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Health Technology Assessment (HTA)

HTA Report

Title	Statins for primary prevention of cardiovascular events and mortality in Switzerland
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Executive Summary

BACKGROUND: Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity worldwide. High blood cholesterol is linked to CVD events. In addition to lifestyle optimization, statins are the first-choice treatment to reduce high blood cholesterol and consequently prevent CVD events. The clinical– and cost-effectiveness of primary prevention of CVD using statins in low or medium risk populations is a topic of debate.

OBJECTIVE: The aim of the HTA is to investigate the clinical efficacy, effectiveness, safety, and cost-effectiveness (covering all HTA domains) of statins compared to no treatment (including lifestyle adaptations) in primary prevention of CVD in certain CVD risk groups.

METHODS: Systematic literature searches were performed in PubMed (MEDLINE) and Embase to identify relevant published evidence for the HTA domains. For the clinical and cost-effectiveness domains, data was extracted from the included studies in predefined evidence tables and summary tables were made for different study types. For the other domains (including ethical, legal, social, and organisational issues), the evidence was described narratively. The preliminary literature search on the cost-effectiveness of statins for primary prevention of CVD in Switzerland did not provide sufficient evidence. Therefore, a de novo cost-effectiveness Markov model was developed, characterising the natural history of the disease in a patient's lifetime in the Swiss clinical practice. This cost-effectiveness model was used to determine the cost-effectiveness of statin therapy versus no statin therapy for primary prevention of CVD applying a lifetime time horizon, discounting of costs and effects with 3%, and assuming real-world adherence (69% in year 1, 60% in subsequent years). The uncertainty around input parameters was explored in sensitivity and scenario analyses. In addition, the maximum annual population-level healthcare costs assuming real-world adherence were estimated.

RESULTS: Evidence from two high quality systematic reviews including data of 37 randomized controlled trials (RCTs) informed the HTA domains efficacy and safety of statin therapy for primary prevention of CVD in adults. Two high quality non-randomised studies provided additional data on

effectiveness and safety. No studies were found on the efficacy of lifestyle adaptations (in combination with statin therapy) for primary prevention of CVD in adults. Statin therapy showed to be effective in the prevention of cardiovascular events and mortality in adults without established CVD. The available data from non-randomised studies was too scarce to draw conclusions on the effectiveness of statins. In most studies, treatment with statins did not result in an increased risk of adverse events. Statin use only resulted in a significant risk increase for hepatic dysfunction (low quality of evidence) and renal dysfunction (moderate quality of evidence). However, there are limitations regarding the definitions of these outcomes in the RCTs. The available evidence for the adverse event myalgia was inconsistent. Although the comparative evidence for safety is inconclusive, the adverse event rate of using statins was low.

No evidence of efficacy, effectiveness, or safety for the different CVD risk groups (low, medium and high) could be presented as risk scores for CVD were hardly reported in the studies.

Results from the de novo economic model showed that from a healthcare payers perspective, applying a lifetime time horizon with discounting, and assuming real-world treatment adherence and no discontinuation due to adverse events, statin therapy for primary prevention of CVD seems to be associated with low ICERs compared to no statin therapy in subgroups with a low, moderate or high CVD risk (i.e. an AGLA risk above 1%), especially for those at younger age and females. ICERs were higher in subgroups with low CVD risk (expressed in AGLA risk), older age and in males.

The scenario and sensitivity analyses showed that a shorter time horizon, applying a higher discount factor, and reduced treatment adherence increased the ICERs significantly. In addition, the effectiveness of statins in reducing CVD events, the proportion of MI versus CVD deaths, and the costs of statin therapy were important parameters that introduced uncertainty about the cost-effectiveness of statin therapy.

Due to a lack of data on the current use of statins for primary prevention of CVD in various CVD risk groups in Switzerland, the budget impact of restricted reimbursement policies compared to the current unrestricted use of statins in Switzerland could not be determined. Instead, the maximum population-level annual healthcare costs of reimbursement policies were estimated assuming all eligible patients would use statins with real-world adherence. The annual costs of reimbursing statin therapies, from a healthcare payers perspective in the Swiss context, ranged from 934 million CHF in case all low, moderate, high and very high risk individuals were to be treated with statins to approximately 4 million CHF in the most restricted reimbursement policy where statin therapies were only reimbursed for people between 60 and 75 years old at high CVD risk.

Relevant legal, social, ethical, and organisational issues identified included that changes in reimbursement policy can further increase health disparities between patients based on sex, race, and socioeconomic status and that real-world adherence to statins differs greatly from adherence in a clinical setting, especially in case of primary prevention.

CONCLUSION: Sufficient evidence shows that statin therapy prescribed to adults without estab-

lished CVD is effec-tive in the prevention of cardiovascular events and mortality under study conditions (i.e. efficacy), but there is limited evidence on safety and effectiveness under real-world settings. Risk scores for CVD were hardly reported in the studies and no stratification of the efficacy, effectiveness, or safety results was available for people with low, medium, or (very) high CVD risk.

Statins can prevent CVD events in patients without CVD without many adverse events at a reasonable cost, especially in subgroups with an AGLA risk score above 1% The cost-effectiveness of statin therapy is highly dependent on model settings and uncertain input parameters. Furthermore, as there is no data on the current use of statins for primary prevention of CVD events in Switzerland, the exact cost savings of disinvestment in statin therapies for the national healthcare budget remain unclear.

Zusammenfassung

HINTERGRUND: Herz-Kreislauf-Erkrankungen (HKE) stellen die weltweit häufigste Todesursache und eine der Hauptursachen für Morbidität dar. Ein hoher Cholesterinspiegel im Blut wird mit HKE-Ereignissen in Verbindung gebracht. Statine sind, zusammen mit einer Optimierung des Lebensstils, die Behandlung erster Wahl, um einen hohen Cholesterinspiegel im Blut zu senken und somit HKE-Ereignisse zu verhindern. Die klinische Wirksamkeit sowie die Kosteneffektivität der HKE-Primärprävention mit Statinen in Populationen mit niedrigem oder mittlerem Risiko sind umstritten.

ZIEL: Das Ziel des HTA besteht darin, die klinische Wirksamkeit, Effektivität, Sicherheit und Kosteneffektivität (was alle HTA-Bereiche abdeckt) von Statinen im Vergleich zu keiner Behandlung (einschliesslich Lebensstilanpassung) in der Primärprävention von HKE in bestimmten HKE-Risikogruppen zu untersuchen.

METHODEN: Systematische Literaturrecherchen wurden in PubMed (MEDLINE) und Embase durchgeführt mit dem Ziel, relevante veröffentlichte Evidenz für die HTA-Domänen zu identifizieren. Für die klinische Wirksamkeit und Kosteneffektivität wurden die Daten aus den eingeschlossenen Studien in vordefinierte Evidenztabellen extrahiert und zusammenfassende Tabellen für verschiedene Studientypen erstellt. Für die anderen Domänen (einschliesslich ethischer, rechtlicher, sozialer und organisatorischer Probleme) wurde die Evidenz narrativ beschrieben. Die vorläufige Literaturrecherche zur Kosteneffektivität von Statinen zur Primärprävention von HKE in der Schweiz lieferte keine ausreichende Evidenz. Daher wurde ein De-novo-Markov-Modell zur Kosteneffektivität entwickelt, das den natürlichen Verlauf der Erkrankung im Leben eines Patienten in der schweizerischen klinischen Praxis charakterisiert. Dieses Kosteneffektivitätsmodell wurde verwendet, um die Kosteneffektivität einer Statintherapie im Vergleich zu keiner Statintherapie zur Primärprävention von HKE zu bestimmen, wobei ein lebenslanger Zeithorizont, eine Diskontierung von Kosten und Effekten mit 3 Prozent und eine Real-World-Adhärenz (69 Prozent im ersten Jahr, 60 Prozent in den folgenden Jahren) angenommen wurden. Die Unsicherheit hinsichtlich der Eingabeparameter wurde in Sensitivitäts- und Szenarioanalysen untersucht. Zudem wurde die maximalen jährlichen Gesundheitskosten auf Bevölkerungsebene unter der Annahme einer Real-World-Adhärenz geschätzt.

