD, SFSO	Calculated by multiplying estimated prevalence from GBD by SFSO population by sex and age	Sex, age	See Appendix Table A 1, ±30%	NA
The number of incident cases in the secondary prevention	MedStat, GBD	Incident cases taken directly from MedStat, incidence in year 1 and later were projected based on average annual growth rates from GBD data (2009-2018)	Sex, age	See Appendix Table A 1, ±30%	NA
Health states at model entry	GBD	Distributions for prevalent and incoming incident cases derived by dividing the number of prevalent/incident cases for the respective outcome by the total number of prevalent/incident CVD cases		See Table 6, ±30%	NA
Characteristics of sub-cohorts	FIRE		Sex, age, LDL-c category, history of CVD	See Appendix Tables A 2-A 4, CVD + very high risk with no prior events, Very high risk with no prior events	NA

Key: GBD, Global Burden of Disease; SFSO, Swiss Federal Statistical Office; MedStat, Medical Statistics of Hospitals; FIRE, Family medicine ICPC Research using Electronic medical records; CVD, cardiovascular Disease; UI, uncertainty interval.

Health states at model entry

At model entry prevalent cases are distributed between the ACS post and Stroke post health states. The allocation fractions were estimated by dividing the total number of prevalent cases with the respective condition by the sum of prevalent cases with IHD and ischaemic stroke obtained directly from the GBD database.

Incident population entering the model were distributed between the first year ACS and first year stroke according to the MedStat data. For instance, the fraction of stroke entries in the incident population were calculated by dividing the total number of patients with no prior CVD who had a stroke, excluding those that died from their stroke in the hospital, by the sum of patients that had an ACS event or stroke in the reference year.

Table 6. Health states at model entry

Health state	Prevalent patients	Incident patients
Very high risk prim	0	0
Revasc post	0	0
ACS 0-1	0	0.566
ACS post	0.729	0
Stroke 0-1	0	0.434
Stroke post	0.271	0

Key: Very high risk prim, very high risk primary prevention (i.e. no prior CVD event); CVD, cardiovascular Disease; PAD, Peripheral Artery Disease; Revasc, cardiac revascularization; ACS, Acute Coronary Syndrome.

Population characteristics

Tabulations from the FIRE database formed the basis for the population characteristics. For each age (5-year bracket), sex, and LDL-c level category (<1.4 mmol/L, ≥1.4 to <1.8 mmol/L, ≥1.8 to <2.6 mmol/L, ≥2.6 mmol/L), the secondary prevention population was characterized with respect to:

- Average age
- Proportion of the age and sex cell in each of the LCL-c categories
- Average LDL-c level
- Proportion receiving any LLT
- Proportion on statin by intensity (low, moderate, high)
- Proportion on ezetimibe
- Proportion on both/either statin by intensity (low, moderate, high) and ezetimibe

For the secondary prevention population small sample sizes by the relevant strata limited data resolution. Patient characteristics along the dimensions described above were available only for broad age groupings 40-74 years and ≥75. These average values were extrapolated across all 5-year age and sex groups under and over 74, i.e. cells in the age group 65 to 69 and younger were assigned the same characteristics as those aged 70 to 74. Average age was assigned based on the mid-point of the interval.

5.3 Model inputs related to natural history of disease and mortality under standard of care treatment

Transition probabilities in the 'world without inclisiran' strategy

To model the transition probabilities from one state to another we used values generated by Novartis based on data from the CPRD [14]. These are currently pending scientific publication. We computed a weighted average of the transition probabilities for patients with diabetes and those without, according to the prevalence of diabetes in the Swiss secondary prevention population (26.6% according to FIRE data). The final values used for the general secondary prevention population are presented in Table 7. Table A 5 in the appendix shows the transition probabilities used for the full very high risk population, comprised of secondary prevention patients and very high risk patients who have not yet experienced a CVD event, and HeHF population.

Table 7. Transition probabilities based on CPRD data for secondary prevention population (26.6% with diabetes)

	Revasc	UA	MI	Stroke	CV death
From health state:					
Very high risk prim	0.22%	0.26%	0.39%	0.36%	0.56%
Revasc post	0.00%	0.44%	0.68%	1.37%	1.67%
ACS 0-1	6.81%	4.82%	2.76%	0.93%	3.74%
ACS post	0.68%	1.79%	1.36%	1.03%	2.83%
Stroke 0-1	0.35%	0.55%	0.73%	3.70%	4.67%
Stroke post	0.35%	0.55%	0.73%	3.70%	4.67%
Stroke post and ACS 0-1	5.43%	6.93%	6.80%	3.37%	11.38%
Stroke 0-1 and ACS post	0.18%	1.59%	1.01%	3.43%	7.40%
Stroke post and ACS post	0.18%	1.59%	1.01%	3.43%	7.40%
CV death	0.00%	0.00%	0.00%	0.00%	100.00%

Key: CPRD, Clinical Practice Research Datalink; revasc, revascularization; UA, Unstable angina; MI, myocardial infarction; CV death, cardiovascular death.

We adjusted the CPRD-based transition probabilities to LDL-c levels in the Swiss populations of interest, for each age and sex group, based on published rate ratios per 1 mmol/L LDL-c change, as described in section 4.4. The rate ratio values were taken from the Cholesterol Treatment Trialists (CTT) meta-analysis published in 2019, based on results from 28 randomized controlled trials [10]. The study provides two different sets of results, one that considers all the identified studies and another set that excludes four studies based on class IV heart failure patients. We considered the latter set of values, which is better in line with our population of interest. Table 8 summarizes the rate ratios used.

Table 8. Impact of LDL-c change on event rates

	Revasc	UA	MI	Stroke	CV death
Rate ratio	0.7500	0.7300	0.7300	0.7900	0.8400
LN(rate ratio)	-0.2877	-0.3147	-0.3147	-0.2357	-0.1744
SE of LN(rate ratio)	0.0169	0.0210	0.0210	0.0129	0.0243

Key: Revasc, revascularization; UA, unstable angina; MI, myocardial infarction; CV, cardiovascular; RR, rate ratio; LN, natural logarithm; SE, standard error.

To achieve a correct age distribution of events, separately by sex, we further adjusted CPRD rates for age- and sex groups according to real cases in Switzerland for the year 2018. We

computed the risk of having a second IHD, stroke or coronary revascularization procedure for all relevant age- and sex groups. We took the number of events in secondary prevention patients (MedStat data, 2018), subtracted in-hospital deaths and divided the resulting number by the number of prevalent secondary prevention patients as described in 5.2. We then normalized these risks to the age group 65-69, which corresponds to the average age of the CPRD population, and redistributed the events of the other age- and sex groups. Further details on the use of the resulting Swiss age adjustment factors in the model are provided in section 4.4.

We followed a similar procedure for the fatal CVD events.

For the occurrence of non-acute revascularizations in secondary prevention cases, limited data availability necessitated a modified approach. We used the estimated total number of revascularizations per year in the secondary prevention population as estimated in section 6.1.1. In the absence of Swiss data, we used the same age and sex distribution in 2018-2019 in the UK [24] in combination with the number of secondary prevention patients per age- and sex-group (as described above), to estimate age specific revascularization risks. The drop of revascularizations in the older age groups may be less pronounced in Switzerland than in the UK. On the other hand, the UK values excluded CABG surgeries, i.e. procedures that may be prone to an even steeper decrease with age then PTCAs. This might compensate this potential bias.

The resulting Swiss age adjustment factors we used are represented in Table 9.

Table 9. Swiss age adjustment factors for event rates

	Females			Males		
Age (years)	Revasc	IHD event or stroke	CVD death	Revasc	IHD event or stroke	CVD death
40 to 44	1.30	0.66	0.22	3.34	1.39	0.74
45 to 49	0.87	0.78	0.30	1.61	1.46	0.73
50 to 54	1.64	0.82	0.44	2.05	1.42	0.81
55 to 59	1.22	0.98	0.50	1.40	1.33	0.73
60 to 64	1.41	0.97	0.57	1.28	1.16	0.94
65 to 69	1	1	1	1	1	1
70 to 74	0.91	1.04	1.29	0.70	0.97	1.31
75 to 79	0.85	1.24	1.49	0.80	1.04	1.85
80 to 84	0.44	1.41	2.74	0.38	1.20	3.05
85 to 89	0.58	1.57	5.05	0.70	1.38	5.43
90 +	0.07	1.05	7.68	0.08	1.06	9.50

Key: Revasc, revascularization; IHD, ischaemic heart disease; CVD, cardiovascular disease.

Mortality in the 'world without inclisiran' strategy

CVD-related mortality was modelled according to the transition probabilities derived from the CPRD study as detailed above.

Non-CVD-related mortality was estimated based on the age- and sex-specific probability of non-CVD death. The latter was calculated from the WHO Mortality Database [20]. The database provides the number of deaths by cause of death, characterized by an ICD-10 code, stratified by age (five-year age brackets) and sex as well as the corresponding population sizes, until the year 2016. Within each age-sex group, non-CVD deaths were calculated by subtracting from the all-cause mortality counts the number of CVD deaths (See Table 4 for ICD-10 codes selected). Using the 2015 and 2016 data we then calculated the annual age- and sex-specific death rate from causes other than CVD by dividing the respective number of deaths in 2016 over the mid-year population (an average between 2015 and 2016). In the model, the rates were converted into transition probabilities.

5.4 Model inputs related to clinical effectiveness

Given a lack of direct evidence of inclisiran effects on the reduction of CV events and CV deaths, we considered LDL-c reduction as an intermediate outcome linked to reduction in CV events and CV deaths. Thus, to measure effectiveness, we considered the LDL-c reduction obtained in the ORION 10 trial [3], namely 52.3% of LDL-c reduction after 510 days from baseline. The LDL-c reduction of HeFH patients was taken from ORION 9 trial results [2] and it is equal to 47.9% at day 510.

Table 10 summarizes the LDL-c reduction effects of inclisiran on the IHD secondary prevention and HeFH populations.

Table 10. Efficacy of inclisiran in terms of LDL-c reduction

Input Parameter/s	Source	Derivation/application to model/assumption	Distribution	Expected value and 95% CI
LDL-c reduction (%) in IHD secondary prevention population	ORION 10 trial: Ray et al., 2020	LDL-c reduction (%) at 510 days	Normal	52.3 (CI: 48.8, 55.7)
LDL-c reduction (%) in HeFH population	ORION 9 trial: Raal et al., 2020	LDL-c reduction (%) at 510 days	Normal	47.9 (CI: 53.5, 42.3)

Key: CI, confidence interval; IHD, ischaemic heart disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-c, low-density lipoprotein cholesterol.

The reduction in LDL-c levels was translated into a reduced probability of CV events, as described in section 4.4. As before, required rate rates were taken from evidence provided by the Cholesterol Treatment Trialists (CTT) meta-analysis [10], shown in Table 8.

5.5 Model inputs related to utilities

All model inputs related to utilities are summarised in Tables 11-12.

Baseline health state utility

For the secondary prevention population the baseline health state utility values (HSUV) for patients entering the model were represented by the baseline utility of those that have not yet

experienced a CVD event. The respective Swiss utility values were not immediately available for this population but were derived by combining Swiss and UK data sources. Specifically, Swiss age and sex adjusted utility values for the general population were estimated using the formula by Perneger et al. [25]:

$$HSUV_{a,s} = 0.8482 - 0.0209 * SEX - 0.0209 * (AGE - 50) - 0.00002 * (AGE - 50)^2$$

To convert these HSUV to values for the population free from CVD, we applied a scaling factor derived from Ara and Brazier EQ-5D equations parameterized with UK data [26]:

$$HSUV_{a,s} = 0.9509 - 0.0212 * SEX - 0.0003 * AGE - 0.00003 * AGE^2$$
$$HSUV_{a,s}^{non-CVD} = 0.9455 - 0.0256 * SEX - 0.0002 * AGE - 0.00003 * AGE^2$$

The equations were used to predict HSUV for the general and non-CVD populations at average age and sex characterizing the CVD prevalent population in Switzerland. The average age and sex (% male) for the Swiss CVD prevalent population were derived from the GBD study. As noted in Table 4, in the GBD database CVD refers to patients with a history of IHD and/or ischaemic stroke. We summed prevalent cases for the two conditions by age and sex and used these cell counts as a weight to obtain average age and proportion male for the prevalent cohort. We then plugged these values into the equation above to predict HSUV for the general and non-CVD populations and calculated the scaling factor as a ratio of the two predicted utilities.

Applying this scaling factor to convert the Swiss background HSUV for the general population to those with no prior CVD implies proportional health detriment of utility due to CVD in UK and Swiss populations.

Table 11. Health state utility values

Input Parameter(s)	Source	Derivation/ application to model/ assumption	Heteroge neity	Expected value and UI	Distribution
Parameters for age- and sex-specific utility	Perneger et al. [25]	Predicted by plugging average age and % male into HSUV equations	Sex, age		NA
Multiplier for difference between gen. pop. and gen. pop. without CVD	Ara & Brazier [26]	Calculated as a ratio of non-CVD and general population HSUV		1.0618, 1	NA
Multipliers for event and post-event states	Ara & Brazier [26]			See Table 12, ±30%	Normal

Key: CVD, cardiovascular Disease; UI, uncertainty interval

Multipliers for event and post-event states

Utility multipliers for the initial health states and subsequent events were taken directly from Ara and Brazier [26].

Table 12. Multipliers for event and post-event states

Event	Event multiplier, 1st year	Event multiplier, beyond year 2
PAD	-	0.924
Revasc	-	1
ACS	0.765	0.924
Stroke	0.775	0.822

Key: Revasc, cardiac revascularization; ACS, Acute Coronary Syndrome

Adverse event disutilities

Analyses of the pooled ORION 9,10, and 11 data indicated that in patients that received at least one dose of inclisiran the only Treatment Emergent Adverse Event (TEAE) was injection site reaction occurring on average about 5% more often in the inclisiran compared to the placebo arm. These TEAEs were localized at the injection site and resolved without further sequalae. Otherwise the safety profile of inclisiran was similar to placebo.

Given the relatively light severity of the TAEAs reported in the clinical studies and, following earlier evaluations of other PCSK9 inhibitors that demonstrated similar safety profiles, we assumed the injection site TEAEs will have a negligible impact on health-related quality of life and costs and therefore did not consider these in the analysis. Adverse events associated with the comparator strategy were similarly excluded.

5.6 Model inputs related to healthcare resource use and unit costs

The model principally considers the following costs:

- Costs of care for high risk patients without a prior ischaemic cardiac or cerebrovascular event. CVD treatment costs for secondary prevention patients were assumed to be covered by first year and subsequent years MI, UA and stroke costs
- Disease costs for MI, UA and stroke. For these diseases we distinguished fatal event costs, non-fatal event costs in the first year and non-fatal event costs in subsequent years
- Costs for revascularization. We considered PTCA and CABG, to the extent these treatments were not performed for the acute treatment of ACS events
- Background drug treatment costs including costs for statins and ezetimibe.
- Costs for inclisiran including drug administration costs.

Costs for diseases, revascularization and background drug treatment were drawn from published Swiss studies and cost values referring to earlier price years were adjusted to 2018 Swiss Francs (CHF) where applicable, based on the development of the per capita health care costs in Switzerland. 2018 is the most recent year for which health care costs were published by the Swiss Federal Statistical Office [27]. All other cost parameters were based on current Swiss tariffs and prices, i.e. cost values for a more recent price year than 2018 were used as is. [redacted]

The following section gives an overview on all cost input parameters and data sources used in the model. Details regarding each input parameter are provided thereafter.

5.6.1 Overview on cost input parameters and data sources

Table 13 provides an overview on the model cost input parameters and data sources.

Table 13. Overview on unit cost parameters and data sources

Input Parameters	Parameter value (CHF)	Source	Derivation/application to model/assumption
Disease costs			
MI, fatal event	9'067	Wieser et al. 2012 [28]	Swiss cost-of-illness study on the acute coronary syndrome; adjusted to the year 2018 based on the development of the per capita health care costs
MI, non-fatal acute event, first year	35'275		
MI, non-fatal event, subsequent years	2'910		
UA, fatal event	3'873		
UA, non-fatal acute event, first year	23'732		
UA, non-fatal event, subsequent years	2'490		
Stroke, fatal event	11'613	Pletscher et al. 2013 [29]	Swiss cost-effectiveness study of dabigatran for stroke prevention; adjusted to the year 2018 based on the development of the per capita health care costs
Stroke, non-fatal acute event, first year	36'251		
Stroke, non-fatal event, subsequent years	12'899		
Costs for revascularization procedures			
PTCA	13'854	Moschetti et al. 2016 [30]	Cost-minimization analysis of different strategies for cardiac revascularization; analysis conducted for Switzerland, Germany, UK and USA; adjusted to the year 2018 based on the development of the per capita health care costs. Based on the derivation in section 6.1.1, we assumed 87.4% PTCAs and 12.6% CABG surgeries, leading to a weighted average of CHF 17'358 per procedure
CABG	41'711		
Background drug treatment costs			
Statin costs per year	240	Schur et al. 2020 [31]	Helsana drug report; based on current Swiss prices we assumed similar costs for different intensities of statin treatment
Ezetimibe costs per year	453		
Long-term costs of care for high risk patients (pre first event)			
Unit cost for a cardiologist visit	688.04	Moschetti et al. 2016 [30]	Cost-minimization analysis of different strategies for cardiac revascularization; analysis conducted for Switzerland, Germany, UK and USA; adjusted to the year 2018 based on the development of the per capita health care costs; we assumed that each high risk patient would have one cardiologist visit per year
Unit cost for a primary care physician visit	85.06	Tarmed [32, 33]	We assumed that such a GP visit would last on average 30 minutes and each high risk patient would have two GP visits per year
[redacted]			

Key: CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; UA, unstable angina.

5.6.2 Costs of cardiovascular events

Unstable angina and myocardial infarction
The costs of UA and MI were calculated based on a Swiss cost-of-illness study on the acute coronary syndrome by Wieser et al. 2012 [28]. In this study MI included ST-elevation MI (STEMI) (ICD-10: I21.0, I21.1-3, I22.0-1, I22.8) and Non-ST-elevation MI (NSTEMI) (ICD-10: I21.4, I21.9, I22.9). The unit costs of MI were calculated by weighting the total costs of MI to the number of STEMI and NSTEMI patients. UA was identified based on the ICD-10 code I20.0.