ERGEBNISSE: Die Evidenz aus zwei hochwertigen systematischen Übersichtsarbeiten, die Daten aus 37 randomisierten kontrollierten Studien (RCTs) enthielten, bildete die Grundlage für die HTA-Domänen Wirksamkeit und Sicherheit der Statintherapie zur Primärprävention von HKE bei Erwachsenen. Zwei hochwertige nicht-randomisierte Studien lieferten zusätzliche Daten zur Wirksamkeit und Sicherheit. Es wurden keine Studien zur Wirksamkeit von Lebensstilanpassungen (in Kombination mit einer Statintherapie) zur Primärprävention von HKE bei Erwachsenen gefunden. Die Statintherapie hat sich bei der Prävention von kardiovaskulären Ereignissen und der Sterblichkeit bei Erwachsenen ohne bestehende HKE als wirksam erwiesen. Es standen zu wenige Daten aus nicht-randomisierten Studien zur Verfügung, um Rückschlüsse auf die Wirksamkeit von Statinen ziehen zu können. In den meisten Studien führte die Behandlung mit Statinen nicht zu einem erhöhten Risiko für unerwünschte Ereignisse. Die Anwendung von Statinen führte lediglich zu einer signifikanten Erhöhung des Risikos für Leberfunktionsstörungen (geringe Qualität der Evidenz) sowie Nierenfunktionsstörungen (moderate Qualität der Evidenz). Allerdings gibt es Einschränkungen bezüglich der Definitionen dieser Endpunkte in den RCTs. Die vorhandene Evidenz für das unerwünschte Ereignis Myalgie war inkonsistent. Obwohl die vergleichende Evidenz zur Sicherheit nicht eindeutig ist, war die Rate unerwünschter Ereignisse bei der Anwendung von Statinen gering.

Es konnte keine Evidenz für die Wirksamkeit, Effektivität oder Sicherheit für die verschiedenen HKE-Risikogruppen (niedrig, mittel und hoch) vorgelegt werden, da in den Studien HKE-Risikoscores kaum erfasst wurden.

Die Ergebnisse des de novo ökonomischen Modells zeigten, dass aus der Sicht der Kostenträger im Gesundheitswesen, unter Anwendung eines lebenslangen Zeithorizonts mit Diskontierung und unter der Annahme einer Real-World-Therapieadhärenz und keiner Abbrüche aufgrund von unerwünschten Ereignissen, eine Statintherapie zur Primärprävention von HKE im Vergleich zu keiner Statintherapie in Untergruppen mit niedrigem, moderatem oder hohem HKE-Risiko (d. h. einem AGLA-Risikoscore über 1 Prozent) mit niedrigen ICERs assoziiert zu sein scheint, insbesondere für jüngeren Personen und für Frauen. Die ICERs waren höher in Untergruppen mit niedrigem HKE-Risiko (ausgedrückt mittels AGLA-Risikoscore), höherem Alter und bei Männern.

Die Szenario- und Sensitivitätsanalysen zeigten, dass ein kürzerer Zeithorizont, die Anwendung eines höheren Diskontierungsfaktors und eine geringere Therapieadhärenz zu einer signifikanten Erhöhung der ICERs führen. Zudem war die Effektivität von Statinen bei der Reduktion von HKE-Ereignissen, das Verhältnis von Myokardinfarkt zu HKE-Todesfällen und die Kosten der Statintherapie wichtige Parameter, die zu Unsicherheiten hinsichtlich der Kosteneffektivität der Statintherapie führten.

Aufgrund fehlender Daten über den aktuellen Einsatz von Statinen zur HKE-Primärprävention in verschiedenen HKE-Risikogruppen in der Schweiz konnte die Budgetauswirkung einer eingeschränkten Erstattungspolitik im Vergleich zum aktuellen uneingeschränkten Einsatz von Statinen in der Schweiz nicht bestimmt werden. Stattdessen wurden die maximalen jährlichen Gesundheitskosten auf Bevölkerungsebene für die Erstattungspolitik unter der Annahme geschätzt, dass aller berechtigten Patienten Statine mit Real-World-Adhärenz verwenden würden. Die jährlichen

Kosten für die Erstattung von Statin-Therapien aus Sicht der Kostenträger in der Schweiz reichten von 934 Mio. CHF für den Fall, dass alle Personen mit niedrigem, moderatem, hohem und sehr hohem Risiko mit Statinen behandelt würden, bis zu etwa 4 Mio. CHF bei der restriktivsten Erstattungspolitik, bei der Statin-Therapien nur für Personen zwischen 60 und 75 Jahren mit hohem HKE-Risiko erstattet würden.

Zu den relevanten rechtlichen, sozialen, ethischen und organisatorischen Problemen, die identifiziert wurden, gehörte, dass Änderungen in der Erstattungspolitik die gesundheitlichen Ungleichheiten zwischen Patienten auf der Basis von Geschlecht, Rasse und sozioökonomischem Status weiter verstärken können und dass die Adhärenz für Statine in der realen Welt sich stark von der Adhärenz in einer klinischen Umgebung unterscheidet, insbesondere im Fall der Primärprävention.

FAZIT: Es liegt ausreichende Evidenz dafür vor, dass eine Statintherapie, die Erwachsenen ohne bestehende HKE verschrieben wird, unter Studienbedingungen bei der Prävention kardiovaskulärer Ereignisse und der Sterblichkeit wirksam ist (d. h. Wirksamkeit). Jedoch gibt es nur begrenzte Evidenz für die Sicherheit und Effektivität unter Real-World-Bedingungen. Risikoscores für HKE wurden in den Studien kaum berichtet und es gab keine Stratifizierung der Ergebnisse betreffend Wirksamkeit, Effektivität oder Sicherheit für Personen mit niedrigem, mittlerem oder (sehr) hohem HKE-Risiko.

Statine können HKE-Ereignisse bei Patienten ohne HKE zu vertretbaren Kosten und ohne, dass viele unerwünschte Ereignisse auftreten, verhindern, insbesondere in Untergruppen mit einem AGLA-Risikoscore über 1 Prozent. Die Kosteneffektivität der Statintherapie ist in hohem Masse von den Modelleinstellungen und unsicheren Eingabeparametern abhängig. Da überdies keine Daten zum aktuellen Einsatz von Statinen in der Primärprävention von HKE-Ereignissen in der Schweiz vorliegen, bleiben die exakten Kosteneinsparungen durch eine Einschränkung der Erstattung von Statintherapien für das nationale Gesundheitsbudget unklar.

Synthèse

CONTEXTE: les maladies cardiovasculaires (MCV) sont la première cause de décès et l'une des principales causes de morbidité dans le monde. Un taux de cholestérol élevé dans le sang est associé à un risque d'accident cardiovasculaire. Outre l'amélioration du mode de vie, la prise de statines constitue le traitement de première intention pour réduire un taux de cholestérol élevé et, partant, prévenir les accidents cardiovasculaires. Or le rapport coût-efficacité clinique des statines dans la prévention primaire des MCV au sein des populations présentant un risque faible ou moyen fait débat.

OBJECTIF: le but de l'ETS est d'étudier l'efficacité potentielle, l'efficacité réelle, l'innocuité et le rapport coût-efficacité (dans tous les domaines de l'ETS) des statines par rapport à l'absence de traitement (y compris l'adaptation du mode de vie) dans la prévention primaire des MCV au sein de certains groupes à risque de MCV.

MÉTHODOLOGIE: des recherches de littérature systématiques ont été effectuées dans PubMed (MEDLINE) et Embase afin d'identifier les données probantes publiées pertinentes pour les domaines de l'ETS. Pour les domaines de l'efficacité clinique et du rapport coût-efficacité, les données ont été

extraites des études incluses dans des tableaux de preuves prédéfinis, et des tableaux récapitulatifs ont été élaborés pour différents types d'études. Pour les autres domaines (y compris les questions éthiques, juridiques, sociales et organisationnelles), les données probantes ont été décrites de façon narrative. La recherche de littérature préliminaire sur le rapport coût-efficacité des statines dans la prévention primaire des MCV en Suisse n'ayant pas fourni de données probantes suffisantes, un modèle coût-efficacité de Markov *de novo* caractérisant l'histoire naturelle de la maladie au cours de la vie d'un patient dans la pratique clinique suisse a été développé. Ce modèle a été utilisé pour déterminer le rapport coût-efficacité du traitement par statines par rapport à l'absence d'un tel traitement dans la prévention primaire des MCV en se fondant sur l'horizon temporel d'une vie entière, sur une actualisation des coûts et des effets de 3 % et sur une adhésion thérapeutique réelle (69 % la première année, 60 % les années suivantes). L'incertitude entourant les paramètres d'entrée a été explorée dans différentes analyses de sensibilité et de scénarios. Les coûts annuels maximaux de la santé ont en outre été estimés à l'échelle de la population sur la base de conditions d'adhésion réelles.