The costs of fatal MI and UA consist of the costs for outpatient care before hospital admission and acute inpatient care. The costs of outpatient care before hospital admission consist of the costs for transportation to the hospital (by ambulance or helicopter) and emergency primary care physician or cardiologist visit. The non-fatal costs consist of the costs for outpatient care before hospital admission, acute inpatient care, inpatient rehabilitation, as well as outpatient care after hospital discharge. The costs for outpatient care after discharge consist of the costs for primary care physician and cardiologist visits, diagnostic tests, medication, and outpatient rehabilitation. The maintenance costs consist of the costs for outpatient care after hospital discharge. A more detailed summary of the calculation of these costs can be found in Eichler et al. 2019 [34] and Wieser et al. 2012 [28].

Stroke
The costs of stroke were calculated based on a Swiss cost-effectiveness study of dabigatran for stroke prevention by Pletscher et al. 2013 [29]. For this calculation, stroke was defined as ischaemic stroke (ICD-10: I63.0-I63.9, I64) or haemorrhagic stroke (ICD-10: I60.0-I62.1, I62.9). Besides the one-time treatment costs, stroke may also cause future disability leading to long-term follow-up costs depending on the severity of the disability (for more details see Pletscher et al. 2013 [29]). Disability was categorised into independency, moderate dependency, and total dependency. The costs were weighted by the share of the patients in each disability group.

The costs of fatal stroke consist of the costs for ambulance transportation, emergency primary care physician visit, acute inpatient care, and inpatient rehabilitation. The non-fatal costs depending on the patient's disability consist of the costs for ambulance transportation, emergency physician visit (including primary care physicians, neurologists, psychiatrists), acute inpatient care, diagnostic tests, medication, outpatient and inpatient rehabilitation, outpatient and inpatient nursing, and physiotherapy. The maintenance costs consist of the costs for physician visits, diagnostic tests, medication, outpatient and inpatient nursing, and physiotherapy. A more detailed summary of the unit costs of stroke can be found in Eichler et al. 2019 [34].

5.6.3 Costs for revascularization procedures

Costs for PCI and CABG were based on the study by Moschetti et al. 2016 [30] who conducted a cost-minimization analysis of different strategies for cardiac revascularization. This study

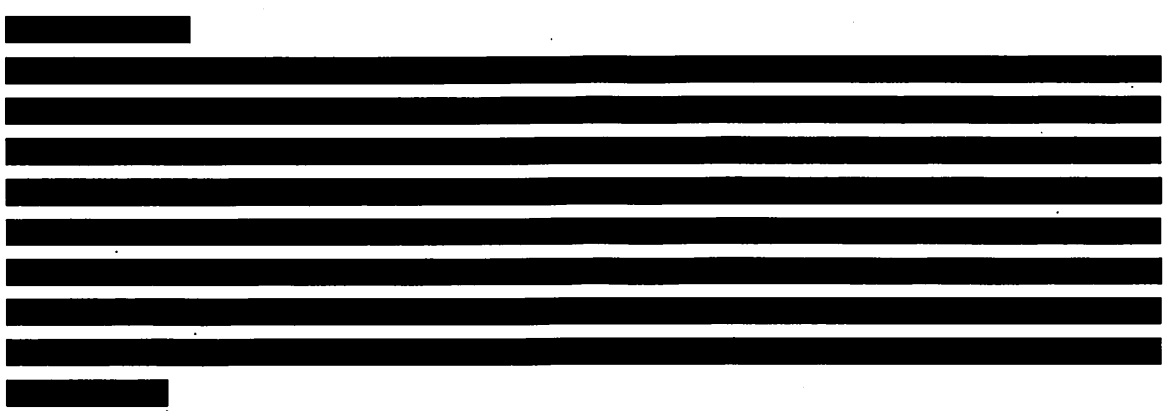
used data from the European cardiovascular magnetic resonance registry, which also includes patients from Switzerland. Based on the derivation in section 6.1.1, we assumed 87.4% PTCAs and 12.6% CABG surgeries, leading to a weighted average of CHF 17'358 per procedure.

5.6.4 Long-term costs of care for high risk patients

High risk patients that have not yet had a CVD event incur long-term costs of care beside background drug treatment costs. Such costs include cardiologist visits and primary care physician visits. Costs for a cardiologist visit were based on Moschetti et al. 2016 [30] and we assumed that a high risk patient would have one cardiologist visit per year. Costs for a primary care physician visit were based on the Swiss medical tariff code for outpatient services (Tarmed) [32, 33]. We applied Tarmed positions 00.0010 «Konsultation, erste 5 Min. (Grundkonsultation)», 00.0020 «Konsultation bei Personen über 6 Jahren und unter 75 Jahren, jede weiteren 5 Min. (Konsultationszuschlag)» and 00.0030 «Konsultation, letzte 5 Min. (Konsultationszuschlag)» and assumed that such a primary care physician visit would last on average 30 minutes. Costs per consultation were calculated by multiplying the resulting tax points according to Tarmed with the average of the tax point values set by the cantons [33]. We further assumed that a high risk patient would have two related primary care physician visits per year.

5.6.5 Drug treatment costs

Background drug treatment costs
The model considers background drug treatment costs of statins and ezetimibe. Per capita costs per year of statin and ezetimibe treatment were based on the Helsana drug utilization report [31], which used health insurance claims data from one of the biggest health insurance companies in Switzerland and extrapolated costs to the whole country considering specifics of their insurees. Given the current Swiss prices [5], we did not differentiate costs for different intensities of statin treatment.



5.7 Model inputs related to treatment uptake

[redacted]

6. Calibration and validation

6.1 Calibration

In the absence of transition probabilities for Swiss secondary prevention patients, and, in fact, any Swiss CVD patients, calibration to expected event numbers in the Swiss secondary prevention population was required to achieve realistic model results. The approach to calibration is described in section 4.4 and the derivation of calibration targets, below.

6.1.1 Calibration targets

Number of revascularizations

The number of revascularizations that were not an immediate, acute treatment of an ACS episode, in the secondary prevention population, was estimated in several steps:

- According to MedStat, there were 18'694 PTCAs and 2'343 CABG surgeries in persons from age 40 years, in 2018 in Switzerland [23]. According to Nestelberger et al., there were 27'318 PTCAs (in the publication termed PCIs) in Switzerland in the same year [35]. Assuming that the difference in the number of PTCAs between the two sources was due to the occurrence of outpatient procedures, would imply 31.6% outpatient procedures. For comparison, the proportion of outpatient procedures indicated by the UK British Society of Interventional Cardiology (BCIS) Audit 2018-2019 was approximately 25% [24]. A proportion of 31.6% would thus seem plausible for Switzerland. We thus estimated that the total number of outpatient procedures in Switzerland in patients from age 40 years was 29'661 in 2018. (Nestelberger et al. did not provide results by age group but the occurrence of PTCA in the population younger than 40 years can be assumed to be very small.)
- Nestelberger et al. also indicated a fraction of 40.4% acute PTCAs (including 2.4% in patients with cardiogenic shock) [35]. This would again seem plausible for Switzerland in light of an estimate of 33.2% in the UK BCIS Audit 2018-2019 [24]. We thus estimated the fraction of PTCAs performed in non-acute/stable patients at 59.6%, implying 18'625 non-acute cardiovascular revascularization procedures in 2018 in Switzerland (2'343 CABG, 27'318 * 0.596 = 16'282 PTCA.

- According to MedStat data provided to us by the SFSO [19], 25.57% of the patients hospitalised for an ischaemic cardiac event were secondary prevention patients, i.e. had been hospitalised before for a cardiovascular event. Schulman et al. [36] reported for the USA that among patients undergoing PTCA between mid-2009 and end of 2014, 32.4% had a prior PTCA and 16.6% a prior CABG, which makes the MedStat-based estimate seem plausible. In the absence of better sources, we assumed that a fraction of 25.57% of non-acute cardiovascular revascularization procedures were performed in secondary prevention patients, leading to a calibration target for revascularizations of 4'762 per year.

Number of non-fatal CVD events

The model was calibrated to the total numbers of non-fatal CVD events in the secondary prevention population shown in Table 14. These data were not directly covered by any Swiss or global data source. We thus derived these calibration targets from MedStat data. These data were directly provided to use by MedStat aggregated by sex, age, and history of CVD.

For each outcome, the number of events in 2018 was aggregated across all age-sex groups, restricting the sample to the population aged 40 and above. We subtracted from these event totals the number of in-patient deaths related to the respective outcome. We then scaled the resulting numbers by the fraction of the population with a history of CVD of those that reported having experienced at least one event of the respective CVD type (i.e. MI, UA or ischaemic stroke). The history of CVD referred to a broad range of CVD-related conditions (see Table 13 for ICD-10 codes selected). The fraction of the population with a history of CVD of those that experienced a specific CVD outcome in 2018 varied from 25% of those reporting an IHD event to over 40% of those reporting an MI; a similarly large variation in the fraction of secondary events was estimated for the five-year age-sex groups within each of the CVD outcomes. The resulting calibration targets are provided in Table 14.

Table 14. Number of non-fatal and fatal CVD events among patients aged 40 years or older: MedStat, 2018

Outcome	Total events	Total secondary prevention events
MI	18'800	8'167
UA	2'793	1'042
Stroke	17'101	6'789
CVD death	8'988	4'045

Key: MI, myocardial infraction; UA, unstable angina.

Number of fatal CVD events

Data on CVD mortality in the secondary population were not explicitly covered by any Swiss or global data source. Similar to non-fatal events we derived the calibration targets from CVD deaths in general population.

Specifically, the WHO Mortality Database was used to obtain the number of CVD deaths in the Swiss population covering both primary and secondary prevention populations [20]. The number of CVD deaths in the general population, including those in patients with no prior event, was obtained by aggregating death counts by age and sex in those age 40 years and above with cause of death within the broad CVD definition (ICD-10 codes: G45, G45.0-9, I20,

I20.0-9, I21, I21.0-9, I22, I22.0-9, I23, I23.0-9, I24, I24.0-9, I25, I25.0-9, I63, I63.0-9, I64, I65, I65.0-9, I66, I66.0-9). We considered several strategies to allocate the total number of deaths between the CVD primary and secondary prevention populations. We reasoned that the secondary prevention population is likely to account for a relatively larger fraction of deaths than non-fatal events as repeated events increase the likelihood of death. Thus, suggesting that the MedStat-derived fraction based on the distribution of non-fatal events is likely to under-estimate the number of deaths in the secondary prevention population which led us to search for additional sources to inform the allocation. We identified AMIS Plus – a Swiss registry of acute myocardial infraction – as an alternative, albeit narrow in terms of the disease target, data source [21]. From the registry, we obtained 1-year mortality counts stratified by history of CVD. CVD history covered previous MI, UA, PCI, CABG, cerebrovascular events (cerebrovascular insult with few or no residuals as well as patients with transient ischaemic attacks according to Charlson Comorbidity Index). From these counts, we then calculated the fraction of MI deaths in the secondary prevention population of all MI deaths. The AMIS Plus fraction was estimated at 0.45 compared to 0.26 based on MedStat for the non-fatal CVD-related events. The resulting calibration target for the number of CVD deaths in the secondary prevention population is shown in Table 14.

For comparison, applying the MedStat fraction to CVD wide deaths yields 4'836 deaths in the secondary prevention population, compared to the base-case target of 4'045. In scenario analyses, calibration targets ± 30% were evaluated to address the substantial degree of related uncertainty (see section 7.1.3.2).

6.2 Validation

Given the timeline of the project, we could not perform a formally complete validation of the model and analyses performed, fully covering all areas described by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) taskforce report on model transparency and validation (i.e., face validation, internal validation, cross validation, external validation) [37] or all elements described by the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool [38]. We prioritised validation steps to reach the highest possible degree of confidence achievable given the time constraints. All validations for which the modelled population mattered, were performed for the Swiss secondary prevention population. The vast majority of validation steps showed fully satisfactory results. As a single exception, our model may moderately over-estimate life expectancy/age at death. However, this is 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. Details are provided in Table 15 and in the text following it. The table also shows the validation types addressed by each step.

Table 15. Model validation steps

Validation type	Validation step	Approach	Result
Face	Review of modelling approaches in CVD	We reviewed published literature, internet sources and, close to the topic, the committee papers of the alirucumab submission to NICE (TA393; [39]) and the global models for inclisiran provided by Novartis	A dynamic population model (see section 4.4) was identified as the most feasible solution for the decision problem and aims at hand
Face	Selection and work-up of data sources	We used personal experience/institutional knowledge, exchange with colleagues (including from Novartis), and targeted searches to identify the most suitable data sources and approaches to the generation of model input parameters. Wherever sensible and possible, alternative approaches to parameter value derivation/identification were pursued and compared	The availability of sources for the different types of required model parameters is mixed, with particularly relevant gaps in the area of epidemiological parameters specifically for the sub-population of secondary prevention patients with a prior ischaemic cardiac or cerebrovascular event, and in the area of Swiss-specific event rates/transition probabilities. Resulting uncertainty is covered by a wide range of sensitivity and scenario analyses
Internal	Double-checking of formulae	All formulae were doubled-checked for correctness by the primary modeller. Given the project timeline and novelty of the approach, double-checking by a separate person was not possible	A small set of issue was identified and solved before the results reported in this document were generated
Internal	Internal consistency of results	All results were checked for 'internal' plausibility, i.e. were plausible given all other model results	There were no issues identified
Internal	Number of persons entering the model correct?	The number of persons entering the model depends on prevalent and incident patient numbers, the latter during several years. We manually calculated the number of patients that should enter the model, with the patients actually counted by the model	Results matched with no deviation
Internal	Is it ensured that in the cost-effectiveness mode, only the prevalent and incident population of the first year enters?	We manually calculated the number of patients that should enter the model, with the patients actually counted by the model	Results matched with no deviation
Internal	Does switch to ensure full inclisiran uptake?	When all patients were treated as eligible, we checked if the number of patients entering the model was equal to the number of patients treated (in the 'world with inclisiran')	Results matched with no deviation
Internal	Considering restrictions based on LDL-c level, background lipid-lowering	Assumptions: eligible patients have at least middle intensity statin treatment (*sw14_LDLc_LLT* = 3) and LDL-c of at least 1.8 mmol/L (*sw14_LDLc_thr* = 3); the uptake in eligible patients is 20% in	Results matched with no deviation

	treatment and treatment uptake assumptions, does the right number of patients get inclisiran?	prevalent and 30% incident patients (stable over time). The expected of patients receiving inclisiran treatment was calculated manually, and compared with the corresponding model output	
Internal	If the inclisiran uptake of prevalent patients is spread over 5 years, is the number of patients getting inclisiran plausible/correct?	In the burden of disease analysis mode, switch *sw01_del_upt* set to 1 and *v_yrs_del_upt* set to 5	The number of patients treated with inclisiran if the uptake of prevalent patients was spread over 5 years was 95.4% of the patients treated in case of immediate uptake. This is fully plausible if one considers that a limited proportion of the prevalent patients will die over the first few years. When the mortality in the mode was set to zero, the number of patients treated was identical when the uptake was spread over 5 years versus not
Internal	Are event probabilities resulting from the formulae built into the model consistent with manual calculation?	Spreadsheet-based calculation: transition probability stems from a population 72.6 years old and with LDL-c 2.6 mmol/L. In male age group 40-44 years in year of model entry and with LDL-c ≥ 2.6 mmol/L, this is adjusted to age 42 years, LDL-c 3.49 mmol/L, with 2 different age corrections. Transition probabilities resulting from application of a 52.3% LDL reduction with inclisiran leads, and of halving the inclisiran effect of LDL-c, are also calculated. The resulting values are compared with model-calculated transition probabilities. It is also checked if resulting transition probabilities are equal for patients entering the model in the same age group but after 10 years	Results matched with no deviation
Internal	If the effect and cost of inclisiran (including administration costs) are set to zero, are the results for both strategies identical?	Relevant parameter values set to zero.	Perfectly fulfilled
Internal	Are the undiscounted life years generated by the model consistent with manual calculation, considering the formulae	Mortality in the model was set to zero, except for the forced death at age 100 and the following expectations were defined: (1) In cost-effectiveness mode, the model should lead to death at age 100;	(1) Age at death very close to age 100 (100.239); the minor deviation is due to non-integer starting ages; (2) Perfectly fulfilled; (3) Perfectly fulfilled; (4) Perfectly fulfilled;

	used to achieve an equivalent of half-cycle correction?	(2) In 'trial mode' and with age at entry set to 65, years, cost-effectiveness mode should lead to death at age 100 and LY lived of 35.5 (*sw01_imm_start* = 1; dying between age 100 and 101) or 35 (sw01_imm_start = 0; due to entry on average 0.5 years later); (3) Burden of disease mode, model run for 1 year: based on prevalent and incident patients entering model, expected life years 170'893 for *sw01_imm_start* = 0 and life years 341'786 for *sw01_imm_start* = 1; (4) As before but model run for 2 years: ased on prevalent and incident patients entering model, expected life years 523'819 for *sw01_imm_start* = 0 and life years 705'852 for *sw01_imm_start* = 1; (5) As (4); delayed inclisiran uptake set to 5 years: equal numbers expected. (6) In cost-effectivenss mode with sw01_imm_start = 1 and no mortality, life years should equal number of cycles times persons entering model (in cost-effectiveness mode, entries occur in the first cycle only)[1]	(5) Perfectly fulfilled; (6) Perfectly fulfilled
Internal	When al utilities and utility multipliers are set to 1, are life years and QALYs equal	Relevant parameter values set to 1	Perfectly fulfilled
Internal	Is the relationship of life years and QALYs plausible?	In burden of disease mode, the model was run for 20 cycles, with the correction of the 'starting' utility to persons without CVD (see section 4.4 and 5.5) turned on or off	Results were plausible and the relationship of the two runs also as expected: (1) Ratio QALYs/life years = 0.749; marginally higher for inclisiran strategy; (2) Ratio QALYs/life years = 0.705; marginally higher for inclisiran strategy
Internal	Do costs per category add up to total costs	Exported to spreadsheet and checked	Perfectly fulfilled
Internal	Are the results for the different cost categories and the differences between the strategies plausible?	Model calculated in cost-effectiveness mode, with discounting set to zero	Magnitudes of costs by category, and directions and magnitudes of cost differences, immediately plausible with one exception: Stroke costs were only marginally smaller in the inclisiran strategy, despite substantially fewer stroke events. Upon further examination:

			(1) The difference is in the expected direction, and equals the relative difference in stroke numbers, when only year 0-1 stroke costs are considered; (2) The difference is in the expected direction (albeit small) when mortality is set equal in both strategies; (3) The difference is in the expected direction (albeit of a smaller magnitude) when year 2+ stroke costs are set to the level of year 2+ ACS costs; (4) All relevant formulae and implementations of cost payoffs were re-checked and no issues identified. Interpretation: the observed apparent discrepancy is not due to a technical issue but a consequence of the timing of stroke events, high stroke costs after year 1, and longer survival in the 'world with inclisiran'
Internal	ACS and stroke costs modelled correctly	(1) In burden of disease mode, model run for 1 cycle and 2 cycles, discounting set to zero, UA and ACS costs set equal, costs of events pre-model entry not considered, mortality set to zero, *sw01_imm_start* set to 1. Then manual calculation of expected ACS and stroke costs; (2) A simpler modelling of ACS and stroke costs was achieved, by removing the formulae implementing the half-cycle correction equivalent. When run in cost-effectiveness mode, slightly higher absolute costs and little impact on difference between strategies expected	(1) and (2) perfectly fulfilled
Internal	Inclisiran costs modelled correctly?	Inclisiran costs were manually calculated, for a number of scenarios, considering the reduced dosing frequency between the first two administration, half cycle correction equivalents equivalents, and the possibility to spread the treatment uptake of prevalent patients over several years	Results matched with no deviation
Internal	Years treated with inclisiran modelled correctly?	(1) Years treated with inclisiran were manually calculated, for the scenarios mentioned in the previous line; (2) When assuming full and immediate inclisiran uptake, and no discounting, years treated with inclisiran should equal life years lived	(1) and (2) perfectly fulfilled

Internal	Does assuming immediate start as opposed to on average mid-year initiation of inclisiran treatment impact on results in expected directions?	Expected: higher costs, higher effect, relatively stable ICER	Perfectly fulfilled
Internal	Does an age limitation of inlisiran use reduce costs, QALYs and increase event numbers in the inclisiran strategy, and is the impact on cost effectiveness, budget impact plausible?	When setting maximum treatment age to 85 years, expect more events, lower total costs (inclisiran costs down, event costs up), lower QALYs, limited impact on ICER	Perfectly fulfilled
Internal	Does assuming immediate restricted persistence impact on results in expected directions? Does switch on of persistence functionality but still assuming full persistence leave results unchanged?	Expected for first part: lower costs, lower effect, ICER relatively stable; expected for second part: no change	Perfectly fulfilled
Internal	Do stricter (higher) LDL-c treatment thresholds impact on results in expected directions?	Expected: smaller treated populations, better ICERs	Perfectly fulfilled
Internal	Do stricter eligibility criteria in terms of background lipid-lowering treatment impact on results in expected directions?	Expected: smaller treated populations, ICERs relatively stable, dependent on LDL-c levels eligible for treatment	Perfectly fulfilled
Internal	Does variation of discount rate change results in expected direction?	When set to 0% and 5%, costs and effects expected to increase and decrease, respectively; ICER expected to improve and deteriorate substantially	Perfectly fulfilled

Cross-validity/external	Is the age at death consistent with that generated by the Novartis global cost-effectiveness model	The dynamic population model has a functionality to approximately perform single-cohort cost-effectiveness analyses, as they are typically used for randomised clinical trial-based cohort analyses. On this basis, we compared the results of our model with those of the Novartis global cost-effectiveness model for inclisiran, with the discounting set to zero. Details are provided in the main text	With the calibration to Switzerland turned off, the age at death generated with our model was moderately lower than for a same-aged member of the ASCVD population in the Novartis model. With the calibration turned on, it was moderately higher, potentially moderately too high after considering the difference in life expectancy between Switzerland and the UK. Details and interpretation are provided in the main text
Cross-validity	Comparison with the main results of the Novartis global cost-effectiveness model	The dynamic population model has a functionality to approximately perform single-cohort cost-effectiveness analyses, as they are typically used for randomised clinical trial-based cohort analyses. On this basis, we compared the results of our model with those of the Novartis global cost-effectiveness model for inclisiran. Details are provided in the main text	With the calibration to Switzerland turned off, the results generated with our model were highly consistent with those of the Novartis global model. Activation of the calibration for Switzerland led to substantially lower QALY differences and somewhat less favourable ICER results, which was expected. Details and interpretation are provided in the main text
Cross validity	Downwards correction of inclisiran effect in year 1, upwards correction of inclisiran effect after year 1: impact on results in expected directions and of similar magnitude as in the Novartis global cost-effectiveness model?	Expected: ICER gets worse if only year 1 effect adjusted; improves with increasing counter adjustment	Impact as expected and magnitude consistent with that in the Novartis global model
External/internal	When run over 1 year, does the model produce the event numbers expected for the Swiss secondary prevention population of patients with a prior ischaemic cardiac or cerebrovascular event?	Events in the 'world without inclisiran' were compared with the calibration targets (see sections 4.4 and 6.1.1). A deviation of up to 10 events absolute was regarded as acceptable. The assessment was made using both our own and the Wilson-based approach to age-adjustment of transition probabilities [11]	Perfectly fulfilled
External	Comparison model results with expected results	Based on the experience of the study team, all results were checked for plausibility in the Swiss context	There were no issues identified, apart from the specific issues a addressed in the next lines

External	Comparison of modelled age at death with expected age at death	The model was run in cost-effectiveness mode, with the discounting set to zero.	The modelled real-world secondary prevention population of patients with a prior ischaemic cardiac or cerebrovascular event had an average age at entry into the model of 71.0 years and an average age at death of 85.5 years. This compares with a Swiss general population life-expectancy of 83.6 years in 2018. Interpretation is provided in the main text

1 Due to input parameters changes since the validation analyses were performed, some of the manually collected 'target' values are no longer consistent with the latest model version.

Key: ACS, acute coronary syndrome; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALYs, quality-adjusted life years; UA, unstable angina.

For comparison with the Novartis global cost-effectiveness model for inclisiran, implemented for the UK [redacted] we used our model's functionality to approximately perform single-cohort cost-effectiveness analyses. Key model settings were made as similar as possible in both models, as follows:

- Our model was set to cost-effectiveness mode, with patients entering only and immediately at model start, with full inclisiran uptake in the 'world with inclisiran' strategy
- Our model was set to 60 cycles but forced death at age 100; the Novartis model settings were not changed in this respect (i.e. kept at 40 cycles)
- Our model used the same cohort characteristics as the Novartis model for the ACS, Other CHD, IS and PAD populations: age 64.75 years, 34% female and baseline LDL 3.47 mmol/L
- The proportion of diabetes patients in the Novartis model was set to 26.6% (in sheet PLD, cell C8), for consistency with our model
- The source of transition probabilities was set to 'CPRD' in the Novartis model; our model also uses these transition probabilities in a slightly different way (see section 5.X)
- The LDL-c reduction achieved with inclisiran was set to 52.3% in our model compared to 52.1% in the Novartis model (MTD SA2)
- [redacted]
- Discount rates for costs and effects were set at 3% in both models
- Other settings were left unchanged in both models.

[redacted]

[redacted] From our model, two sets of results were generated, using our Swiss age adjustment factors and the Wilson-based approach to age adjustment of transition probabilities [11], as detailed in sections 4.4 and 5.3. In addition, the calibration steps to achieve event numbers expected for Switzerland were first turned off, then on. Results:

[redacted]

We conclude that with the calibration to achieve event numbers expected for Switzerland turned off in our model, the behaviour of the two models is fully consistent in this comparison. When the calibration is activated, differences arise as expected. The calibration is required to achieve credible results for Switzerland.

We also used the above-described approach to compare the life expectancy/age at death generated by the model, with the discount rate now set to zero in both models. With the calibration to Switzerland turned off, the age at death generated with our model for a person

entering at age 64.75 years was 77.5 years or 78.4 years, depending on the approach used for the age adjustment of event risks. The age at death with the calibration turned on was 83.2 or 82.7 years. This result compares with a life expectancy of 79.0 years for a same-aged member of the ASCVD population in the Novartis model. Considering the difference in general population life expectancy between Switzerland (83.6 years in 2018) and the UK (81.2 years in 2018), the calibrated values for Switzerland may be moderately too high. This notion may be supported by an estimated age at death of the real-world secondary prevention population addressed in the main analysis, of 85.5 years. It should be noted, though, that the expected life expectancy of a population where many people have already reached and enter the model at a high age, is not straightforward to predict. In any case, the relatively high life expectancy/age at death is a consequence of the necessary calibration to plausible fatal CVD event numbers in our model for Switzerland, which has conservative implications on the cost-effectiveness of inclisiran. (With the calibration turned off, the age at death was 83.0 years.)

7. Results

7.1 Results: cost-effectiveness

7.1.1 Main results

Table 16 presents results of the base-case cost-effectiveness analysis in the Swiss secondary prevention population. Life years per person, QALYs and costs are presented for the 'world with inclisiran' and the 'world without inclisiran'. The differences between the two strategies are presented for the whole population including those that are not eligible/not treated with inclisiran, and for those treated with inclisiran only (54.9%). To reiterate, it is assumed that all prevalent and incident secondary prevention patients in the start year of the model initiate inclisiran treatment if they have an LDL-c level of ≥1.8 mmol/L and any background LLT.

[redacted] The impact of inclisiran is nearly twice that when restricted to those treated. [redacted] These are discounted results. For undiscounted effectiveness estimates, please refer to the burden of disease section (section 7.2).

Table 16. Cost-effectiveness secondary prevention population, discounted

[redacted]

Key: CHF, Swiss francs; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

7.1.2 Results for other high risk populations of interest

Very high risk populations other than or broader than the secondary prevention patients covered in the main analyses are also likely to benefit from inclisiran treatment. Approximate cost-effectiveness results of inclisiran in some of these very high risk populations are summarized in Table 17.

Extending inclisiran treatment to the very high risk patients outside of the secondary prevention population considered in the main analyses (including those with PAD and very high risk patients that have not yet had a prior ischaemic cardiac or cerebrovascular event) [redacted] In a scenario analysis assuming lower treatment uptake in the patients with LDL-c level of ≥1.8 mmol/L and <2.6 mmol/L, compared to those with LDL-c level of ≥2.6 mmol/L, based on the treatment uptake assumptions also used in the burden of disease and budget impact analyses, [redacted] These results are best compared with scenario analysis for the secondary prevention population alone (see section 7.1.3.2).

Approximated gains in the HeFH patients, on the other hand, are substantially higher than those in the secondary prevention population, nearly twice as high in HeFH primary prevention patients (0.395 QALYs per person treated compared to 0.291) and nearly three times as high in the HeFH secondary prevention patients (0.844 QALYs per person gained). The corresponding cost differences were [redacted] in the primary prevention and secondary prevention HeFH populations respectively, leading to ICERs [redacted] per QALY gained.

Table 17. Cost-effectiveness in other very high risk populations, discounted

Key: CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; CHF, Swiss francs; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

7.1.3 Results of uncertainty analyses

7.1.3.1 Univariate sensitivity analysis

Table 18 shows the results of the deterministic univariate sensitivity analysis, when key model input parameters are modified one at a time. They are ranked from the smallest to the widest ICER variation with respect to the base case. Overall, the ICER results remained very stable¨, with a narrow range of variation of ± CHF 5'000 around the base value.

Figure 3 shows in a Tornado diagram a graphical representation of the values in the table. Variation of the parameters represented in the upper part of the graph generated the biggest variation from the base-case ICER. We find the variation of the unit costs of MI and UA being the most influential, with an [redacted] The second-most influential parameter is the background utility, which led to an [redacted] followed by reduction of LDL-c achieved with inclisiran, allowed to change from the lower to the upper bound of the CI of the base-case level, [redacted]. Also the unit cost of stroke (acute event) and the utility multiplier for the ACS post state triggered quite important ICER variations [redacted]. By contrary, parameters as the unit cost of first inclisiran administration, the proportion of fatal ACS events (opposed to stroke events), as well as the unit cost of statin treatment and ezetimibe or the unit cost of fatal MI and UA event, showed only small variation from the base-case ICER.

Figure 3. Deterministic sensitivity analysis of cost-effectiveness: Tornado diagram

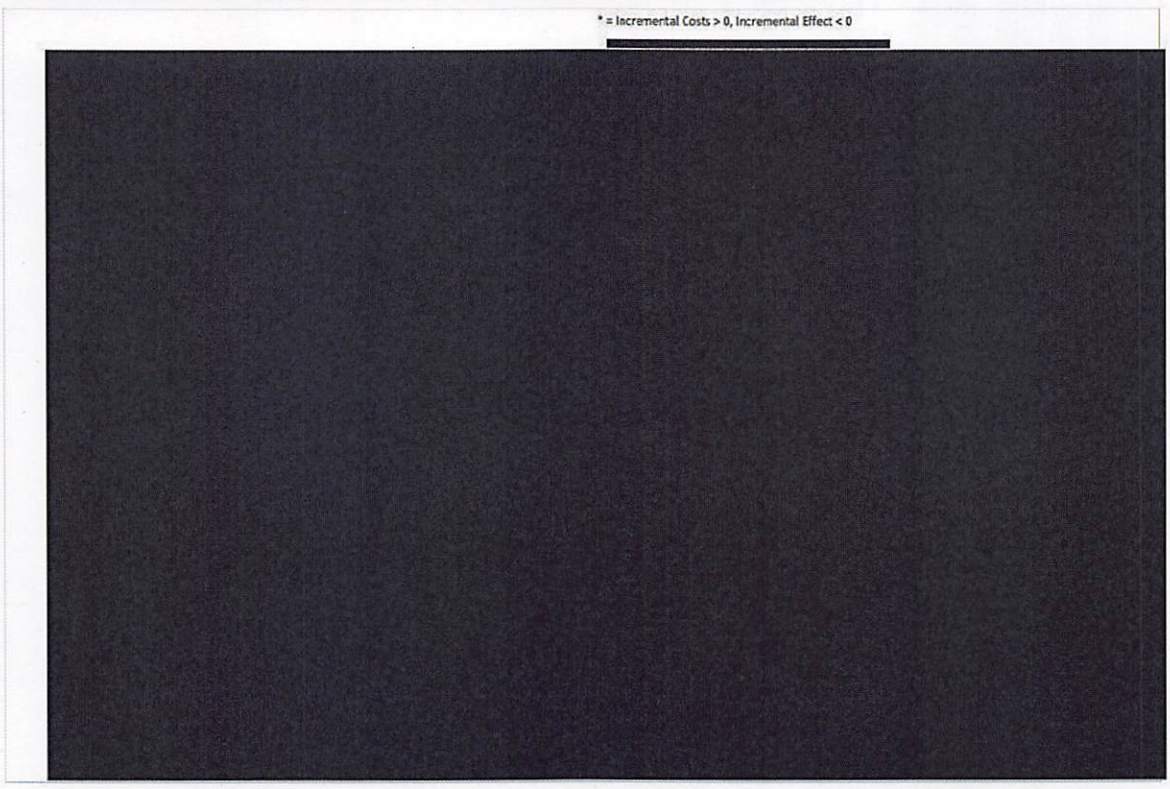


Table 18. Deterministic sensitivity analysis of cost-effectiveness

Key: CV, cardiovascular; ACS, acute coronary syndrome; MI, myocardial infarction; UA, unstable angina; CVD, cardiovascular disease; LDL-c, Low-density lipoprotein cholesterol.