RÉSULTATS: les données probantes de deux revues systématiques de haute qualité incluant les résultats de 37 essais randomisés contrôlés (ERC) informent sur l'efficacité et l'innocuité du traitement par statines dans la prévention primaire des MCV chez les adultes. Les données obtenues dans ces deux domaines de l'ETS ont été complétées par deux études non randomisées de haute qualité. Le traitement par statines s'est révélé efficace pour prévenir les accidents cardiovasculaires et la mortalité chez les adultes ne présentant pas de MCV. Les données provenant des études non randomisées étaient trop limitées pour tirer des conclusions sur l'efficacité des statines. Dans la plupart des études, le traitement par statines n'a pas augmenté le risque d'effets indésirables, sauf pour le dysfonctionnement hépatique (faible niveau de preuve) et le dysfonctionnement rénal (niveau de preuve modéré), pour lesquels une augmentation significative du risque a été constatée. Il existe toutefois des limitations quant à la définition de ces résultats dans les ERC. Les données probantes disponibles concernant les myalgies susceptibles d'être provoquées par la prise de statines sont incohérentes. Bien que les preuves comparatives d'innocuité ne soient pas concluantes, la fréquence des effets indésirables est faible.

Aucune preuve de l'efficacité potentielle, de l'efficacité réelle ou de l'innocuité pour les différents groupes présentant un risque (faible, moyen et élevé) de MCV n'a pu être établie du fait que les scores de risque de MCV figurent rarement dans les études.

Du point de vue des agents payeurs du système de santé, les résultats du modèle économique *de novo* ont révélé que, si l'on se fonde sur l'horizon temporel d'une vie entière, sur une actualisation des coûts et des effets de 3 %, sur une adhésion thérapeutique réelle et sur l'absence d'interruption pour cause d'effet indésirable, le traitement par statines au titre de prévention primaire des MCV semble correspondre à un RCED faible comparé à l'absence d'un tel traitement dans les sous-groupes présentant un risque de MCV faible, moyen ou élevé (c.-à-d. un risque GSLA supérieur à 1 %), en particulier parmi les jeunes et les femmes. Les RCED étaient plus élevés dans les sous-

groupes présentant un faible risque de MCV (exprimé sous forme de risque GSLA), chez les personnes plus âgées et chez les hommes.

Les analyses de scénarios et de sensibilité ont indiqué qu'un horizon temporel plus court, un facteur d'actualisation plus élevé et une adhésion thérapeutique réduite augmentaient considérablement le RCED. De plus, l'efficacité des statines dans la réduction des accidents cardiovasculaires, la proportion de décès par infarctus du myocarde par rapport aux décès par MCV et le coût des traitements à base de statines constituaient des paramètres importants qui entraînaient une incertitude quant au rapport coût-efficacité de ces traitements.

Vu le manque de données concernant l'utilisation actuelle des statines dans la prévention primaire des MCV au sein des divers groupes présentant des risques de MCV en Suisse, il n'a pas été possible de déterminer l'impact budgétaire de politiques de remboursement restrictives comparé à la situation actuelle d'utilisation illimitée des statines dans notre pays. En guise d'alternative, les coûts annuels maximaux de la santé résultant de la politique de remboursement à l'échelle de la population ont été estimés en tablant sur le fait que tous les patients éligibles prendraient des statines dans des conditions d'adhésion thérapeutique réelles. Dans la perspective des agents payeurs du système de santé, les coûts annuels résultant du remboursement des traitements par statines dans le contexte suisse représentaient entre 934 millions de francs, dans l'hypothèse où l'ensemble des individus présentant un risque faible, modéré, élevé ou très élevé serait traité à l'aide de statines, et environ 4 millions de francs, dans le cas de la politique de remboursement la plus restrictive ne finançant les traitements par statines que pour personnes âgées de 60 à 75 ans présentant un risque de MCV élevé.

Parmi les questions juridiques, sociales, éthiques et organisationnelles pertinentes identifiées figurait le risque qu'une modification de la politique de remboursement creuse encore plus les inégalités sanitaires liées au sexe, à la race et au statut socioéconomique des patients et que l'adhésion réelle au traitement par statines soit très différente de celle observée dans un cadre clinique, en particulier en cas de prévention primaire.

CONCLUSION: Il existe suffisamment de données probantes pour établir l'efficacité d'un traitement par statines chez des adultes ne présentant pas de MCV pour prévenir les accidents cardiovasculaires et la mortalité dans des conditions d'études (c.-à-d. l'efficacité potentielle), mais pas pour prouver l'innocuité et l'efficacité du traitement dans des conditions réelles. Les scores de risque de MCV sont rarement fournis dans les études et aucune stratification des résultats relatifs à l'efficacité potentielle, l'efficacité réelle ou l'innocuité chez les personnes présentant un risque de MCV faible, moyen ou (très) élevé n'est disponible.

Les statines permettent de prévenir les accidents cardiovasculaires chez les patients ne présentant pas de MCV sans provoquer d'effets indésirables majeurs et à un coût raisonnable, en particulier dans les sous-groupes où le score de risque GSLA est supérieur à 1 %. Le rapport coût-efficacité du traitement par statines dépend fortement des options du modèle et de paramètres d'entrée incertains. Par ailleurs, vu l'absence de données sur l'utilisation actuelle des statines dans la prévention primaire

des accidents cardiovasculaires en Suisse, le coût exact des économies qui résulteraient d'une restriction des remboursements des traitements par statines pour le budget national en matière de santé demeure flou.

Sintesi

SITUAZIONE INIZIALE: le malattie cardiovascolari (MCV) sono classificate come la prima causa di mortalità e sono tra le principali cause di morbilità in tutto il mondo. L'ipercolesterolemia è collegata ad eventi cardiovascolari (eventi CV). Oltre a migliorare lo stile di vita, le statine sono il trattamento di prima linea per ridurre l'ipercolesterolemia e quindi per prevenire gli eventi CV. L'efficacia clinica e il rapporto costo-efficacia della prevenzione primaria di MCV impiegando le statine in gruppi di popolazione a rischio MCV medio o basso è un argomento dibattuto.

OBIETTIVO: lo scopo della valutazione delle tecnologie sanitarie (Health Technology Assessment HTA) è esaminare l'efficacia, l'appropriatezza, la sicurezza nonché il rapporto costo-efficacia (in tutti i settori in cui è applicata l'HTA) dell'impiego di statine rispetto ai casi in cui il trattamento non è adottato (incluse le modifiche dello stile di vita) nella prevenzione primaria di MCV in determinati gruppi a rischio MCV.

METODOLOGIA sono state condotte ricerche della letteratura sistematica in PubMed (MEDLINE) ed Embase per identificare le evidenze di rilievo per i settori HTA. I dati riguardanti i settori dell'efficacia clinica e dell'analisi costo-efficacia sono stati estratti dagli studi inclusi nelle tabelle di evidenza predefinite dopodiché sono state allestite tabelle riassuntive per i diversi tipi di studio. Per gli altri aspetti (inclusi quelli etici, legali, sociali e organizzativi), le evidenze sono state descritte in modo narrativo. La ricerca preliminare della letteratura sul rapporto costo-efficacia delle statine per la prevenzione primaria di MCV in Svizzera non ha prodotto prove sufficienti. Pertanto, è stato sviluppato il nuovo modello di analisi costo-efficacia di Markov, che descrive il decorso naturale della malattia durante la vita di un paziente nella prassi clinica svizzera. Questo modello di analisi è stato utilizzato per determinare il rapporto costo-efficacia dell'applicazione del trattamento statinico rispetto a una sua non applicazione, della prevenzione primaria di MCV mediante una stima dei costi e dei benefici in tempo-vita, applicando un tasso di sconto del 3 per cento per l'efficacia dei costi ed assumendo un'adesione alla terapia farmacologica in condizioni reali (69 % nell'anno 1, 60 % negli anni successivi). L'incertezza dei parametri di input è stata studiata mediante analisi di sensibilità e analisi di scenario. Inoltre, sono stati stimati i costi sanitari massimi annuali della popolazione ipotizzando un'aderenza alla terapia farmacologica in condizioni reali.