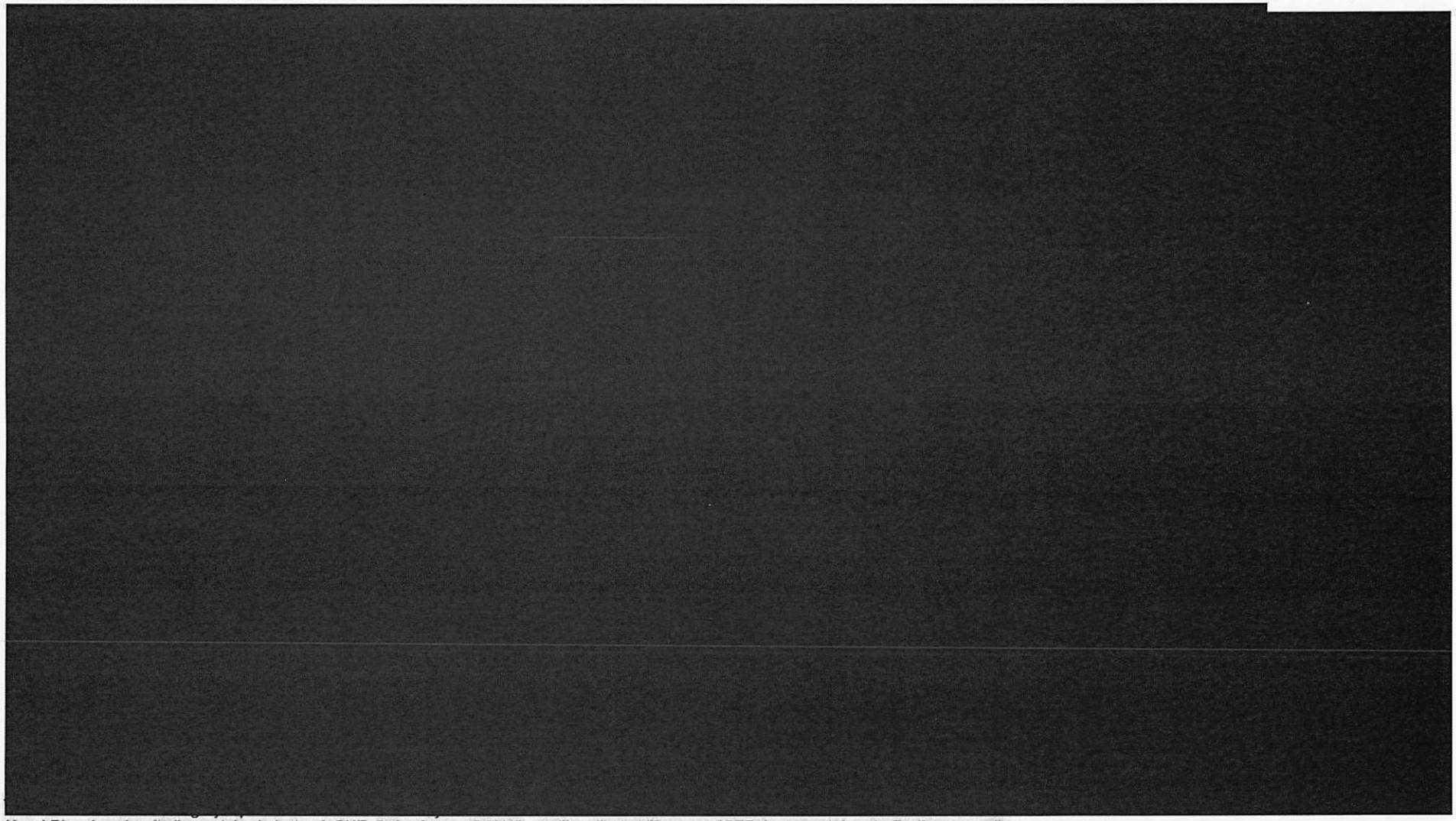
7.1.3.2 Scenarios analyses

Scenario analyses considered the impact of structural assumptions and possibilities that could not be sufficiently captured in the deterministic sensitivity analysis and the PSA. Table 19 presents the impact of different price points per dose of inclisiran in combination with LDL-c eligibility thresholds in the secondary prevention population. The cost-effectiveness outcomes for the base-case scenario assuming a [redacted] and an LDL-c threshold at or above 1.8 mmol/L are highlighted in grey.

Varying the price of the therapy along the base-case LDL-c level of at or above 1.8 mmol/L produces expected changes with respect to both the costs and the ICER of inclisiran: [redacted] The relationship between the price of the therapy and the ICER is non-linear, changes in price result in a disproportionally greater change in the estimated ICER. The range in the estimated ICER bounded by the lowest and highest price points evaluated [redacted] per QALY gained.

Lowering the LDL-c eligibility threshold to 1.4 mmol/L increases the pool of secondary prevention patients eligible for the new therapy. As these patients have a lower average risk of CVD events than the population with LDL-c ≥1.8 mmol/L there are fewer events to avert per person and a lower CVD mortality. This results in a higher cost difference between the strategies, per person treated with inclisiran, across all price points. At the same time, the QALY difference per person treated with inclisiran drops to 0.256 QALYs per person compared to 0.291 in the base-case. Consistent with these dynamics, the estimated ICERs for this broader population are above the base-case of [redacted] per QALY gained for all price points [redacted] per dose of inclisiran.

On the other hand, restricting eligibility to LDL-c levels above 2.6 mmol/L reduces the size of, and effectively further restricts, the eligible patient pool to the most at risk patients in the secondary prevention population. These patients are likely to benefit the most from the therapy. The estimated QALYs per person treated with inclisiran are about a third higher than in the base-case. The estimated ICERs are substantially lower for all price points compared to the base-case. The ICER is below [redacted] per QALY gained at price points below [redacted] per inclisiran dose.



Key: LDL-c, low-density lipoprotein cholesterol; CHF, Swiss francs; QALYS, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

Scenarios covering additional eligibility criteria, uncertainties related to the effectiveness of the therapy and its discontinuation over the patient life-cycle, and technical features of the model are presented in Table 20. On average base-case model estimates appear fairly robust to the structural uncertainties (scenarios considered produce ICER differences <20%). Nonetheless it is worthwhile to consider some of these assumptions more closely.

Scenarios 1 and 2 evaluate the impact of inclisiran if one assumes that only patients on high intensity statins, or on high intensity statins and ezetimibe will be treated with inclisiran. Compared to the base-case, these restrictions with regard to background LLT increase the fraction of inclisiran treated people that are not in the highest LDL-c group in the eligible patient pool due to the intensive LLT therapy they receive. Hence the benefit of inclisiran is lower (0.290 and 0.288 QALYs gained per person treated with inclisiran compared to 0.291) and ICERs are higher (by 11.7 and 4.9% respectively) in these subpopulations.

Applying 'mixed' uptake assumptions that specify a slower uptake for those at LDL-c level ≥1.8 to <2.6 mmol/L and a relatively higher uptake for patients with LDL-c level ≥2.6 mmol/L (see section 5.7), based on the treatment uptake assumptions provided by Novartis, shifts the patient pool toward the more at risk patients resulting in a higher QALY gain per person treated with inclisiran and a relatively lower ICER compared to the base-case (0.314 compared to 0.291 QALYs gained per person treated and [redacted].

We evaluated separately two assumptions relating to the time course of the treatment effect of inclisiran [15]. Predictably, due to the long time horizon of the study, reducing efficacy of the therapy in the first year has only a modest impact on the ICER (an increase of 5.8%). Allowing for a correction factor to compensate for the reduced efficacy in the first year, which is implemented in the model by multiplying the rate ratios per 1 mmol/L LDL-c change with 0.95, yields a substantially lower ICER (a decrease of nearly 16%) compared to the base-case.

Persistence assumptions have further important implications for the cost-effectiveness of the therapy (scenarios 6 and 7). Allowing for discontinuation of treatment increases the estimated ICER by about 8% if increasing from 0% to 20% over the first 3 years on therapy and held at year 3 level thereafter. Relaxing this assumption to allow further discontinuation of treatment through year 10 at an annual rate of 8% increases the ICER by about 13%. Closely related to implementation of the new therapy under real-world conditions is scenario 7 that introduces an age cut-off at which inclisiran is no longer administered in older patients above age 85 years that might be less likely to benefit from additional therapy due to comorbidities or other factors. For the base-case secondary prevention population introducing the cut-off increases the estimated ICER only modestly (by about 6.4%), suggesting the bulk of the benefit of the drug is borne by relatively younger patients.

The distribution of patient characteristics with respect of the LDL-c status by sex and age is another area of uncertainty in the model. Small sample sizes in the secondary prevention population limited the resolution of the data shared with us by the FIRE team. Only

aggregate estimates were provided for patients younger than 75 years and 75 years and above, averaging out any differences in the distribution of relevant characteristics across sex and age within these large age groups. Re-running the model with cohort characteristics informed by the broader population of all very high risk patients (including those with no prior CVD event; scenario 9) produced ICERs comparable to the base-case.

Following Ara and Brazier [26], we evaluated the quality of life-detriment resulting from cardiovascular events relative to a population with no prior CVD. An alternative assumption on background health state utility based on the general population that includes those with prior CVD events was evaluated in scenario 10. A lower background HSUV resulted in a relatively lower gain in QALYs in those treated with inclisiran and a somewhat higher ICER although the difference compared to the base-case is fairly modest (6.2% increase in ICER per QALY gained).

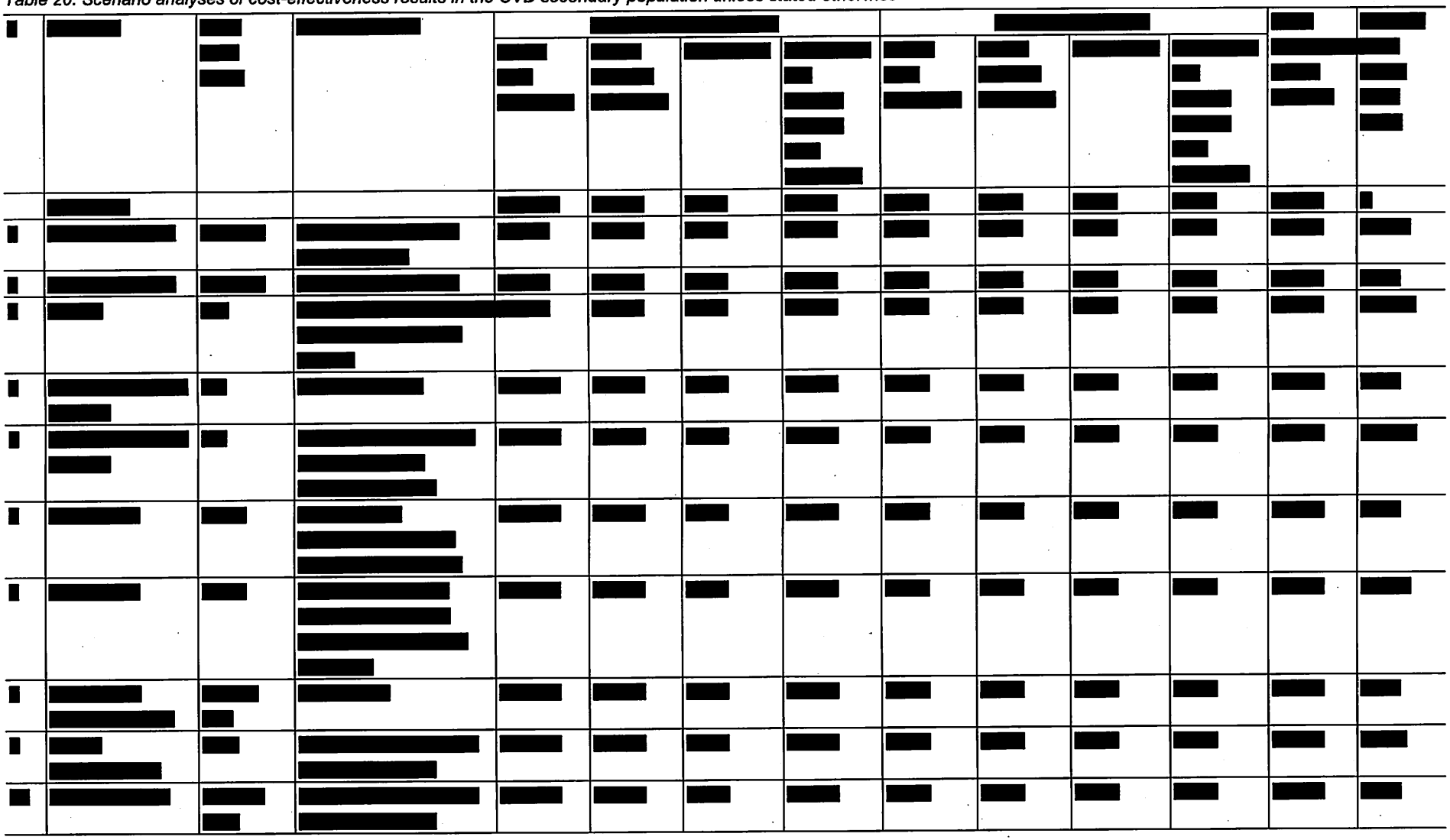
Scenarios 11-18 consider the uncertainty about the incidence and the distribution of CVD events in the secondary prevention population in Switzerland, implicitly also covering uncertainty about the size of this population. Toward this end, cost-effectiveness estimates were produced for model variants fitted to fatal and non-fatal CVD event calibration targets that were varied by ± 30% jointly and in isolation. While relatively robust to assumptions on mild states such as revascularization, the modelled predictions are highly sensitive to changes in targets related to cardiovascular mortality, ACS, and stroke particularly when varied jointly. Predicted QALYs gained per person treated with inclisiran increase when a higher bound target is used and decrease when a lower value is used. At its lowest the new therapy is predicted to add 0.212 QALYs for persons treated, at its highest – 0.361. The resulting ICERs describe a range between [redacted] per QALY gained obtained when all targets are jointly decreased and increased by 30% (scenarios 17 and 18).

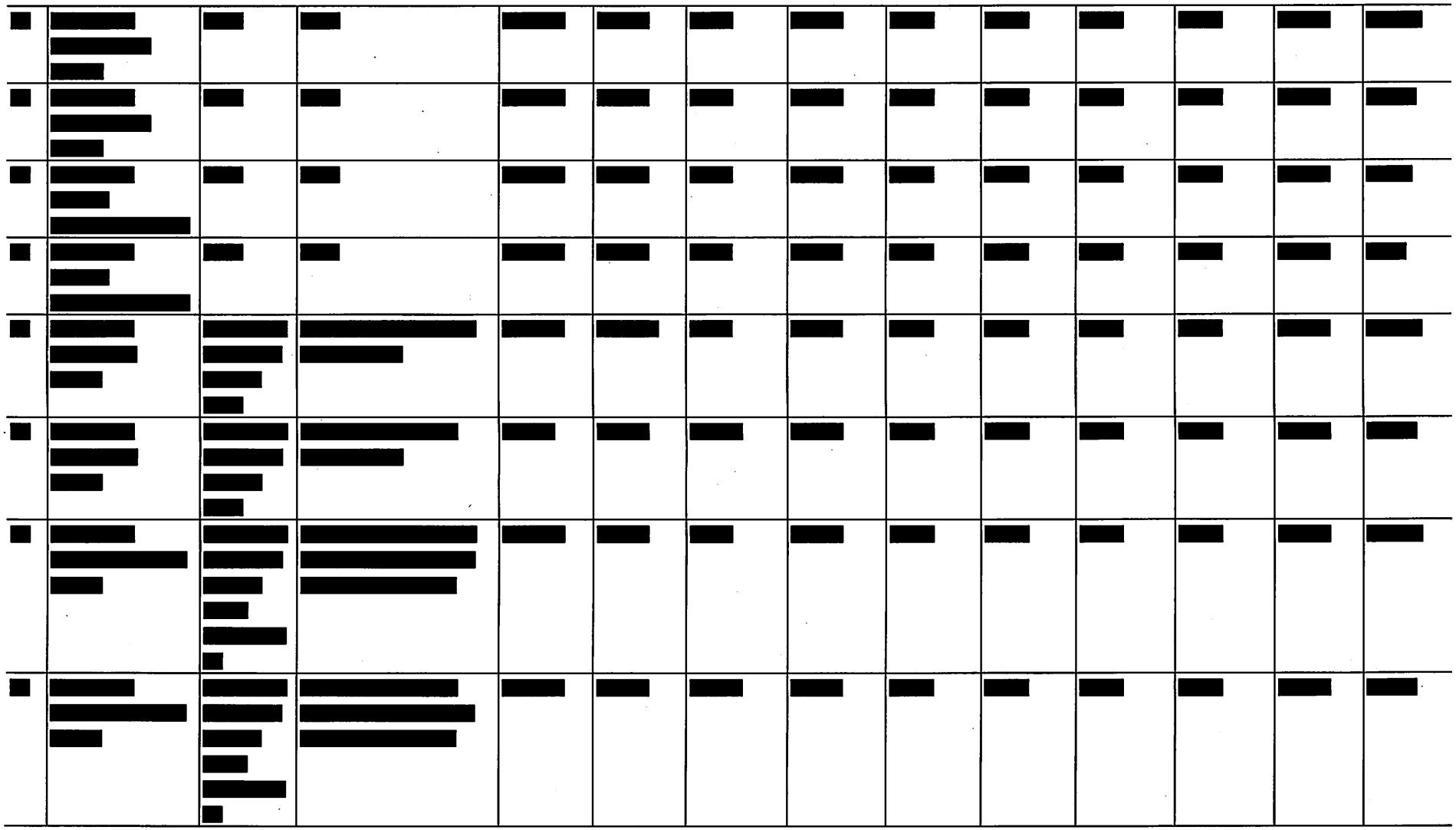
As discussed earlier in section 5.3 Swiss transition probabilities were not available at the time of this study. Thus, Swiss age adjustment factors were derived to adapt UK-based transition probabilities to the Swiss population. An alternative approach that captured the impact of age on cardiovascular risks and transitions developed by Wilson [11] was also evaluated. The Wilson age adjustment factors result in a somewhat different distribution of cardiovascular risk in the 'word without inclisiran'; at a higher burden the therapy results in greater gains in QALYs at an ICER that was over 9% lower than the base-case scenario.

The predicted ICER appears to robust to how the costs of ischaemic cardiac and cerebrovascular events incurred prior to model entry are treated. Included fully under the base-case scenario (see section 4.5), the estimated ICER is decreased by a little under 7% when these costs are halved.