RISULTATI: l'evidenza di due riesami sistematici di elevata qualità, che includono dati di 37 studi randomizzati controllati (RCT), ha fornito informazioni sui settori HTA dell'efficacia e della sicurezza della terapia statinica per la prevenzione primaria di MCV negli adulti. Due studi non randomizzati di elevata qualità hanno fornito dati supplementari sull'efficacia e sulla sicurezza. La terapia statinica si è rivelata efficace nella prevenzione di eventi CV e della mortalità negli adulti non affetti da MCV accertate. I dati disponibili provenienti dagli studi non randomizzati non erano sufficienti per trarre conclusioni sull'efficacia delle statine. Nella maggior parte degli studi, l'applicazione di trattamenti

statinici non ha fatto emergere un rischio accresciuto di eventi avversi. L'impiego di statine ha mostrato unicamente un aumento significativo del rischio d'insorgenza di disfunzioni epatiche (bassa qualità delle evidenze) e renali (qualità moderata delle evidenze). Tuttavia, ci sono restrizioni per quanto riguarda le definizioni di questi risultati negli RCT. Le evidenze disponibili per l'evento avverso della mialgia non erano sufficienti. Nonostante l'evidenza comparativa in materia di sicurezza fosse insufficiente, il tasso di eventi avversi in caso di applicazione di trattamenti statinici era basso.

Non è stato possibile presentare alcuna prova di efficacia, efficienza o sicurezza per i diversi gruppi a rischio MCV (basso, medio ed elevato), poiché gli studi non riportavano, in pratica, alcuna classificazione di rischio per le MCV.

I risultati del nuovo modello economico hanno mostrato che dal punto di vista dei paganti del settore sanitario, applicando una stima dei costi e dei benefici in tempo-vita nonché tassi di sconto e assumendo un'aderenza senza discontinuità alla terapia farmacologica in condizioni reali dovuta a eventi avversi, la terapia statinica per la prevenzione primaria di MCV sembra essere associata a un ICER basso (rapporto incrementale costo-efficacia) rispetto alla non applicazione di questa terapia tra i sottogruppi a rischio MCV basso, medio o elevato (cioè un rischio superiore all'1 % - calcolato secondo l'AGLA, il Gruppo di lavoro lipidi e aterosclerosi della Società Svizzera di Cardiologia), specialmente per i gruppi più giovani e per le persone di sesso femminile.

Le analisi di sensibilità e le analisi di scenario hanno mostrato che su un arco temporale breve, applicando un tasso di sconto più elevato e con una minore aderenza alla terapia farmacologica in condizioni reali, l'ICER aumenta in modo significativo. Inoltre, l'efficacia delle statine nel ridurre gli eventi CV, la proporzione d'infarti miocardici (MI) rispetto ai decessi MCV, e i costi della terapia statinica erano parametri importanti che hanno introdotto incertezza sul rapporto costo-efficacia di questa terapia.

Data la mancanza di dati sull'impiego attuale delle statine per la prevenzione primaria di MCV in diversi gruppi a rischio MCV, non è stato possibile determinare l'impatto sul bilancio della politica restrittiva di rimborso rispetto all'attuale impiego non restrittivo delle statine in Svizzera. Invece, i costi sanitari annuali massimi della popolazione dovuti alle politiche di rimborso sono stati stimati assumendo che tutti i pazienti idonei facciano uso di statine mantenendo un'aderenza alla terapia farmacologica in condizioni reali. Secondo la prospettiva dei paganti, in Svizzera i costi annuali della rimunerazione delle terapie statiniche variano da 934 milioni di franchi, nel caso in cui tutte le persone a rischio MCV basso, medio e (molto) elevato siano trattate con statine, fino a circa 4 milioni di franchi nel caso di una politica di rimborso il più restrittiva possibile, in cui le terapie statiniche siano rimunerate solo per le persone a rischio elevato MCV in età compresa tra i 60 e i 75 anni.

Gli aspetti legali, sociali, etici e organizzativi rilevanti identificati includono che i cambiamenti della politica di rimborso possono acuire ulteriormente le disparità di salute tra i pazienti in base al sesso, all'origine etnica e allo status socioeconomico e che l'aderenza alla terapia farmacologica statinica in condizioni reali differisce notevolmente dall'aderenza in un contesto clinico, specialmente in caso di prevenzione primaria.

CONCLUSIONE: Vi è un'evidenza sufficiente a prova che la terapia statinica prescritta ad adulti senza MCV accertata è efficace nella prevenzione degli eventi CV e della mortalità in condizioni di studio (ossia l'efficacia), ma l'evidenza sulla sicurezza e l'efficacia in condizioni reali è limitata.

I punteggi di rischio MCV non sono riportati negli studi e nessuna stratificazione dei risultati di efficacia, efficienza o sicurezza era disponibile per le persone a rischio MCV basso, medio o (molto) elevato.

Le statine possono prevenire eventi CV in pazienti senza MCV senza eventi avversi frequenti a un costo ragionevole, soprattutto nei sottogruppi con un punteggio di rischio AGLA superiore all'1 per cento. Il rapporto costo-efficacia della terapia statinica dipende notevolmente dalle impostazioni del modello e dall'incertezza dei parametri di input. Inoltre, dato che non ci sono dati sull'impiego attuale delle statine per la prevenzione primaria degli eventi CV in Svizzera, il risparmio esatto dei costi dovuto al mancato investimento nelle terapie statiniche per il bilancio sanitario nazionale rimane poco chiaro.

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Abbreviations and acronyms

ACC/AHA	American College of Cardiology/American Heart Association
AGLA	Schweizer Arbeitsgruppe Lipide und Atherosklerose/Swiss Atherosclerosis Association
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-Effectiveness
CHD	Coronary Heart Disease
CHEC	Consensus Health Economic Criteria
CHF	Swiss Franc
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular Disease
e.g.	Exempli gratia (for example)
FOPH	Federal Office of Public Health
FRS	Framingham Risk Score
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé (French National Authority for Health)
HMG CoA	Hydroxymethyl glutaryl coenzyme A reductase
HRQoL	Health-Related Quality of Life
hs-CRP	High sensitivity C-reactive protein
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
i.e.	Id est (that is)
IRR	Incidence Rate Ratio
LDL-C	Low Density Lipoprotein Cholesterol
LY(s)	Life Year(s)
MESH	Medical Subject Headings
MI	Myocardial Infarction
NA	Not Applicable
NHS	National Health Service
NHS/EED	National Health Service Economic Evaluation Database

NICE	National Institute for Health and Care Excellence
NR	Not Reported
OTC	Over The Counter
OWSA	One-Way Sensitivity Analysis
PDC	Percentage of days covered
PICO	Patients, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROCAM	Prospective Cardiovascular Münster Model
PSA	Probabilistic Sensitivity Analysis
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
QRISK	Prediction algorithm for cardiovascular disease
RCT/RCTs	Randomised Controlled Trial/Randomised controlled trials
SCORE	Systematic Coronary Risk Evaluation
SD	Standard Deviation
SMR	Standard Mortality Rate
SR/SRs	Systematic Review/ Systematic Reviews
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
US	United States
WHO	World Health Organisation
ZiN	Zorginstituut Nederland (National Health Care Institute)

Objective of the HTA report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of statin therapy in adults without established cardiovascular disease (CVD) and with low, medium, and (very) high CVD risk, because its clinical- and cost-effectiveness compared to no treatment and/or lifestyle adaptations has been questioned.

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent, and involves multiple stakeholders. The domains covered in an HTA report include clinical efficacy, effectiveness and safety, cost-effectiveness, budget impact, legal, social, ethical, and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable, and high-quality health system.

1 Policy question and context

Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity worldwide. High blood cholesterol is linked to CVD events. Statins, cholesterol lowering drugs, are the first-choice treatments to reduce high blood cholesterol.

There is strong evidence of the effectiveness of statins in people who experienced a cardiovascular event (secondary prevention)[1] and in people at high risk of CVD (primary prevention)[1]. Evidence on the effectiveness and cost-effectiveness of statin use in people at low or medium risk of CVD is limited.[2] Therefore, the clinical- and cost-effectiveness of primary prevention of CVD using statins in low or medium risk populations is not known. As the size of these lower risk groups is large, prescribing statins to all these people has a large impact on the national healthcare budget.

The aim of the HTA theme brought forward by the applicant curafutura[a] is to investigate the clinical effectiveness, safety, and cost-effectiveness (including all HTA domains) of statins in primary prevention of CVD in Switzerland.

2 Research question

What are the efficacy, effectiveness, and safety, as well as the costs (cost-effectiveness) and budget impact of statin therapy in adults (and for different age groups) without established CVD and with low, medium, and (very) high CVD risk (i.e. primary prevention) compared to placebo, no treatment, or adaption of lifestyle?

3 Medical background

CVDs are a group of disorders of the heart and blood vessels and comprise a wide range of diseases. According to the definition of the World Health Organisation (WHO), CVDs include the following.[3]

- Coronary heart disease (disease of the blood vessels supplying the heart muscle), including myocardial infarction (MI), and angina.
- Cerebrovascular disease (disease of the blood vessels supplying the brain), including ischaemic and haemorrhagic stroke.

[a] Curafutura is a Swiss health insurer association.

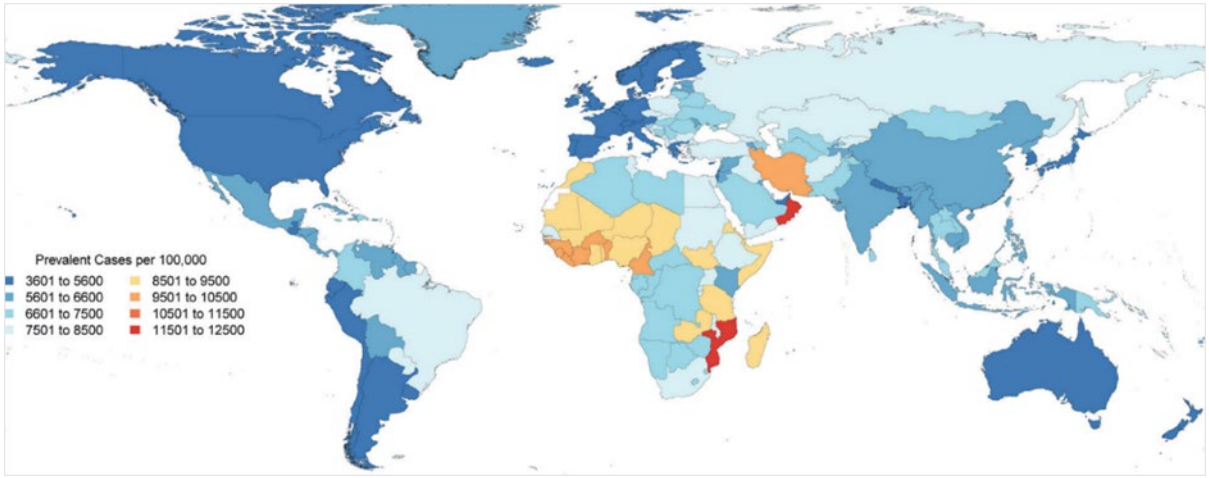
- Peripheral arterial disease (disease of blood vessels supplying the arms and legs).
- Rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria).
- Congenital heart disease (malformations of heart structure existing at birth).
- Deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs).

There are often no symptoms of the underlying disease of the blood vessels; a heart attack or stroke may be the first sign of underlying disease. Symptoms of a heart attack include pain or discomfort in the centre of the chest, in the arms, left shoulder, elbows, jaw, or back. Stroke is mostly associated with sudden weakness of the face, arm, or leg; mostly on one side of the body. Symptoms of rheumatic heart disease include shortness of breath, fatigue, irregular heartbeats, chest pain, and fainting.[4]

CVDs place a high social burden on developed countries, including impaired quality of life, reduced economic activity, and large use of health service resources.[2] Furthermore, CVDs remain the leading cause of morbidity and mortality for both women and men in Western countries, such as Switzerland.[5] Globally, there were about 423 million prevalent CVD cases in 2015. The age-standardised prevalence of CVD varied by country; in Switzerland the number of prevalent cases per 100,000 was in the range of 3,601 to 5,600, as in most neighbour countries (Figure 1).[6]

In 2016, approximately 17.6 million deaths were attributed to CVD globally, which represents an increase of 14.5% from 2006. In Switzerland the age-adjusted death rate for CVD was 112.1 per 100,000 in men and 44.7 per 100,000 in women.[7]

Figure 1. Global map of age-standardised prevalence of CVD in 2015[6]



Important risk factors for CVD include genetic factors and behavioural factors such as tobacco use, unhealthy diets, physical inactivity, and harmful use of alcohol. The effects of these behaviours may appear in individuals as raised blood pressure, raised blood glucose, raised blood lipids, overweight, and obesity.[4]

As documented by genetic, pathology, observational, and intervention studies, dyslipidaemia and especially hypercholesterolaemia plays a crucial role in the development of CVD. Most cholesterol is normally carried in the blood in low-density lipoprotein (LDL). There is a strong positive association between LDL and CVD risk: reducing the plasma LDL concentration by 1.0 mmol/L causes a corresponding 20% to 25% risk reduction in CVD mortality and non-fatal MI.[8] This correlation exists in both men and women and in those with and without established CVD. The reduction of LDL is therefore of prime concern in the prevention of CVD.[9] LDL consists of several subclasses of particles with different sizes and densities, which have different atherogenic potential. For example small dense LDL has great atherogenic potential, therefore the small dense LDL proportion is a better marker for prediction of CVD than total LDL.[10]

Smoking cessation, healthy diets, and regular physical activity can lower the risk of CVD. In addition, drug treatment may be necessary to reduce the plasma LDL-C concentration and as a result lower the CVD risk.[4] Statins are a class of lipid-lowering drugs and are first choice agents for reducing plasma LDL-C.[2–11] Statins may be used for the primary or secondary prevention of CVD: primary prevention comprises treating people without established CVD (but who may be at risk of future CVD events), whereas secondary prevention involves treating persons with established CVD.[11]

It is important for clinicians to be able to assess CVD risk rapidly and accurately, so that they can make the right management decisions. Prevention of CVD should be adapted to an individual's total CVD risk: the higher the risk, the more intense the action should be.[9] Several scoring systems, with various advantages and disadvantages, exist to assess CVD risk, such as the Prospective Cardiovascular Münster Model by the Arbeitsgruppe Lipide und Atherosklerose, a workgroup of the Swiss Society of Cardiology (PROCAM/AGLA[b]), Systemic Coronary Risk Estimation tool (SCORE[c]), QRISK tool[d] (a prediction algorithm for CVD), American College of Cardiology/American Heart Association (ACC/AHA[e]) pooled cohort equation, and the Framingham Risk Score (FRS[f]).

The working group on lipids and atherosclerosis (AGLA) promotes the use of the AGLA or SCORE risk score for the estimation of CVD risk, but the AGLA score is most often used in Swiss clinical practice.[12] The AGLA risk score is based on the Prospective Cardiovascular Münster (PROCAM) Weibull model.[13] The AGLA adjusted the PROCAM by a calibration factor (0.7) to the lower risk of coronary heart disease

[b] https://www.agla.ch/risikoberechnung/agla-risikorechner

[c] https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts

[d] https://qrisk.org/

[e] http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

[f] https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease

(CHD) in Switzerland compared to Germany.[14] SCORE is the European risk scoring system based on the Systematic COronary Risk Evaluation project.[15] The main difference between the risk scoring systems is that AGLA provides the risk of fatal CHD events and non-fatal MI, while SCORE provides the risk of fatal CVD events (including MI, stroke, and coronary revascularization). Romanens et al. showed that the agreement between the AGLA and SCORE risk scores is limited. Many people with an AGLA risk below 10% were at intermediate or even at high risk with SCORE.[14]

Table 3.1. CVD risk group classification according to AGLA and SCORE

Risk group	Low	Intermediate	High	Very High
AGLA[12]				
10-year risk of fatal CHD event or non-fatal MI	<10%	10-20%	>20%	>20%
LDL-C			>4.9 mmol/l	>4.9 mmol/l
Blood pressure			>180 mmHg	>180 mmHg
Other				- Known CAD/ Atherosclerosis - Type 2 diabetes mellitus; Type 1 diabetes mellitus with organ damage - GFR <30 ml/ min/ 1.73 m^2
SCORE[15]				
10-year risk of fatal CVD event	<1%	1-5%	≥5%	
Total cholesterol			>8.0 mmol/l	
Blood pressure			≥180 mmHg	

Abbreviations: CVD = cardiovascular disease, AGLA = Swiss Atherosclerosis Association, SCORE = Systematic COronary Risk Evaluation, MI = myocardial infarction.