[redacted]

Table 20. Scenario analyses of cost-effectiveness results in the CVD secondary population unless stated otherwise





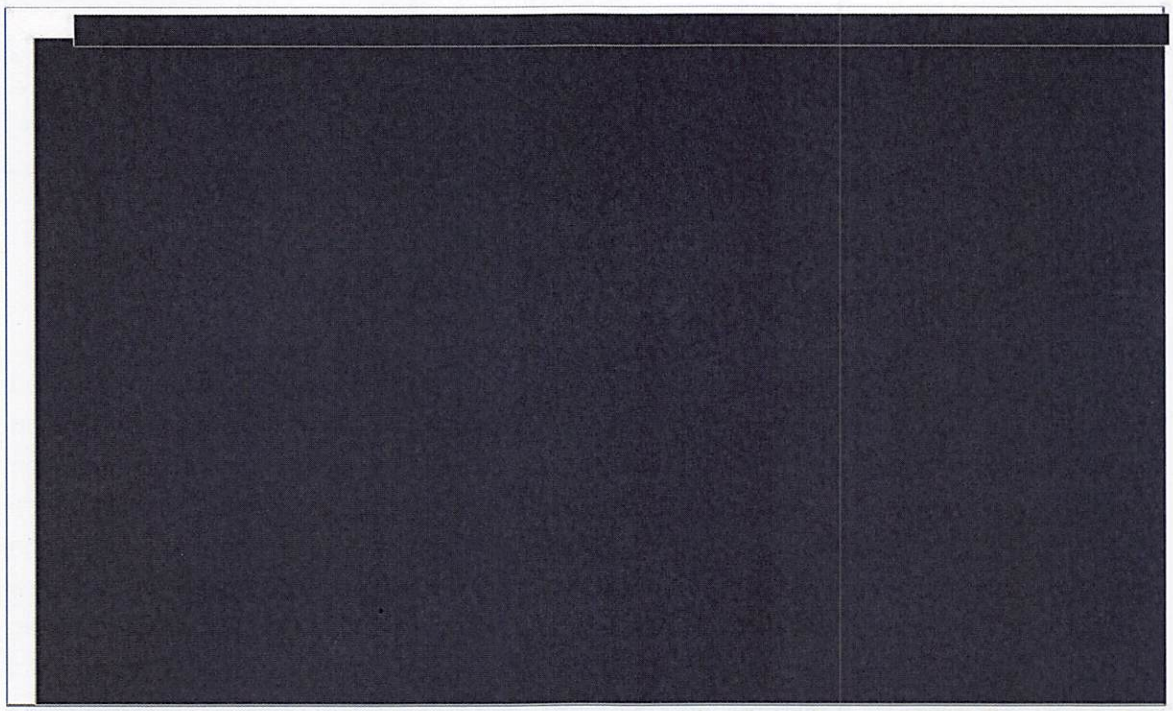
Key: LDL-c, low-density lipoprotein cholesterol; CVD, cardiovascular disease; NF, non-fatal; UA, unstable angina; MI, myocardial infraction; Stroke, ischaemic stroke; F, fatal; ACS, acute coronary syndrome; CHF, Swiss francs; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

7.1.3.3 Probabilistic sensitivity analysis

The PSA of the cost effectiveness of the secondary prevention population, with 1'000 iterations, yielded a cost difference of [redacted] and 0.289 difference in QALYs gained, with a resulting ICER of [redacted] per QALY gained. This is consistent with the base case analysis. Figure 4 shows the corresponding cost-effectiveness scatterplot.

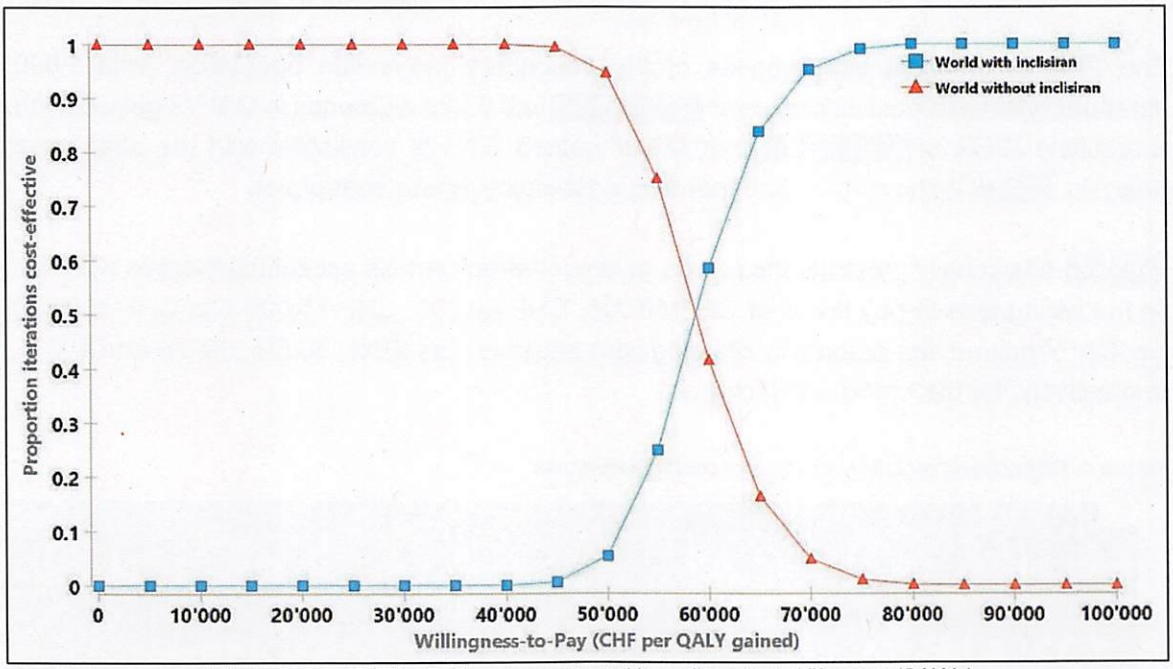
Figure 5 additionally presents the results as a cost-effectiveness acceptability curve (CEAC). At the willingness-to-pay levels of CHF 50'000, CHF 60,000, CHF 75,000 and CHF 100'000 per QALY gained, the probability of being cost-effective was 5.4%, 58.5%, 99.0% and 100%, respectively, for the 'world with inclisiran'.

Figure 4. Probabilistic sensitivity analysis of cost-effectiveness



Key: Cost expressed in Swiss francs (CHF); effectiveness expressed in quality-adjusted life years (QALYs). The cost and QALY differences shown are per person treated with inclisiran. The additional lines represent CHF 100'000 per QALY gained and CHF 50'000 per QALY gained. The population size is 319'742 and the percentage treated is 0.54%.

Figure 5. Cost-effectiveness acceptability curve (CEAC)



Key: Cost expressed in Swiss francs (CHF); effectiveness expressed in quality-adjusted life years (QALYs)

7.2 Results: burden of disease

Burden of disease analyses expands the evaluation beyond the prevalent and incident cohort of the first year to consider additionally incident cases that enter the secondary prevention population each year. Results summarizing cardiovascular events in this population cumulated over a ten-year period in the 'world with inclisiran' and 'world without inclisiran' are reported in Table 21 below. In the 'world with inclisiran' patients in the secondary prevention population with LDL-c level ≥1.8 mmol/L under any background LLT were treated with the new therapy. The base case burden of disease estimates represent modelled impact of inclisiran under the treatment uptake projected in the budget impact base case (not the 100% assumed in the cost-effectiveness analysis) in the real-world Swiss secondary prevention population.

Reflecting the base-case eligibility criteria about 10% of the secondary prevention population or 48'823 patients will be treated with inclisiran. Introducing inclisiran on top of background LLT is estimated to gain 3'118 life years, which translates to 0.006 [0.0065] life years per patient and 0.064 life years per patient treated. In terms of quality of life, an average of 0.006 [0.0059] QALYs per patient and 0.058 QALYs gained per patient treated with inclisiran were estimated by the model. [redacted]

In the first 10 years following its introduction, inclisiran is estimated to reduce the number of revascularization procedures by 1'849, the number of non-fatal ACS events including unstable angina and myocardial infraction by 3'425, the number of ischaemic strokes by 1'961 and the

number of cardiovascular deaths by 1'025. The overall mortality reduction is somewhat lower than the reduction in cardiovascular mortality (788 compared to 1'025 CVD deaths), reflecting competing risks.

Table 21. Burden of disease estimates for the Swiss healthcare system, during 10 years

Parameter	World with inclisiran	World without inclisiran	Difference
Patients treated with inclisiran[1]	48'823	0	48'823
Population size[2]	482'408	482'408	0
Total life-years	3'009'397	3'006'279	3'118
Life years per person	6.238	6.232	0.006
Life year difference per person treated with inclisiran	-	-	0.064
Total QALYs	2'246'587	2'243'733	2'854
QALYs per person	4.657	4.651	0.006
QALY difference per person treated with inclisiran	-	-	0.058
Number revascs	43'681	45'529	-1'849
Number ACS (non-fatal)	87'849	91'274	-3'425
Number strokes	68'918	70'880	-1'961
Number CVD deaths	48'384	49'409	-1'025
Number all-case deaths	165'452	166'240	-788

1 Patients treated with inclisiran indicates the number of patients who were ever treated during 10 years.
2 Population size indicates the number of patients who ever entered the model during 10 years.
Key: QALY, quality-adjustment life-years; CVD, cardiovascular; ACS, acute coronary syndrome; revascs, revascularization.

Similar to the cost-effectiveness results, scenario analyses for the burden of disease study considered several settings characterizing the 'world with inclisiran' that covered the different eligibility requirements, plausible alternative assumptions on the efficacy of the therapy and its evolution over time. For the 'world without inclisiran' the scenarios addressed the uncertainty around the size of the secondary prevention population by explicitly varying the calibration targets and evaluating an alternative adjustment of hazard ratios that drive the age distribution of events in the model as discussed in section 4.6.

Assumptions related to the uptake of the new therapy and those effecting eligibility for treatment appear to be most critical when considering the likely impact of inclisiran on the burden of cardiovascular morbidity and mortality. Scenarios assuming full treatment uptake (16-18), implying that inclisiran is administered in all secondary prevention patients meeting the respective LDL-c threshold starting and requirement regarding background LLT with year 1 onward, defines the upper bound potential of the new therapy in Switzerland. Compared to the modest treatment uptake under Novartis assumptions, the number of patients treated under the full uptake increases over five-fold (scenario 18 compared to base-case) with proportionate increases in both life-years and QALYs gained, as well as deaths averted including all-cause mortality.

Varying eligibility based on the background LLT (scenarios 1, 2) results in the lowest QALYs gained at secondary prevention population level when inclisiran eligible patients are proxied with the population on high intensity treatments and ezetimibe. The size of this patient group is less than one fifth of the base-case yielding a total of 416 QALYs over the 10 year period.

The second lowest gains in QALYs were estimated for a somewhat broader yet still fairly restrictive eligibility criterion requiring high-intensity statins only (scenario 2). Similarly, lower absolute gains, proportional to the size of the population treated with inclisiran, were estimated for LDL-c threshold ≥2.6 mmol/L (scenario 3).

Burden of disease estimates appear to be robust to uncertainty around the efficacy of inclisiran as described by its lower and upper bound values (scenarios 4 and 5). Introducing the age cut-off, while fairly marginal when considering changes to the predicted ICER (stopping treatment reduces both costs and benefits of the intervention), produces strong effects in the burden of disease analysis (scenario 6). The total effectiveness in terms of both QALYs gained and deaths avoided is reduced by about 30%.

Of the scenarios that address uncertainty about the number of and the distribution of cardiovascular events in secondary prevention population (scenarios 7-14), the impact estimates are most sensitive to calibration targets for fatal cardiovascular events. When varied singly, changes in calibration targets for fatal cardiovascular events results in an about ±20% change in terms of total QALYs gained and nearly ±30% when they are varied jointly with the calibration targets for non-fatal outcomes.

The estimates appear to be robust to different approaches to the age adjustment of transition probabilities (scenario 15). Changes to the distribution of CVD events introduced by the Wilson adjustment compared to the base-case approach of using Swiss age adjustment factors lead to a somewhat higher impact in terms of life-years and overall effectiveness however the difference between the two estimates is well within 5% for all outcomes.

Table 22. Scenario analyses of burden of disease results, during 10 years

#	Scenario	Base case value	Scenario value	Patients treated with Inclisiran[1]	Population size[2]	Difference 'world with inclisiran' and 'world without inclisiran'						
						Total life-years	Total QALYs	Number revascs	Number ACS (non-fatal)	Number strokes	Number CVD deaths	Number all-case deaths
	Base-case			48'823	482'408	3'118	2'854	-1'849	-3'425	-1'961	-1'025	-788
1	Background LLT	Any LLT	High-intensity statins	26'785	482'408	1'594	1480	-1016	-1813	-1047	-521	-407
2	Background LLT	Any LLT	High-intensity statins and ezetimibe	8'130	482'408	437	416	-314	-531	-310	-141	-114
3	Eligible LDL-c level	≥1.8 mmol/L	≥2.6 mmol/L	25'234	482'408	2'080	1'920	-1'320	-2'425	-1'341	-683	-527
4	LDL-c reduction achieved with inclisiran	0.523	0.488	48'823	482'408	2'936	2690	-1'755	-3'248	-1'851	-965	-742
5	LDL-c reduction achieved with inclisiran	0.523	0.557	48'823	482'408	3'291	3010	-1'937	-3'591	-2'066	-1'083	-832
6	Maximum age for inclisiran treatment	Unrestricted	85 years	41'558	482'408	2'105	2'070	-1'707	-2'832	-1'637	-610	-536
7	Calibration target: CVD deaths	4045	2832	48'980	482'408	2'275	2259	-1'869	-3'499	-2'020	-764	-584
8	Calibration target: CVD deaths	4045	5259	48'669	482'408	3'892	3402	-1'830	-3'354	-1'905	-1'255	-969
9	Calibration targets: revascularizations	4762	3333	48'823	482'408	3'118	2854	-1'300	-3'425	-1'961	-1'025	-788
10	Calibration targets: revascularizations	4762	6191	48'823	482'408	3'118	2854	-2'387	-3'425	-1'961	-1'025	-788
11	Calibration targets: NF events	UA= 1042; MI= 8167; stroke= 6789	UA= 729; MI= 5715; stroke= 4752	48'828	482'408	3'013	2591	-1'685	-2'320	-1'358	-985	-756

12	Calibration targets: NF events	UA= 1042; MI= 8167; stroke= 6789	UA=1355; MI= 10'617; stroke= 8826	48'819	482'408	3'224	3125	-2'022	-4'613	-2'575	-1'066	-821
13	Calibration targets: F and NF events	UA= 1042; MI= 8167; stroke= 6789; deaths=4045	UA= 729; MI= 5715; stroke= 4752; revasc= 3333; deaths= 2832	48'983	482'408	2'196	2010	-1'197	-2'370	-1'397	-733	-559
14	Calibration targets: F and NF events	UA= 1042; MI= 8167; stroke= 6789; deaths=4045	UA=1355; MI= 10'617; stroke= 8826; revasc= 6191; deaths= 5259	48'663	482'408	4'021	3684	-2'582	-4'516	-2'500	-1'303	-1008
15	Age-adjustment	Swiss age adjustment	Wilson	48'791	482'408	3'183	2938	-2'244	-3'649	-2'048	-1'011	-801
16	Uptake	Partial, LDL-c ≥1.8 mmol/L	Full, LDL-c ≥1.4	336'191	482'408	20'327	18'399	-10'524	-20'312	-11'865	-6'317	-4'774
17	Uptake	Partial, LDL-c ≥1.8 mmol/L	Full, LDL-c ≥1.8	250'834	482'408	17'420	15'784	-9'168	-17'713	-10'194	-5'414	-4'084
18	Uptake	Partial, LDL-c ≥1.8 mmol/L	Full, LDL-c ≥2.6	99'296	482'408	9'614	8'805	-5'556	-10'590	-5'814	-2'978	-2'257

1 Patients treated with inclisiran indicates the number of patients who were ever treated during 10 years.
2 Population size indicates the number of patients who ever entered the model during 10 years.
Key: LLT, lipid-lowering treatment; LDL-c, Low-density lipoprotein cholesterol; CVD, cardiovascular; QALY, quality-adjusted life year.

7.3 Results: budget impact

Table 23 shows the results of the budget impact analysis for the years 1 to 5 and for 5 years in total.

[redacted]

The cost of inclisiran and inclisiran administration is estimated at [redacted] for the first year and at [redacted] over 5 years. The cost of background LLT in the first year is estimated at [redacted], with no relevant difference in the world with and without inclisiran. After 5 years, the estimated background LLT costs sum up to [redacted] in the world with inclisiran and slightly less [redacted] in the world without inclisiran. The costs of CVD events (including deaths) in the first year are [redacted] in the world with inclisiran and slightly higher [redacted] in the world without inclisiran. The total costs in the cardiovascular prevention population at the end of 5 years are estimated at [redacted] in the world with inclisiran versus [redacted] in the world without inclisiran. The estimated net budget impact is equal to [redacted] About 30% of the inclisiran and inclisiran administration costs were offset by reduced costs of CVD events.

Scenario analyses show very different results if assumptions regarding the cost of inclisiran or eligibility criteria for inclisiran treatment are changed. Variation of other assumptions are much less influential (Table 24).

More specifically, assuming a price of [redacted] per dose of inclisiran would imply a total budget impact over [redacted] whereas a price of [redacted] would lead to a budget impact equal to [redacted] Secondly, we changed the assumptions on eligible background LLTs. Limiting inclisiran uptake to only those patients who are already treated with high-intensity statins would mean a decrease in the budget impact of [redacted] A further restriction of inclisiran uptake to those treated with high-intensity statins and ezetimibe would imply an even smaller budget impact [redacted] The changes induced by these alternative assumptions on eligible background LLTs were largely a function of fewer patients being treated. An eligibility based on a higher LDL-c level (≥2.6 mmol/L instead of ≥1.8 mmol/L) would reduce the budget impact by [redacted] also to a substantial part driven by fewer patients being treated.

The scenario analyses covering uncertainty about the number and distribution of cardiovascular events in the Swiss secondary prevention population (scenarios 6-13) show a much more limited impact. Here, budget impact estimates are more sensitive to calibration targets for non-fatal cardiovascular events (± 11% change from base-case budget impact)

rather than to calibration targets for fatal events (±0.6% change). When the calibration targets for non-fatal and fatal events are changed jointly by ±30%, this results in an about ±15% change from the base case budget impact. Finally, budget impact estimates are robust to using the approach to age adjustment of transition probabilities based on Wilson et al. [11], instead of Swiss age adjustment factors (scenario 14). When Wilson adjustment is in place, the budget impact changes by -2.1% compared to the base-case approach.

Table 23. Estimated budget impact analysis, costs in million CHF, years 1-5

1 In years 1-5, the numbers shown indicate patients treated in this year. In the 'Total' column, the number shown indicates patients ever treated during the 5-year time horizon of the analysis, including those that have already died by year 5.

2 In years 1-5, the numbers shown indicate patients alive in the model, in this year. In the 'Total' column, the number shown indicates the size of the secondary prevention population that ever entered the model during the 5-year time horizon of the analysis, including those that have already died by year 5. Numbers in year 5 are slightly smaller than in the previous years due to a projected decreasing CVD population growth rate.

3 The sharp increase of CVD events and deaths between years 1 and 2 is due to the model assumption that patients enter at mid-year; no similar effect is visible for the inclisiran costs due to the more dense dosing at treatment start.

Key: CHF, Swiss francs; CVD, cardiovascular.

Table 24. Scenario analyses of budget impact results in the CVD secondary population, costs in million CHF, 5 years

[redacted]

1 Budget impact results are the difference between results obtained in the 'world with inclisiran' and in the 'world without inclisiran'.
Key: LLT, lipid-lowering treatment; LDL-c, Low-density lipoprotein cholesterol; CVD, cardiovascular; F, fatal; NF, non-fatal; UA, unstable angina; MI, myocardial infarction; revasc, revascularization; ACS, acute coronary syndrome; CHF, Swiss francs.

8. Discussion

This report details a health economic model for inclisiran and the resulting estimates of the cost-effectiveness, budget impact and burden of disease implications of this new LLT in the real-world Swiss secondary prevention population. Approximate cost-effectiveness results for the full very high risk population, including patients that have not yet had a cardiovascular event, and for patients with HeFH are also covered. The strength of the modelling approach presented lies in the scope of the model that in one structure offers capabilities to generate predictions at cohort and population levels, thus facilitating coherence across the health-economic outcomes. The model developed supports decision making on the adoption of new health technologies. The analysis makes an important contribution with new modelled evidence on the likely impact and cost-effectiveness of inclisiran in the real-world Swiss population. The data collated throughout the study related to CVD and characteristics of the secondary prevention population in Switzerland support adequate interpretation of the modelled estimates and help further contextualize the findings.

For the main population of interest, the Swiss secondary cardiovascular prevention population with a prior ischaemic cardiac or cerebrovascular event, we assumed eligibility for inclisiran treatment in the presence of an LDL-c level ≥1.8 mmol/L and any prior LLT. [redacted] per dose of inclisiran, the new therapy yielded an additional 0.291 QALYs per person treated at an incremental cost of [redacted] leading to an ICER of [redacted] per QALY gained. At population level, partial treatment uptake assumptions suggested by [redacted] Under these assumptions, the new therapy was estimated to gain an undiscounted total of 2'854 QALYs, equivalent to 0.058 QALYs per person treated with inclisiran, and to avert 3'425 non-fatal ACS events, 1'961 strokes and 1'025 CVD deaths over the first 10 years following introduction. The yearly net budget impact was predicted to increase from [redacted] over the first five years.

The ICER was shown to be fairly robust to assumptions on cost of cardiovascular events, utilities and the treatment effect of inclisiran, with a range of ± [redacted] when varied in deterministic sensitivity analysis. Scenario analyses provided broader ranges reflecting the uncertainty about the size and characteristics of the target population (most importantly, event rates and resulting total event numbers in the 'world without inclisiran' comparator strategy), treatment uptake and price. Of the scenarios evaluated, assumptions on price and those that impact the number of persons treated including the LDL-c thresholds or background LLT, treatment uptake, and estimated event numbers used for calibration (critically with respect to cardiovascular deaths) defined an ICER range between [redacted] per QALY gained. Both the highest and the lowest bounds were produced under the more/less restrictive and highest/lowest assumptions on LDL-c eligibility threshold and price per dose of inclisiran. At the base-case LDL-c threshold and base case [redacted] the ICER range defined by the scenario analyses was within [redacted] per QALY gained.

We further evaluated the cost-effectiveness of inclisiran considering a scenario under which eligibility was extended to very high risk populations that have not yet had a CVD event. In this mixed population of primary and secondary prevention patients the benefit of inclisiran was somewhat lower (0.271 compared to 0.291 QALY per person treated), while the ICER was somewhat higher but broadly comparable to that seen in the secondary prevention population only ([redacted] per QALY gained).

The therapy was shown to be significantly more impactful for the narrow subpopulation of patients with HeFH. In the HeFH primary prevention population, the estimated benefit of inclisiran was nearly two times higher than in the secondary prevention population. However the costs were also higher, leading to an ICER of [redacted]. Inclisiran appeared to be an exceptionally good value therapy in the HeFH population with a history of CVD. Here, the QALYs gained per person treated were three times higher than in the secondary prevention population (0.844 compared to 0.291), with an ICER of [redacted] per QALY gained.

The analysis presented is subject to limitations. We were thorough to highlight these throughout the report and tackled them directly with extensive uncertainty analyses. The key challenge for the analysis was the difficulty of identifying and describing the size and structure of the Swiss secondary prevention population and the occurrence of events in this population in any available data source. We had to combine Swiss data sources, international data sources reporting or modelling Swiss data (namely, the GBD project and WHO Mortality Database), and data from other industrial countries (namely, the UK) to determine related estimates. Importantly, in the absence of suitable Swiss data, we used transition probabilities derived from the British CPRD database. As the resulting set of data sources was unavoidably partially incoherent in terms of populations covered/studied, methods of data generation and definitions used, it was not possible to achieve a fully consistent set of input parameter values. We addressed this by generating the best possible estimates, comparing different approaches to derivation where available. Related details are provided in the methods part of this document, namely the sections on model input parameter values. 'Middle-of-the-road' and, in cases of doubt, conservative estimates were preferred over extreme ones. This was particularly important in the derivation of calibration factors adjusting the model outputs in the 'world without inclisiran' comparator strategy to numbers of annual non-fatal and fatal cardiovascular events realistically expected in the Swiss secondary prevention population. Our standard deterministic and probabilistic sensitivity analyses could not cover the uncertainty in the 'world without inclisiran strategy' in full, for technical reasons. In particular, the starting transition probabilities based on CPRD data were not varied. This was, as we believe adequately, addressed by scenario analyses varying the aforementioned calibration targets.

A series of further limitations need to be stated. In the absence of detailed information on background LLTs and the reasons behind selecting these, we had to implicitly assume that all patients receiving any background LLT, according to real-world data, are on their maximum tolerated treatment. This assumption does not influence the actual model results but implies that no still unused, suitable treatment options are available for the patients. The impact of this

relatively strong assumption was assessed by restricting the initiation of inclisiran treatment to patients with more intensive types of background LLT. In addition, the use of relatively modest treatment uptake assumptions in the burden of disease and budget impact analyses can also be seen as reflecting that not all patients on any background LLT may already receive their maximum tolerated treatment.

As is typically the case in decision-analytic modelling, simplifying assumptions were required. One major assumption is that the assumed relationship between LDL-c reduction and CVD event occurrence, based on the CTTC 2010 meta-analysis [10], holds for inclisiran and that there is no degradation of the treatment effect of inclisiran over time. These assumptions are consistent with the currently available data but there has, naturally, not been any very long-term observation of inclisiran-treated patients yet. Simplifying assumptions were also made regarding the utility values of patients that have had ACS and stroke events in combination (of two candidate health states, the worse was assumed but utility was not assumed to degrade further), and on CVD treatment costs in such situations (of two candidate unit costs, the higher was assumed but no further increase in costs).

Data sources for the full very high risk population including secondary prevention patients and patients that have not yet had a CVD event, and for patients with HeFH, were even more sparse and also less of a priority given the very tight timeline of the project. The cost-effectiveness results generated for these populations need to be regarded as highly approximate. We had no data basis to estimate results for PAD patients.

Finally, we also had no data basis for amending the adopted Swiss statutory health insurance perspective with a societal perspective considering the population level loss of productivity due to CVD (due to times of inability to work, early retirement, premature death and informal care by family caregivers who, if under the age of retirement, may reduce their paid employment to care for relatives severely affected by CVD).

9. Conclusions

We have established a dynamic population model that allows to consistently generate cost-effectiveness, burden of disease and budget impact estimates for lipid-lowering treatment with inclisiran. Although substantial uncertainties remain, particularly due to limitations in terms of available data sources, we believe to have generated first plausible and, in cases of doubt, conservative estimates of the potential public health impact and health economic properties of inclisiran in Switzerland. Our model estimated that from a Swiss healthcare system perspective and at a [redacted] per dose of inclisiran, the cost-effectiveness compared to the current 'world without inclisiran' standard of care strategy would be [redacted] per QALY gained, assuming treatment of secondary prevention CVD patients with LDL-c ≥1.8 mmol/L under any background LLT. Sensitivity analyses confirmed these results while scenario analyses reflected relevant uncertainty, mostly given limitations of available data sources. [redacted]

[redacted]

Using the same uptake assumptions, the burden of disease analysis predicted that the introduction of inclisiran on the market would reduce CVD deaths by 1'025 cases in ten years. The reduction of non-fatal ACS events and strokes would be 3'425 and 1'961 cases, respectively.

References

1. Mach, F., et al., *2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS).* European Heart Journal, 2019. **41**(1): p. 111-188.
2. Raal, F.J., et al., *Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia.* New England Journal of Medicine, 2020. **382**(16): p. 1520-1530.
3. Ray, K.K., et al., *Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol.* New England Journal of Medicine, 2020. **382**(16): p. 1507-1519.
4. Yarnell, J., *Epidemiology and prevention: a system's based approach*. 2007, New York: Oxford University Press.
5. Swiss Federal Office of Public Health. *Specialty List. http://www.spezialitätenliste.ch/. Accessed 2020-12-16.*
6. Swissmedic. *www.swissmedicinfo.ch. Accessed 2021-01.*
7. Ethgen, O. and B. Standaert, *Population– versus Cohort–Based Modelling Approaches.* PharmacoEconomics, 2012. **30**(3): p. 171-181.
8. Nghiem, N., N. Wilson, and T. Blakely, *Technical Background to the Cardiovascular Disease Model used in the BODE Programme. BODE3 Programme*. 2015, University of Otago, Wellington, New Zealand.
9. Cholesterol Treatment Trialists' Collaborators, *The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials.* Lancet (London, England), 2012. **380**(9841): p. 581-590.
10. Cholesterol Treatment Trialists' Collaboration, *Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials.* Lancet (London, England), 2019. **393**(10170): p. 407-415.
11. Wilson, P.W.F., et al., *An International Model to Predict Recurrent Cardiovascular Disease.* The American Journal of Medicine, 2012. **125**(7): p. 695-703.e1.
12. Drummond, M.F., et al., *Methods for the Economic Evaluation of Health Care Programmes*. 2005: Oxford University Press.
13. TreeAge Software, *TreeAge Healthcare®. https://www.treeage.com/*. 2020-2021: Williamstown, Massachusetts, USA.
14. Morgan, C., et al., *Risk of major adverse cardiovascular events (MACE) in ASCVD, ASCVD-risk equivalent and FH patients with elevated low-density lipoprotein cholesterol (LDL-C).* 2021: Novartis unpublished results.

15. Collins, R., et al., *Interpretation of the evidence for the efficacy and safety of statin therapy.* The Lancet, 2016. **388**(10059): p. 2532-2561.

16. IHME Institute for Health Metrics and Evaluation, *Global Health Data Exchange. http://ghdx.healthdata.org/gbd-results-tool. Accessed 2020-09-29.*

17. Chmiel, C., et al. *The FIRE project: a milestone for research in primary care in Switzerland*. Swiss medical weekly, 2011. **140**, w13142 DOI: 10.4414/smw.2011.13142.

18. Swiss Federal Statistical Office. *Medical Statistics of Hospitals. https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/enquetes/ms.html. Accessed 2020-12-16.*

19. Swiss Federal Statistical Office. *Medical Statistics of Hospitals. https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/enquetes/ms.html. Aggregated data provided by the Swiss Federal Statistical Office upon request.* 2020.

20. World Health Organization, *WHO Mortality database. https://apps.who.int/healthinfo/statistics/mortality/whodpms/. Accessed 2020-10-12. .*

21. AMIS Plus Data Center. *AMIS Plus - National Registry of Acute Myocardial Infarction in Switzerland. https://amis-plus.ch/.*

22. Swiss Health Observatory, *The Swiss Health Observatory (OBSAN). https://www.obsan.admin.ch/en. Accessed 2020-12-10.*

23. Swiss Federal Statistical Office, *Population statistics. https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/stand-entwicklung/bevoelkerung.assetdetail.9486043.html. Accessed 2020-12-16.*

24. Ludman, P.F. and British Cardiovascular Intervention Society, *BCIS National Audit Adult Interventional Procedures 1st April 2018 to 31st March 2019. http://www.bcis.org.uk/wp-content/uploads/2020/12/BCIS-Audit-2018-19-data-ALL-4-5-2020-for-web.pdf. Accessed 2021-02-08.*

25. Perneger, T.V., C. Combescure, and D.S. Courvoisier, *General Population Reference Values for the French Version of the EuroQol EQ-5D Health Utility Instrument.* Value in Health, 2010. **13**(5): p. 631-635.

26. Ara, R. and J.E. Brazier, *Populating an Economic Model with Health State Utility Values: Moving toward Better Practice.* Value in Health, 2010. **13**(5): p. 509-518.

27. Swiss Federal Statistical Office, *Kosten und Finanzierung des Gesundheitswesens seit 1960*. 2018: Neuchâtel.

28. Wieser, S., et al., *Cost of acute coronary syndrome in Switzerland in 2008.* Swiss Med Wkly, 2012. **142**: p. w13655.

29. Pletscher, M., et al., *Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in Switzerland.* Swiss Med Wkly, 2013. **143**: p. w13732.

30. Moschetti, K., et al., *Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the european cardiovascular magnetic resonance registry.* J Cardiovasc Magn Reson, 2016. **18**: p. 3.

31. Schur, N., et al., *Helsana-Arzneimittelreport für die Schweiz 2020. Auswertungsergebnisse der Helsana Arzneimitteldaten aus den Jahren 2016 bis 2019. https://www.helsana.ch/de/helsana-gruppe/medien-publikationen/mitteilungen/arzneimittelreport-2020.html. Accessed 2021-01-12.* 2020.

32. FMH Swiss Medical Association, *TARMED. https://www.fmh.ch/themen/ambulante-tarife/tarmed.cfm. Accessed 2020-12-08.* 2018.

33. Eligo, *Tarmed-Taxpunktwerte-Liste. https://eligo.ch/Tarmed-Taxpunktwerte.html. Accessed 2020-12-08.* 2018.

34. Eichler, K., et al., *Health Technology Assessment (HTA): Self-measurement of blood glucose in patients with non-insulin treated diabetes mellitus type 2.* 2019, Swiss Federal Office of Public Health: Bern.

35. Nestelberger, T., et al. *Coronary and structural heart interventions in Switzerland 2018.* Swiss medical weekly, 2020. **150**, w20200 DOI: 10.4414/smw.2020.20200.

36. Schulman-Marcus, J., et al., *Characteristics of Patients Undergoing Cardiac Catheterization Before Noncardiac Surgery: A Report From the National Cardiovascular Data Registry CathPCI Registry.* JAMA Intern Med, 2016. **176**(5): p. 611-8.

37. Eddy, D.M., et al., *Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7.* Value Health, 2012. **15**(6): p. 843-50.

38. Vemer, P., et al., *AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users.* Pharmacoeconomics, 2016. **34**(4): p. 349-61.

39. NICE National Institute for Health and Care Excellence, *Single technology Appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Committee Papers. www.nice.org.uk/guidance/ta393*. 2016.

Appendices

Table A 1. Entries of prevalent and incident cases sex at model start by sub-cohort

Age (years)	Sex	Prevalent patients			Incident patients			Average annual growth rate for the incident cohort
		Secondary prevention	Secondary prevention + very high risk with no prior CVD	Very high risk with no prior CVD	Secondary prevention	Secondary prevention + very high risk with no prior CVD	Very high risk with no prior CVD	
40-44	Female	2'345	5'757	3'412	75	184	109	-1.18%
40-44	Male	2'780	5'208	2'428	255	478	223	-1.94%
45-49	Female	3'404	8'357	4'953	158	388	230	-1.00%
45-49	Male	5'675	10'632	4'957	480	899	419	-2.05%
50-54	Female	5'363	13'167	7'804	238	584	346	1.20%
50-54	Male	11'376	21'312	9'936	864	1'619	755	0.17%
55-59	Female	7'435	18'254	10'819	327	803	476	1.91%
55-59	Male	17'445	32'682	15'237	1'187	2'224	1'037	1.28%
60-64	Female	9'400	18'654	9'254	383	760	377	0.55%
60-64	Male	22'157	45'283	23'126	1'153	2'356	1'203	0.08%
65-69	Female	12'866	35'313	22'447	554	1'521	967	0.57%
65-69	Male	27'505	67'859	40'354	1'346	3'321	1'975	0.22%
70-74	Female	17'366	38'251	20'885	788	1'736	948	1.66%
70-74	Male	33'027	69'450	36'423	1'397	2'938	1'541	1.98%
75-79	Female	19'037	39'675	20'638	918	1'913	995	0.66%
75-79	Male	29'872	51'604	21'732	1'270	2'194	924	1.63%
80-84	Female	17'700	37'050	19'350	1'136	2'378	1'242	1.51%
80-84	Male	21'806	37'632	15'826	1'225	2'114	889	3.11%
85-89	Female	12'953	27'113	14'160	1'202	2'516	1'314	0.01%
85-89	Male	11'815	20'390	8'575	834	1'439	605	1.90%
90+	Female	7'468	15'632	8'164	826	1'729	903	0.50%
90+	Male	3'943	6'805	2'862	408	704	296	2.90%

Key: CVD, cardiovascular Disease.