4 Technology

4.1 Technology description

Statins, or hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, are one of the most widely prescribed groups of drugs in the world since their introduction to the market more than twenty years ago.[16] Currently, six statin (mono-)drugs are available on the Swiss market.

Statins block the HMG CoA reductase enzymes in the liver which play a key role in cholesterol synthesis.[17,18] Generally, statins are tolerated well by patients. However, some adverse events associated with the intake of statins, e.g. liver dysfunction and myopathy, have been shown to occur.[16]

Typically, statins are administered in the form of tablets, which are to be taken once daily.[19] Often, statin therapy is taken for life, as ceasing statin therapy will result in higher cholesterol levels within a few weeks.

The evidence on the beneficial effects of statin therapy has led to the promotion of their use on a global scale, particularly in the developed world. The overwhelming body of evidence supporting statin therapy, resulted in recommendations in the guidelines of the American Heart Association[20], the European Society of Cardiology[21], and Schweizer Arbeitsgruppe Lipide und Atherosklerose (AGLA).[12] Consequently, statins are currently seen as the first-choice drugs for LDL cholesterol reduction.[22]

4.2 Alternative technologies

Lifestyle changes are often advised before or in conjunction with statin therapy, as these can (further) reduce the cholesterol level and CVD risk. Lifestyle changes that reduce the CVD risk include: 1) healthy and Mediterranean diet, 2) regular exercising, 3) maintaining a healthy weight, and 4) smoking reduction or smoking cessation.[19]

Since the focus of the current project is on the cost-effectiveness of statins, other cholesterol lowering drugs such as PCSK9 inhibitors and ezetimibe are outside the scope of this project.

4.3 Regulatory status / provider

Statins have been used in Switzerland since the 1990's. The Swiss licenced statins are: Atorvastatin (Sortis® and generics), Fluvastatin (Lescol® and generics), Pitavastatin (Livazo®), Pravastatin (Selipran® and generics), Rosuvastatin (Crestor® and generics), and Simvastatin (Zocor® and generics). They must be prescribed by a medical doctor. Currently, statins are reimbursed without any restrictions (if used in their licenced indication) in Switzerland.

5 PICO

Table 5.1. PICO box

P:	Adults (i.e. all ages and according to defined age groups) without established CVD with low, medium, and (very) high CVD risk (according to PRO-CAM/AGLA Tool)
I:	Statins licensed in Switzerland*: atorvastatin (Sortis® and generics), fluvastatin (Lescol® and generics), pitavastatin (Livazo®), pravastatin (Selipran®, Mevalotin® and generics), rosuvastatin (Crestor® and generics), and simvastatin (Zocor® and generics)
C:	Placebo, or no treatment, and/or adaption for lifestyle (i.e. reduction in smoking or smoking cessation, diet adaptation, or increasing physical activity)
O (clinical):	1. All-cause mortality 2. CV mortality (i.e. mortality related to CVD as defined in the included studies). 3. Fatal and non-fatal CV events: a. Fatal CVD not further specified (i.e. fatal CVD in general or multiple diagnoses of fatal CVD grouped together without stratification of the data for the specific diagnosis) b. Non-fatal CVD not further specified (i.e. non-fatal CVD in general or multiple diagnoses of non-fatal CVD grouped together without stratification of the data for the specific diagnosis) c. Specific fatal CVD events (i.e. a fatal event of a specific diagnosis of CVD, such as fatal stroke) d. Specific non-fatal CVD events (i.e. a non-fatal event of a specific diagnosis of CVD, such as non-fatal stroke) e. Fatal CHD not further specified (i.e. fatal CHD in general or multiple diagnoses of CHD grouped together without stratification of the data for the specific diagnosis) f. Non-fatal CHD not further specified (i.e. non-fatal CHD in general or multiple diagnoses of CHD grouped together without stratification of the data for the specific diagnosis) g. Specific fatal CHD events (i.e. a fatal event of a specific diagnosis of CHD, such as fatal MI) h. Specific non-fatal CHD events (i.e. a non-fatal event of a specific diagnosis of CHD, such as non-fatal MI) 4. Combined endpoints (e.g. fatal CVD, non-fatal CVD, fatal CHD, and non-fatal CHD combined) 5. Change in blood cholesterol concentration: a. Change in total blood cholesterol concentration b. Change in LDL-C blood cholesterol concentration 6. Treatment-associated adverse events (i.e. arthritis, cancer, diabetes mellitus type 2, headache/nausea, haemorrhagic stroke, hepatic dysfunction, myalgia, myopathy, renal dysfunction, rhabdomyolysis) 7. Revascularisation 8. Stop/compliance/adherence of/to statin medication** 9. Quality of life 10. Life expectancy
O (health economic):	1. Health-care costs (total and incremental) a. Prevention related: costs of statins, control visits, and treatment of adverse events/side effects

	b. CVD related: costs of treatment of cardiovascular events, follow-up, medication etc. c. Future unrelated healthcare costs: costs in life years gained due to treatment 2. Non-health related care costs within a specific time period † a. Productivity (loss) costs b. Travel costs c. Caregiver costs 3. Incremental cost effectiveness ratio (ICER within a specific time period. 4. Budget impact

* Lovastatin (Mevacor® and generics) is excluded, because it is not licensed in Switzerland; † Non-health related care costs will not be used in the model, but will be collected in the data extraction sheet to provide insight in interpreting the cost-effectiveness results of the published studies. ** Compliance is when a patient deliberately follows a doctor's instructions (passive behaviour). Adherence is when a patient adapts his/her lifestyle based on the doctor's instructions (proactive behaviour).

6 Key HTA questions

Key questions - efficacy, effectiveness, and safety

For the evaluation of the technology the following key questions covering the efficacy, effectiveness, and safety were addressed (definitions provided by the FOPH):

1. What is the efficacy of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high CVD risk compared to placebo, or no treatment, and/or adaption of lifestyle?
2. What is the effectiveness of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high CVD risk compared to placebo, or no treatment, and/or adaption of lifestyle?
3. What is the safety of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high CVD risk compared to placebo, or no treatment, and/or adaption of lifestyle?

Key questions - costs, budget impact, and cost-effectiveness

For the evaluation of the technology the following key questions covering the cost-effectiveness were addressed:

1. What types and amounts of resources are used by patients with and without statin therapy (resource-use identification)?
2. What are the Swiss unit costs of the resources identified in question 1?
3. What are the utilities associated with statin therapy (including disutility of taking a pill every day), adverse events, and CVD events?
4. What are the estimated differences in costs and outcomes of the statin therapy for primary prevention of CVD compared to no statin therapy in adults without established CVD and with low, medium, and (very) high CVD risk?

5. What is the likely budget impact of restricted use compared to unrestricted use of statin therapy for primary prevention of CVD in adults without established CVD and with low, medium, and (very) high CVD risk?
6. What are the uncertainties surrounding the costs and outcomes of the statin therapy for primary prevention of CVD compared to no statin therapy in adults without established CVD and with low, medium, and (very) high CVD risk?

Key questions - legal, social, and ethical issues

For the evaluation of the technology the following key questions covering the legal, social and ethical issues were addressed:

1. Are there specific legal issues associated with a potential change in reimbursement of the statin therapy?
2. What are the morally relevant consequences of a potential change in reimbursement of statin therapy?

Key questions - organisational issues

For the evaluation of the technology the following key question covering the organisational question were addressed:

1. What organisational issues are attached to statin therapy?

7 Efficacy, effectiveness, and safety

7.1 Methodology efficacy, effectiveness, and safety

A systematic review (SR) is a method to collect, critically appraise, and summarise the best available evidence in a transparent and systematic way using generally accepted evidence-based principles. The applied SR methodology follows international standards, such as the Cochrane Collaboration guidelines for performing SRs, and the reporting of this SR follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23,24]

The SR process consists of the following fundamental steps:

1. Formulation of the research questions
2. Comprehensive information search, including defining data sources and search strategy
3. Selection procedure, applying pre-determined inclusion and exclusion criteria
4. Critical appraisal (quality and risk of bias assessment)
5. Data extraction and data synthesis

6. Quality control

The following sections describe the applied systematic review methodology of the efficacy, effectiveness, and safety of statins in primary prevention of CVD; the methodology of the cost-effectiveness SR is described in detail in Chapter 8.1.

7.1.1 Databases and search strategy

Since a large amount of studies is published on statin therapy for the prevention of CVD events and mortality in adults without established CVD, we implemented a stepwise approach for the efficacy, effectiveness, and safety systematic literature search:

I. Search for SRs and meta-analyses.
II. Update search for RCTs based on the most relevant/recent included SRs on statin therapy for primary prevention of CVD events and mortality.
III. Search for long-term outcomes in non-randomised studies (i.e. non-randomised controlled trials, cohort studies, case-control studies).

In search step I a systematic literature search was conducted to find relevant SRs on our review objectives. Other new RCTs might have been published after the closing search date of the included SRs. Therefore, we conducted update searches in a second review step to fill the gap for recently published RCTs. RCTs do not report on effectiveness outcomes and mostly not on long-term safety outcomes; to close the gap on these specific outcomes a third search step to identify non-randomised studies was incorporated. This project also aims to close the gap to the HTA published in 2013 in the report 'Statine zur Primärprävention kardiovaskulärer Erkrankungen' by the Swiss Medical Board.[25]

Search strategy

PubMed (MEDLINE) and Embase.com databases were searched for peer-reviewed scientific literature. The searches were built using the PICO framework (Table 5.1). Since there is large overlap in studies included in other literature databases (such as Cochrane Library) for the efficacy, effectiveness, and safety search it was decided to search in these two main databases. Given the various outcomes of interest, it was decided to keep the search broad. Only search strings on 'Patient' (i.e. CVD) and 'Intervention' (i.e. primary prevention with statins) were compiled in combination with a search string for study designs. The applied search filters were publication period (2013-2019 for the reviews and non-randomised studies search; and 2012-2019 for the RCT search, based on the search strategies of the included SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2]) and the language of the publications (German, English,

French, and Dutch). Furthermore, animal studies, case reports, and non-pertinent publication types (e.g. editorials, letter, and comments) were excluded with additional search strings. Also, SRs were excluded with a search string in review step II and III. The details of the search strategies are included in Appendix 15.1. The search for SRs was conducted on 22 May 2019, and the search for RCTs and non-randomised studies was conducted on 9 July 2019. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract), was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and further manually deleted.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment. In case of doubt, the study was assessed in full text.
2. Screening of full article: the articles selected during the first phase were assessed in full text. Articles were included if the reported information was relevant and of sufficient quality, based on the inclusion and exclusion criteria (see below).

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. The implemented quality control during the selection process is described in a next section.

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes of the three search steps are presented in Table 7.1.

Table 7.1. Inclusion and exclusion criteria efficacy, effectiveness, and safety systematic literature search

	Inclusion	**Exclusion**
Period publication	• 1st step: 2013-22 May 2019 (search in English) • 2nd step: - 2018-9 July 2019 for outcomes reported in Yebyo, 2019 (search in 4 languages); - 2012-9 July 2019 for outcomes reported in Taylor, 2013 (search in 4	

	languages); - 2012-31 December 2017 for outcomes reported in Yebyo, 2019 not covered with their search in English (search in French, German, Dutch) • 3rd step: 2013-9 July 2019 (search in 4 languages)	
Language of publication	German, English, French, Dutch	All other languages
Country of study	Western countries*	All other countries
Study design/ type	• 1st step: SR/meta-analysis • 2nd step: RCTs • 3rd step: non-randomised studies (i.e. non-RCT, cohort study, case-control study)	• Narrative review, without transparent and systematic reporting of the study results • RCTs which were already reported in the SRs included in the scoping & HTA report • Meta-analysis including primary and secondary prevention trials • Cross-sectional studies • Case reports • Non-pertinent publication types (e.g. expert opinion, letter to editor, editorial, comment)
Study quality	• Sufficient methodological quality (see Chapter 7.1.3.)	• Insufficient methodological quality (both inherent methodology as well as insufficient description of inherent methodology provided)
Study population	• Patients ≥18 years who received statins for **CVD indications** • 1st step: - Reviews on CVD in general in patients ≥18 years without established CVD with low, medium, or (very) high CVD risk - Reviews in populations with mixed CVD risk (i.e. not aimed at a specific risk group or age group) • 2nd/3rd step: - Studies on CVD in general or a specific CVD disease (e.g. stroke) in patients ≥18 years without established CVD with low, medium, or (very) high CVD risk - Studies in multiple populations or a specific risk group (e.g. diabetes mellitus)	• Patients <18 years • Patients with chronic diseases who received statins for **non-CVD indications** (e.g. Alzheimer's disease, rheumatoid arthritis, renal disease or aortic stenosis) • Subpopulations of patients (patients with CVD and with e.g. cancer, lung diseases, or hepatic diseases)
Study intervention	• Statins licensed in Switzerland† • Treatment duration ≥12 months • Length of follow-up of outcomes ≥6 months	• All other interventions • Treatment duration <12 months • Length of follow-up of outcomes <6 months
Study comparison	• Placebo • No treatment • Adaption for lifestyle (smoking reduction or stop, diet adaptation, physical activity)	• Statin vs. statin • Statin vs. other cholesterol-lowering drug (e.g. ezetimibe, PCSK9 inhibitors) • Statin vs. lipid-lowering agents (e.g. fibrates) • Different doses of statins • No comparison
Study outcomes	See PICO-Box†	• Other outcomes

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf); † See Table 5.1; Abbreviations: RCT = randomised controlled trial, PICO = Patient population - Intervention – Comparator – Outcome.

Quality control

The following quality control measures were applied during the selection process:

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher. Both researchers categorised the titles as 'include for full-text assessment', 'exclude for full-text assessment', or 'doubt'. If there were differences between the two researchers regarding more than 2% of the articles selected as 'include for full-text assessment', another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 2% discrepancy at 50% of the duplicate selection, the screening of title and abstracts would have been done fully in duplicate by two independent researchers. If the two reviewers disagreed on the relevance of a study, this was discussed. If the differences remained after discussion, the study was assessed in full text. During screening there was less than 2% discrepancy between the two researchers.
- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers. The results were compared and discussed early in the process. If there were differences between the two researchers regarding more than 5% of the articles screened in duplicate, another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 5% discrepancy at 50% of the duplicate selection, the screening of full-text articles would have been done fully in duplicate by two independent researchers. During screening there was less than 5% discrepancy between the two researchers. The remaining full-text selection was done by one researcher in close collaboration with a second reviewer; any doubts were discussed in detail. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

7.1.2 Other sources

During the full-text screening phase, reference lists of relevant SRs found with our systematic literature search were checked to find any other studies or SRs that were not captured with our literature search. For the efficacy, effectiveness, and safety review, three SRs were included by this process and assessed in full text in the scoping phase.

7.1.3 Assessment of quality of evidence

Systematic reviews

The quality of the included SRs was assessed with the AMSTAR-2 checklist (see Appendix 15.2).[27]

RCTs

No additional RCTs were included in the scoping phase. For the quality assessment of the individual RCTs included in the two selected SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2], we built on the applied assessments in these SRs and we did not redo their critical appraisal. Both SRs used the Cochrane risk of bias tool for RCTs (see Appendix 15.2)[28], which categorises the risk of bias of the domains in low risk of bias, moderate or unclear risk of bias, or high risk of bias. Furthermore, Yebyo et al. 2019[26] summarised the risk of bias values for each of the domains and interpreted the overall quality of a RCT as: Good quality: all criteria met (i.e. low risk of bias for each domain) using the Cochrane risk of bias tool; Fair quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; Poor quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results. We also applied these summarised risk of bias values to the RCTs reported only in Taylor et al. 2013[2], as they did not report this themselves.