Table A 2. Characteristics of sub-cohorts: secondary prevention (FIRE database)

Age	Sex	LDL-c level (mmol/L)	Age mean	LDL-c level proportion	LDL-c mean (mmol/L)	Any lipid-lowering treatment	High intensity statin	Ezetimibe	Statin or ezetimibe	High intensity statin + ezetimibe
≤74	Female	<1.4	65.69	0.086	1.14	0.873	0.490	0.236	0.873	0.145
≤74	Female	≥1.4 to <1.8	63.29	0.185	1.63	0.899	0.569	0.269	0.882	0.202
≤74	Female	≥1.8 to <2.6	65.49	0.349	2.21	0.862	0.448	0.250	0.862	0.125
≤74	Female	≥2.6	64.94	0.380	3.41	0.742	0.330	0.217	0.738	0.074
≤74	Male	<1.4	63.19	0.128	1.18	0.876	0.618	0.225	0.876	0.156
≤74	Male	≥1.4 to <1.8	62.61	0.235	1.61	0.912	0.651	0.310	0.910	0.22
≤74	Male	≥1.8 to <2.6	63.27	0.391	2.15	0.871	0.612	0.382	0.868	0.267
≤74	Male	≥2.6	61.95	0.246	3.470	0.807	0.480	0.272	0.807	0.153
>74	Female	<1.4	79.76	0.084	1.13	0.842	0.541	0.079	0.842	0.079
>74	Female	≥1.4 to <1.8	81.16	0.151	1.58	0.853	0.484	0.132	0.853	0.074
>74	Female	≥1.8 to <2.6	80.58	0.380	2.2	0.825	0.398	0.146	0.825	0.082
>74	Female	≥2.6	80.94	0.384	3.73	0.665	0.275	0.168	0.659	0.058
>74	Male	<1.4	79.09	0.140	1.17	0.860	0.476	0.172	0.860	0.097
>74	Male	≥1.4 to < 1.8	79.89	0.224	1.61	0.893	0.464	0.174	0.893	0.101
>74	Male	≥1.8 to < 2.6	79.79	0.407	2.16	0.852	0.510	0.221	0.852	0.122
>74	Male	≥2.6	80.24	0.230	3.260	0.693	0.322	0.163	0.693	0.085

Key: LDL-c, Low-density lipoprotein cholesterol.

Table A 3. Characteristics of sub-cohorts: very high risk with no prior cardiovascular disease event (FIRE database)

Age	Sex	LDL-c level (mmol/L)	Age mean	LDL-c level proportion	LDL-c mean (mmol/L)	Any lipid-lowering treatment	High intensity statin	Ezetimibe	Statin or ezetimibe	High intensity statin + ezetimibe
≤74	Female	< 1.4	66.57	0.043	1.18	0.784	0.212	0.162	0.784	0.081
≤74	Female	≥1.4 to <1.8	65.59	0.106	1.62	0.802	0.232	0.110	0.802	0.033
≤74	Female	≥1.8 to <2.6	65.27	0.313	2.21	0.653	0.196	0.037	0.653	0.019
≤74	Female	≥2.6	63.52	0.538	3.54	0.443	0.163	0.048	0.443	0.026
≤74	Male	<1.4	64.02	0.081	1.12	0.737	0.364	0.145	0.737	0.072
≤74	Male	≥1.4 to <1.8	64.5	0.113	1.62	0.764	0.396	0.099	0.764	0.042
≤74	Male	≥1.8 to <2.6	64.1	0.307	2.19	0.641	0.243	0.088	0.640	0.049
≤74	Male	≥2.6	63.5	0.499	3.530	0.333	0.110	0.037	0.333	0.015
>74	Female	<1.4	80.87	0.061	1.07	0.833	0.241	0.033	0.833	0.033
>74	Female	≥1.4 to <1.8	79.95	0.114	1.59	0.607	0.130	0.071	0.607	0.018
>74	Female	≥1.8 to <2.6	80.49	0.298	2.2	0.623	0.201	0.048	0.623	0.014
>74	Female	≥2.6	81.14	0.527	3.59	0.337	0.065	0.035	0.337	0.008
>74	Male	<1.4	79.27	0.145	1.16	0.757	0.323	0.043	0.757	0.029
>74	Male	≥1.4 to <1.8	79.52	0.176	1.6	0.682	0.364	0.071	0.682	0.071
>74	Male	≥1.8 to <2.6	79.75	0.333	2.16	0.559	0.179	0.037	0.559	0.019
>74	Male	≥2.6	79.95	0.347	3.390	0.375	0.086	0.065	0.375	0.024

Key: LDL-c, Low-density lipoprotein cholesterol.

Table A 4. Characteristics of sub-cohorts: secondary prevention and very high risk with no prior cardiovascular disease event (FIRE database)

Age	Sex	LDL-c level (mmol/L)	Age mean	LDL-c level proportion	LDL-c mean (mmol/L)	Any lipid-lowering treatment	High intensity statin	Ezetimibe	Statin or ezetimibe	High intensity statin + ezetimibe
≤69	Female	<1.4	66.96	0.059	1.23	0.826	0.318	0.130	0.826	0.087
≤69	Female	≥1.4 to <1.8	67.04	0.132	1.61	0.902	0.432	0.235	0.902	0.137
≤69	Female	≥1.8 to <2.6	67.26	0.354	2.22	0.752	0.310	0.102	0.752	0.073
≤69	Female	≥2.6	67.15	0.455	3.43	0.562	0.182	0.102	0.562	0.045
≤69	Male	<1.4	66.99	0.101	1.13	0.784	0.447	0.225	0.784	0.147
≤69	Male	≥1.4 to <1.8	67.23	0.150	1.61	0.836	0.500	0.250	0.836	0.184
≤69	Male	≥1.8 to <2.6	67.08	0.306	2.18	0.745	0.431	0.216	0.739	0.161
≤69	Male	≥2.6	67.27	0.444	3.62	0.360	0.126	0.064	0.360	0.02
70-74	Female	<1.4	72.08	0.078	1.1	0.846	0.400	0.179	0.846	0.077
70-74	Female	≥1.4 to <1.8	72.03	0.140	1.61	0.843	0.358	0.200	0.843	0.129
70-74	Female	≥1.8 to <2.6	72.01	0.348	2.21	0.718	0.207	0.126	0.718	0.046
70-74	Female	≥2.6	72	0.434	3.55	0.599	0.237	0.120	0.594	0.051
70-74	Male	<1.4	72.14	0.110	1.13	0.822	0.464	0.133	0.822	0.078
70-74	Male	≥1.4 to <1.8	72.01	0.192	1.6	0.815	0.490	0.153	0.815	0.076
70-74	Male	≥1.8 to <2.6	71.98	0.397	2.17	0.738	0.372	0.188	0.735	0.111
70-74	Male	≥2.6	71.61	0.301	3.37	0.476	0.191	0.106	0.476	0.045
>74	Female	<1.4	76.85	0.076	1.08	0.912	0.515	0.088	0.912	0.088
>74	Female	≥1.4 to <1.8	76.9	0.139	1.58	0.855	0.339	0.113	0.855	0.065
>74	Female	≥1.8 to <2.6	76.93	0.352	2.21	0.777	0.373	0.134	0.777	0.083
>74	Female	≥2.6	76.95	0.433	3.69	0.518	0.149	0.135	0.518	0.036
>74	Male	<1.4	76.78	0.161	1.17	0.814	0.424	0.157	0.814	0.098
>74	Male	≥1.4 to <1.8	76.81	0.196	1.62	0.823	0.470	0.129	0.823	0.089
>74	Male	≥1.8 to <2.6	76.93	0.396	2.16	0.781	0.450	0.187	0.781	0.116
>74	Male	≥2.6	76.89	0.248	3.31	0.554	0.222	0.153	0.554	0.07

Key: LDL-c, Low-density lipoprotein cholesterol.

Table A 5. Transition probabilities for populations with different characteristics, based on Novartis analysis of CPRD data

	Revasc	UA	MI	Stroke	CV death
Secondary prevention and very high risk with no prior cardiovascular disease event (45.2% with diabetes)					
From health state					
Very high risk prim	0.22%	0.28%	0.39%	0.38%	0.60%
Revasc post	0.00%	0.50%	0.68%	1.73%	1.42%
ACS 0-1	7.34%	4.96%	3.24%	1.06%	4.29%
ACS post	0.69%	1.94%	1.51%	1.20%	3.17%
Stroke 0-1	0.35%	0.62%	0.88%	4.03%	5.21%
Stroke post	0.35%	0.62%	0.88%	4.03%	5.21%
Stroke post and ACS 0-1	5.29%	7.33%	9.09%	3.75%	10.97%
Stroke 0-1 and ACS post	0.19%	1.53%	1.04%	3.76%	8.28%
Stroke post and ACS post	0.19%	1.53%	1.04%	3.76%	8.28%
CV death	0.00%	0.00%	0.00%	0.00%	100.00%
Very high risk with no prior cardiovascular disease event (63.8% with diabetes)					
From health state					
Very high risk prim	0.22%	0.29%	0.39%	0.39%	0.64%
Revasc post	0.00%	0.57%	0.69%	2.10%	1.18%
ACS 0-1	7.88%	5.09%	3.72%	1.19%	4.85%
ACS post	0.70%	2.09%	1.67%	1.36%	3.51%
Stroke 0-1	0.35%	0.69%	1.03%	4.37%	5.76%
Stroke post	0.35%	0.69%	1.03%	4.37%	5.76%
Stroke post and ACS 0-1	5.15%	7.74%	11.39%	4.13%	10.56%
Stroke 0-1 and ACS post	0.20%	1.47%	1.07%	4.10%	9.15%
Stroke post and ACS post	0.20%	1.47%	1.07%	4.10%	9.15%
CV death	0.00%	0.00%	0.00%	0.00%	100.00%
Primary prevention HeFH (2.4% with diabetes)					
From health state					
HeFH (primary prevention)	0.14%	0.19%	0.14%	0.14%	0.04%
Revasc post	0.00%	0.35%	0.67%	0.89%	1.99%
ACS 0-1	6.11%	4.65%	2.13%	0.76%	3.01%
ACS post	0.66%	1.60%	1.15%	0.81%	2.38%
Stroke 0-1	0.35%	0.46%	0.53%	3.26%	3.96%
Stroke post	0.35%	0.46%	0.53%	3.26%	3.96%
Stroke post and ACS 0-1	5.61%	6.39%	3.82%	2.87%	11.92%
Stroke 0-1 and ACS post	0.16%	1.67%	0.96%	3.00%	6.27%
Stroke post and ACS post	0.16%	1.67%	0.96%	3.00%	6.27%
CV death	0.00%	0.00%	0.00%	0.00%	100.00%
Secondary prevention HeFH (2.4% with diabetes)					
From health state					
HeFH (secondary prevention)	0.70%	0.00%	0.70%	0.00%	0.70%
Revasc post	0.00%	0.35%	0.67%	0.89%	1.99%
ACS 0-1	6.11%	4.65%	2.13%	0.76%	3.01%
ACS post	0.66%	1.60%	1.15%	0.81%	2.38%
Stroke 0-1	0.35%	0.46%	0.53%	3.26%	3.96%
Stroke post	0.35%	0.46%	0.53%	3.26%	3.96%
Stroke post and ACS 0-1	5.61%	6.39%	3.82%	2.87%	11.92%
Stroke 0-1 and ACS post	0.16%	1.67%	0.96%	3.00%	6.27%
Stroke post and ACS post	0.16%	1.67%	0.96%	3.00%	6.27%
CV death	0.00%	0.00%	0.00%	0.00%	100.00%

Based on [14].

Key: CV, cardiovascular; UA, unstable angina; MI, myocardial infarction; revasc, revascularization; ACS, acute coronary syndrome; HeFH, Heterozygous familial hypercholesterolaemia.

Table A 6: Distribution of secondary prevention population with a prior history of ischaemic heart disease/stroke according to LDL-c level

	No restriction in terms of background LLT		*Any background LLT*		*High intensity statins*		*High intensity statins + ezitimibe*	
Eligible LDL-c level	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**
<1.4 mmol/L	34'575.4	1'937.5	29'958.3	1'676.6	19'008.4	1'068.4	4'411.7	242.5
≥1.4 to <1.8 mmol/L	62'669.2	3'489.0	56'217.9	3'123.6	35'660.7	1'974.4	10'536.7	569.6
≥1.8 to <2.6 mmol/L	116'418.1	6'567.5	99'697.0	5'612.2	60'450.6	3'386.7	20'204.0	1'121.1
≥2.6 mmol/L	89'076.7	5'029.6	65'561.2	3'675.9	32'486.8	1'812.7	8'740.9	486.3
Total	302'739.4	17'023.7[1]	251'434.3	14'088.2	147'606.4	8'242.2	43'893.2	2'419.6

1 The total number of people (prevalence + new cases) sums up to 319'763, while in table 23 the total number of people reported was 319'742. This little discrepancy is due to the fact that the proportions of people falling into the different LDL-c categories was rounded to 4 decimals in the model.

Key: LLT, lipid-lowering treatment; LDL-c, Low-density lipoprotein cholesterol.

Table A 7: Distribution of secondary prevention population with a prior history of ischaemic heart disease/stroke according to LDL-c level and age

	No restriction in terms of background LLT		*Any background LLT*		*High intensity statins*		*High intensity statins + ezitimibe*	
Eligible LDL-c level and age class	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**	**Population size (prevalence)**	**Population size (new cases)**
<1.4 mmol/L	34'575.4	1'937.5	29'958.3	1'676.6	19'008.4	1'068.4	4'411.7	242.5
40-44	556.6	39.0	487.0	34.2	318.1	23.3	84.6	6.0
45-49	1'017.6	75.0	890.6	65.6	591.2	44.6	155.5	11.5
50-54	1'914.9	130.8	1'676.1	114.6	1'124.0	78.2	293.7	20.2
55-59	2'868.8	179.8	2'511.1	157.4	1'690.4	107.5	440.5	27.7
60-64	3'639.9	180.3	3'186.2	157.9	2'145.2	107.2	559.0	27.8
65-69	4'621.0	219.7	4'044.7	192.3	2'713.2	129.6	708.8	33.8
70-74	5'712.9	246.3	5'000.1	215.5	3'338.4	143.5	874.9	37.7
75-79	5'779.0	254.8	4'941.0	217.7	2'852.9	126.2	531.6	23.3
80-84	4'539.7	267.0	3'877.2	227.9	2'256.2	133.2	413.4	24.2
85-89	2'743.7	218.0	2'339.9	185.6	1'375.9	110.3	246.4	19.3
90+	1'181.3	126.8	1'004.6	107.8	602.8	64.8	103.2	11.0
≥1.4 to <1.8 mmol/L	62'669.2	3'489.0	56'217.9	3'123.6	35'660.7	1'974.4	10'536.7	569.6
40-44	1'087.4	73.8	986.1	67.1	672.5	46.9	231.4	16.0
45-49	1'963.0	142.0	1'782.1	129.1	1'226.7	90.1	420.5	30.7
50-54	3'664.6	246.8	3'329.2	224.5	2'305.2	157.1	788.3	53.5
55-59	5'473.2	339.1	4'973.6	308.5	3'451.7	215.9	1'179.3	73.5
60-64	6'943.5	341.6	6'309.8	310.6	4'379.5	216.7	1'496.2	73.9
65-69	8'841.3	418.8	8'032.3	380.6	5'562.8	264.3	1'902.2	90.3
70-74	10'971.6	474.1	9'964.2	430.4	6'881.6	296.8	2'355.8	101.7
75-79	9'559.9	422.8	8'421.9	372.0	4'492.9	198.9	887.9	39.0
80-84	7'553.2	445.7	6'638.1	391.2	3'558.1	210.2	690.7	40.4
85-89	4'600.7	368.3	4'030.1	321.6	2'174.0	174.5	411.8	32.3
90+	2'010.7	216.2	1'750.4	188.1	955.8	102.8	172.6	18.5
≥1.8 to <2.6 mmol/L	116'418.1	6'567.5	99'697.0	5'612.2	60'450.6	3'386.7	20'204.0	1'121.1
40-44	1'906.7	126.0	1'653.4	109.5	1'032.3	72.8	392.9	29.9
45-49	3'408.9	243.1	2'958.5	211.3	1'890.9	139.7	741.6	57.1
50-54	6'324.3	420.9	5'491.6	365.9	3'562.5	244.0	1'422.9	100.6
55-59	9'422.7	578.5	8'183.8	502.9	5'339.7	335.3	2'147.5	138.3
60-64	11'952.7	584.9	10'381.3	508.2	6'775.2	336.0	2'725.6	137.2
65-69	15'255.3	720.3	13'247.0	625.7	8'597.4	409.0	3'435.7	164.9

70-74	18'986.7	821.9	16'482.9	713.4	10'622.8	457.7	4'209.1	180.4
75-79	19'389.5	865.4	16'324.5	727.9	9'075.4	402.2	2'076.2	91.6
80-84	15'599.1	930.2	13'108.8	780.8	7'199.3	425.8	1'634.1	96.2
85-89	9'729.8	796.2	8'156.9	666.0	4'408.7	354.7	990.1	78.9
90+	4'442.5	480.1	3'708.4	400.6	1'946.5	209.5	428.5	46.0
≥2.6 mmol/L	89'076.7	5'029.6	65'561.2	3'675.9	32'486.8	1'812.7	8'740.9	486.3
40-44	1'575.1	91.2	1'213.2	71.7	622.8	39.5	170.6	11.7
45-49	2'689.0	178.2	2'086.0	139.9	1'097.5	76.6	309.2	22.5
50-54	4'835.7	302.6	3'769.9	238.4	2'016.8	131.8	578.8	39.2
55-59	7'115.4	416.0	5'558.4	327.6	2'993.5	181.2	865.4	53.8
60-64	9'020.9	429.0	7'047.6	336.7	3'796.7	184.2	1'097.9	54.1
65-69	11'653.1	541.7	9'086.2	423.4	4'863.4	228.6	1'396.6	66.2
70-74	14'721.0	643.1	11'450.8	499.5	6'080.4	263.9	1'730.9	74.7
75-79	14'181.4	644.5	9'622.8	436.8	4'216.6	190.7	1'007.8	45.3
80-84	11'814.1	718.2	7'996.7	485.5	3'479.4	210.4	820.5	49.3
85-89	7'694.0	653.8	5'192.5	440.1	2'240.1	188.5	519.5	43.1
90+	3'777.0	411.4	2'537.1	276.2	1'079.5	117.4	243.5	26.4
Total	302'739.4	17'023.7[1]	251'434.3	14'088.2	147'606.4	8'242.2	43'893.2	2'419.6

1 The total number of patients (prevalent and incident) sums up to 319'763, while in Table 23 the total number of patients reported is 319'742. This small discrepancy is due to the fact that the proportions of people falling into the different LDL-c categories was rounded to 4 decimals in the model.

Key: LLT, lipid-lowering treatment; LDL-c, low-density lipoprotein cholesterol.

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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.

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].

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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	Table; see ESM, Table 4	Not varied[a]		[26]
Sub-cohort characteristics	Table; 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 capita[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 $\geq$1.8 mmol/L to <2.6 mmol/L and LDL-C $\geq$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 $\pm$30%. In the case of utilities and utility multipliers, the difference from 1 was varied by $\pm$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

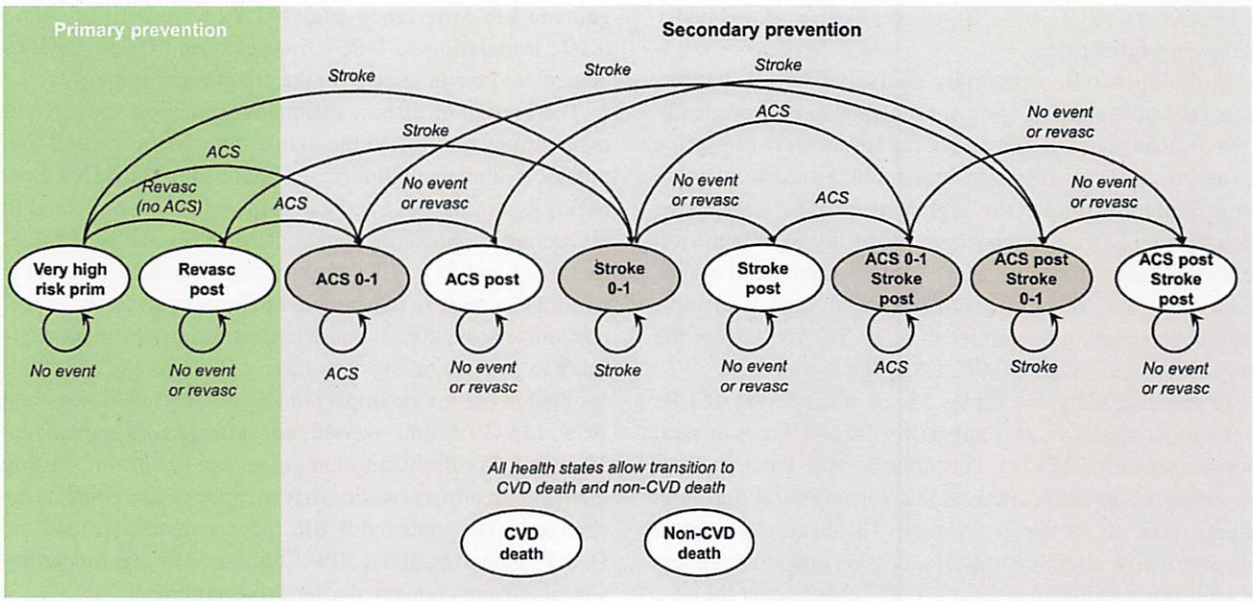


Fig. 1 Markov health state structure. Health states were defined as follows: "Very high risk prim" was used for very high risk patients who have not yet had a prior ischaemic cardiac or cerebrovascular event; "Revasc post" was used for very high risk patients who have not yet had a prior ischaemic cardiac 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 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

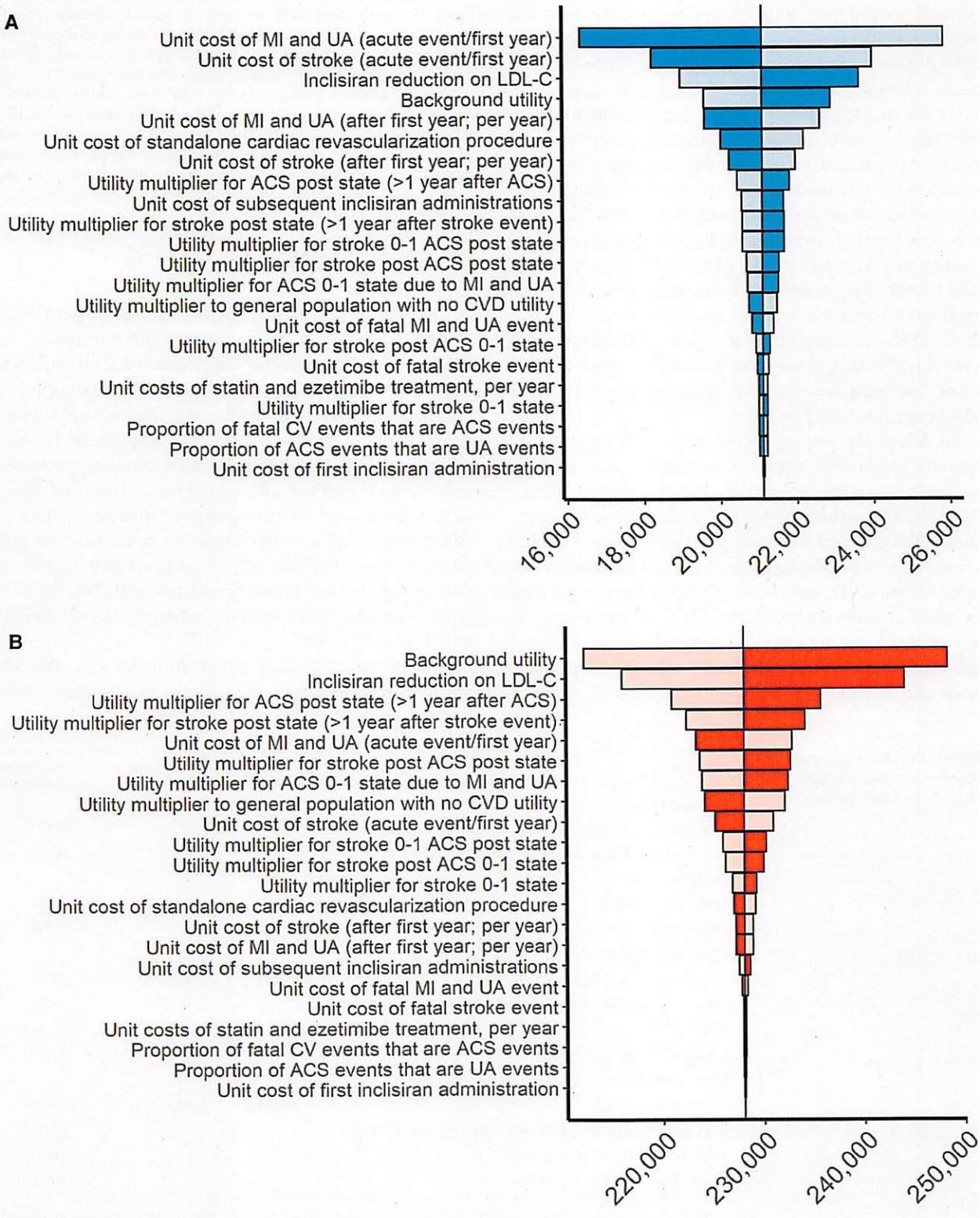
Fig. 2 Univariate sensitivity analysis of cost-effectiveness results by inclisiran price per dose. Panel **A** presents results of the univariate sensitivity analysis under inclisiran price per dose = Swiss francs (CHF) 500. Panel **B** presents results of the univariate sensitivity analysis under inclisiran 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

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



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),

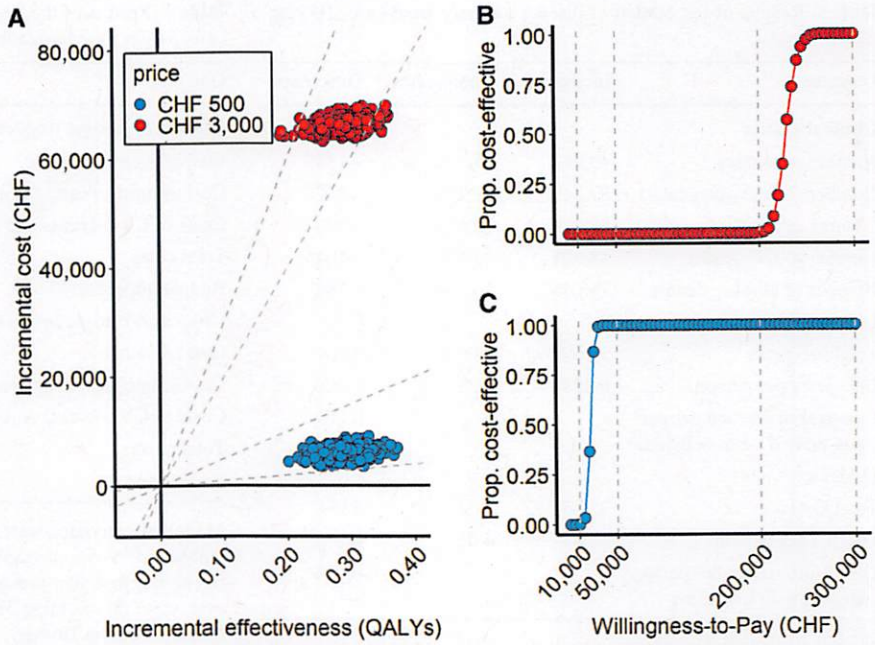


Fig. 3 Probabilistic sensitivity analysis-based cost-effectiveness plane and cost-effectiveness acceptability curves from 10,000 iterations by inclisiran price per dose. Panel **A** shows the cost and quality-adjusted life year (QALY) differences per person treated with inclisiran. *Dashed lines* represent 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.

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Declarations

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Conflicts of interest/competing interests MS received research funding from Novartis via an employment institution and, unrelated to the work reported in the article, remuneration for participation in advisory boards from Amgen and Sandoz. RM received research funding from Novartis and Amgen via an employment institution unrelated to the work reported in the article.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The parameters values used in the modelling study are included in the published article (and its supplementary information files) or are available from the corresponding author on reasonable request for non-commercial purposes, as is the model. Access to underlying data from the Swiss Federal Office of Statistics, the FIRE database and the Global Burden of Disease project is possible via the data owners, following their regulations. Where relevant, contact can be established with the corresponding author.

Code availability The model was implemented in TreeAge and is available from the corresponding author (MS) on reasonable request for non-commercial purposes.

Author contributions MS conceived and designed the study. MS developed and implemented the model in TreeAge, and performed the model validation. KG, PS and RM contributed to the study design and model development. MS, KG and PS performed the analysis. KG and PS collated data and derived model inputs. RM collated data and derived unit costs. YR and RM provided aggregate FIRE data on patient characteristics, treatments and events in secondary cardiovascular prevention patients. KG and MS drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version.

References

1. Swiss Federal Statistical Office. Cause of death statistics 2017. Cardiovascular diseases and cancer continue to be the leading causes of death in Switzerland. https://www.bfs.admin.ch/bfs/de/home/aktuell/medienmitteilungen.assetdetail.11227251.html. Accessed 15 Sep 2021.
2. Swiss Federal Statistical Office. Medical statistics of hospitals. https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/enquetes/ms.html. Accessed 15 Sep 2021.
3. Wieser S, Riguzzi M, Pletscher M, et al. How much does the treatment of each major disease cost? A decomposition of Swiss National Health Accounts. Eur J Health Econ. 2018;19:1149–61.
4. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for Cardiovascular Disease Prevention in Clinical Practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42:3227–37.
5. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72.
6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2019;41:111–88.
7. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. Nat Rev Cardiol. 2018;15:757–69.
8. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393:407–15.
9. De Vera MA, Bhole V, Burns LC, et al. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol. 2014;78:684–98.
10. Ofori-Asenso R, Ilomaki J, Tacey M, et al. Prevalence and incidence of statin use and 3-year adherence and discontinuation rates among older adults with demuentia. Am J Alzheimers Dis Other Demen. 2018;33:527–34.
11. Ofori-Asenso R, Ilomaki J, Tacey M, et al. Switching, discontinuation, and reeinitiation of statins among older adults. J Am Coll Cardiol. 2018;72:2675–7.
12. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158:526–34.
13. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532–61.
14. Meier R, Rachamin Y, Rosemann T, et al. The impact of the 2019 European guideline for cardiovascular risk management: a cross-sectional study in general practice. J Clin Med. 2020;9:2140.
15. Whayne TF Jr. Defining the role of PCSK9 inhibitors in the treatment of hyperlipidemia. Am J Cardiovasc Drugs. 2016;16:83–92.
16. Hlatky MA, Kazi DS. PCSK9 inhibitors: economics and policy. J Am Coll Cardiol. 2017;70:2677–87.
17. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol. 2019;16:155–65.

18. Swiss Federal Office of Public Health. Spezialitätenliste. 2021. https://www.bag.admin.ch/bag/de/home/begriffe-a-z/spezialitaetenliste.html. Accessed 15 May 2021.
19. Lamb YN. Inclisiran: first approval. Drugs. 2021;81:389–95.
20. Swiss Agency for Therapeutic Products. Authorised human medicines with new active substances. 2021. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines.html. Accessed 15 Aug 2021.
21. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382:1520–30.
22. NICE National Institute for Health and Care Excellence. Single technology appraisal. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]. Committee papers. https://www.nice.org.uk/guidance/gid-ta10703. Accessed 15 Dec 2021.
23. Nordon C, Karcher H, Groenwold RH, et al. The "efficacy-effectiveness gap": historical background and current conceptualization. Value Health. 2016;19:75–81.
24. Ethgen O, Standaert B. Population-versus cohort-based modelling approaches. Pharmacoeconomics. 2012;30:171–81.
25. NICE National Institute for Health and Care Excellence. Single technology appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Committee papers. www.nice.org.uk/guidance/ta393. Accessed 15 Dec 2021.
26. Institute for Health Metrics and Evaluation (IHME). Global health data exchange. http://ghdx.healthdata.org/gbd-results-tool. Accessed 15 Nov 2021.
27. World Health Organization (WHO). Mortality database. https://apps.who.int/healthinfo/statistics/mortality/whodpms/. Accessed 15 Nov 2021.
28. Swiss Federal Statistical Office. Population statistics. 2020. https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/stand-entwicklung/bevoelkerung.assetdetail.9486043.html. Accessed 15 Dec 2020.
29. Chmiel C, Bhend H, Senn O, et al. The FIRE project: a milestone for research in primary care in Switzerland. Swiss Med Wkly. 2011;140:w13142.
30. Morgan C, Durand A, Loh J, et al. Risk of major adverse cardiovascular events (MACE) in ASCVD, ASCVD-risk equivalent and FH patients with elevated low-density lipoprotein cholesterol (LDL-C). Internal report. Neuchâtel: Novartis; 2020.
31. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–19.
32. Perneger TV, Combescure C, Courvoisier DS. General population reference values for the French version of the EuroQol EQ-5D health utility instrument. Value Health. 2010;13:631–5.
33. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13:59–68.
34. Wieser S, Ruthemann I, De Boni S, et al. Cost of acute coronary syndrome in Switzerland in 2008. Swiss Med Wkly. 2012;142: w13655.
35. Pletscher M, Plessow R, Eichler K, et al. Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in Switzerland. Swiss Med Wkly. 2013;143: w13732.
36. Moschetti K, Petersen SE, Pilz G, et al. Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the European Cardiovascular Magnetic Resonance Registry. J Cardiovasc Magn Reson. 2016;18:3.
37. Schur NTS, Reinau D, Schenkglenks M, Meier CR. Helsana-Arzneimittelreport für die Schweiz 2020. Auswertungsergebnisse der Helsana Arzneimitteldaten aus den Jahren 2016 bis 2019. Basel, Switzerland: Helsana, 2020. https://www.helsana.ch/de/helsana-gruppe/medien-publikationen/mitteilungen/arzneimittelreport-2020.html. Accessed 15 Dec 2021.
38. FMH Swiss Medical Association. Ambulante Tarife Tarmed. Bern, Switzerland: FMH, 2020. https://www.fmh.ch/themen/ambulante-tarife/tarmed.cfm. Accessed 15 Sep 2021.
39. ELIGO. Tarmed-Taxpunktwerte-Liste. Tarmed-Taxunktwerte unter KVG, ab Anfang des Monats. 2018. https://eligo.ch/Tarmed-Taxpunktwerte.html. Accessed 15 Dec 2021.
40. Open Drug Database (ODDB). ODDB, 2021. https://ch.oddb.org/de/gcc/price_history/reg/56195/seq/01/pack/002. Accessed 15 Dec 2021.
41. Nghiem N, Wilson N, Blakely T. Technical background to the cardiovascular disease model used in the BODE programme. BODE3 Programme. University of Otago, Wellington, New Zealand, 2015. https://www.otago.ac.nz/wellington/otago070188.pdf. Accessed 15 Dec 2021.
42. TreeAge Healthcare®. Williamstown (MA): TreeAge Software, LLC. https://www.treeage.com/. Accessed 15 Oct 2021.
43. Federal Statistical Office. Statistic on the costs and financing of the health system. 2020. https://www.bfs.admin.ch/bfs/en/home/statistics/health/costs-financing.html. Accessed 15 Jun 2021.
44. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. Value Health. 2012;15:843–50.
45. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS): explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16:231–50.
46. Kam N, Perera K, Zomer E, et al. Inclisiran as adjunct lipid-lowering therapy for patients with cardiovascular disease: a cost-effectiveness analysis. Pharmacoeconomics. 2020;38:1007–20.
47. ClinicalTrials.gov. Identifier NCT03814187, trial to assess the effect of long term dosing of inclisiran in subjects with high CV risk and elevated LDL-C (ORION-8). Bethesda (MD): National Library of Medicine (US); 2021. https://clinicaltrials.gov/ct2/show/NCT03814187. Accessed 15 Sep 2021.
48. ClinicalTrials.gov. Identifier NCT03705234, a randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). Bethesda (MD): National Library of Medicine (US); 2021. https://clinicaltrials.gov/ct2/show/NCT03705234. Accessed 15 Sep 2021.
49. Ludman P, British Cardiovascular Society. BCIS National Audit Adult Interventional Procedures 1st April 2018 to 31st March 2019. 2018.
50. Schulman-Marcus J, Feldman DN, Rao SV, et al. Characteristics of patients undergoing cardiac catheterization before noncardiac surgery: a report from the National Cardiovascular Data Registry CathPCI Registry. JAMA Intern Med. 2016;176:611–8.