The overall quality of the evidence was assessed by Yebyo et al.[26] using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[29] approach based on five domains:

- Risk of bias: the 'internal validity' of the evidence (as assessed with the Cochrane risk of bias tool for RCTs; see above).
- Inconsistency: the heterogeneity or variability in the estimates of treatment effect across studies.
- Indirectness: the degree of differences between the population, intervention, comparator for the intervention and outcome of interest across studies.
- Imprecision: the extent to which confidence in the effect estimate is adequate to support a particular decision.
- Publication bias: the degree of selective publication of studies.

The overall quality of evidence is classified as high, moderate, low, or very low:

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

Yebyo et al. did not report a detailed GRADE Summary of Findings Table in their SR or supplementary material. The GRADE approach was not applied in the SR of Taylor et al. 2013.

Non-randomised studies

Since both Yebyo et al. 2019 and Taylor et al. 2013 assessed the quality of the included RCTs based on the criteria described in the Cochrane Handbook of Systematic Reviews 5.0.22, we decided to keep in line with Cochrane and use the quality assessment tool for our included non-randomised studies as suggested in that version of the handbook: the Newcastle - Ottawa quality assessment scale (see Appendix 15.2).[30]

7.1.4 Methodology data analyses efficacy, effectiveness and safety

The data extraction and meta-analyses presented in the two included SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2] were the basis for our data synthesis. When outcomes of interest were reported in both SRs, the more up-to-date data reported in the review of Yebyo et al. was preferred over Taylor et al.

Yebyo et al. performed a random-effect pairwise meta-analysis of all statins as a class and estimated the risk ratio (RR) with 95% confidence intervals (CI) for each outcome. Heterogeneity was inspected using the I^2-statistic. Furthermore, they conducted sensitivity analyses and explored the impact on outcomes by excluding RCTs that included participants with for example a higher proportion (>90%) of cases with diabetes mellitus.[26] Taylor et al. used the fixed-effect method for their meta-analysis; unless data were heterogeneous (i.e. I^2 statistic was >50%), then the random-effects model was used. Risk ratios and odds ratios (OR) with 95% CIs were calculated for dichotomous data. For continuous data (e.g. change in blood cholesterol) pooled mean differences (MD) with 95% CIs were calculated. They considered analyses for potential effect modifiers (i.e. for gender, extent of hyperlipidaemia, and age greater than and less than 65 years), but those were abandoned due to lack of adequate reporting.[2]

The risk ratios and odds ratios including 95% CIs for the efficacy and safety outcomes are summarised in an overview figure (see Figure 5 in Chapter 7.2.4). For interpretation of the results, the line of no effect and areas of the plot which represent the outcomes in favour of the statin or in favour of the control group are clearly highlighted.

The data from the two included non-randomised studies was extracted in a data extraction table and descriptively summarised in the sections on effectiveness and safety.

7.2 Results efficacy, effectiveness, and safety

7.2.1 Evidence base pertaining to efficacy, effectiveness and safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

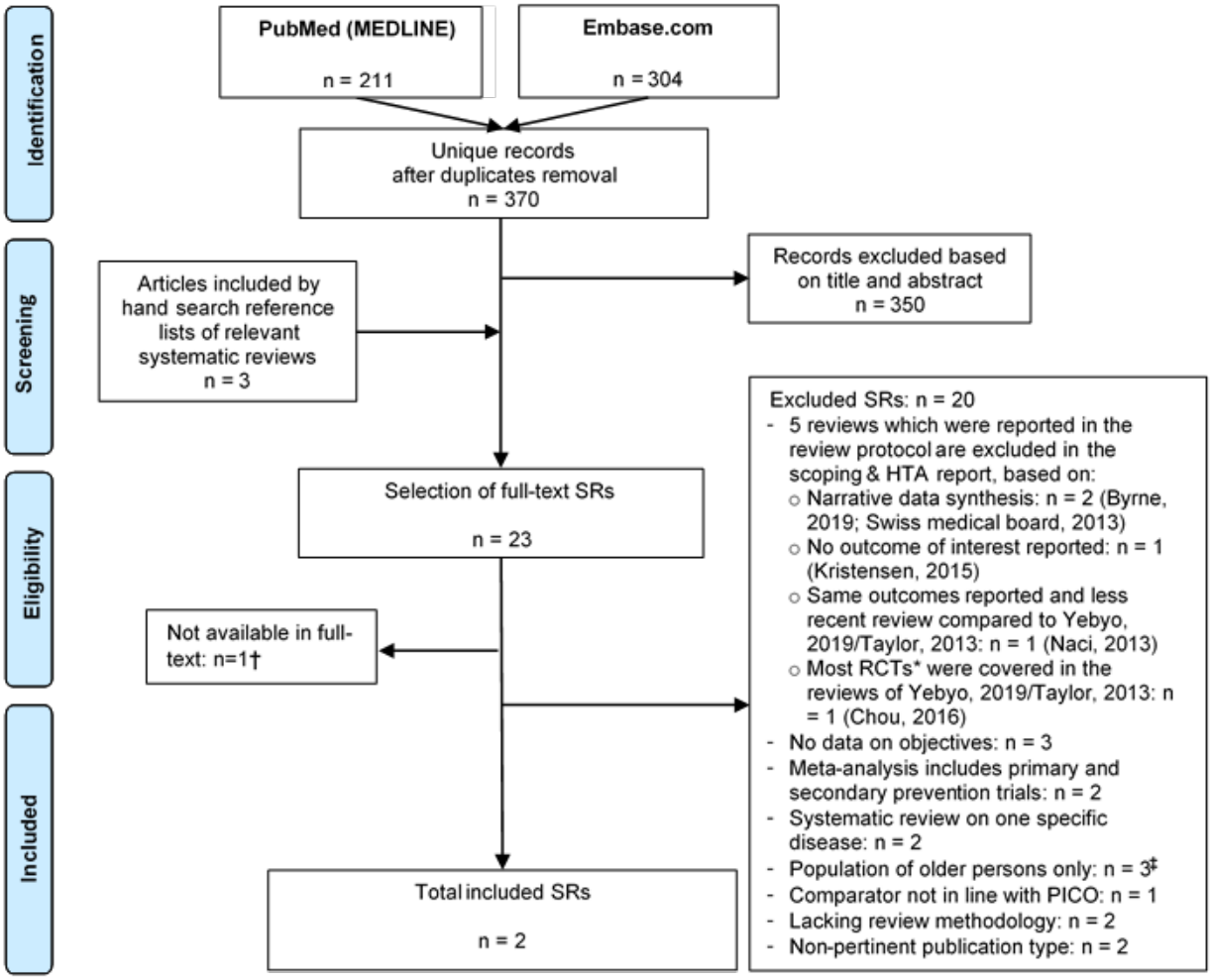
7.2.2 PRISMA flow diagram

Search step I: Search for systematic reviews

In the first search step, 370 unique records were identified in PubMed (MEDLINE) and Embase.com. The PRISMA flowchart is presented in Figure 2. Of those, 350 records were excluded based on their title and abstract. Three SRs were included as a result of the hand-search of reference lists of relevant SRs, resulting in 23 SRs which were screened in full-text. For the first search step, SRs were selected with a broad focus on CVD in populations with mixed CVD risk (i.e. not aimed at one specific CVD disease such as stroke, or a specific risk group such as patients with diabetes mellitus or a population of older persons). The reasons for exclusion were no data on objectives (n=3), meta-analysis includes primary and secondary prevention trials (n=2), SR on one specific disease (n=2), population of older persons only (n=3), comparator not in line with our PICO (n=1), lacking review methodology (n=2), and non-pertinent publication type (n=2). One review was not available in full text (see reference below flowchart). Initially, in the scoping protocol seven SRs were selected on statin therapy for the prevention of CVD events. After more detailed full-text assessment and between-study comparison of the quality and reported outcomes in these SRs, five SRs were eventually excluded (see description of the exclusion reasons in Figure 2) and two SRs (Yebyo et al. 2019[26] and Taylor et al. 2013[2]) were included. The results of two excluded relevant but less recent SRs, Chou et al. 2016[31] and Naci et al. 2013[32], were compared with the results of the SR of Yebyo et al. 2019[26] (see Table II and Table III in Appendix 15.3). We conclude that their review results and conclusions are in line with the included SR of Yebyo et al.[26], and therefore exclusion of the less

recent SRs is justified. The SR of Yebyo et al. 2019 did not include all predefined outcomes of interest, including the outcomes on blood cholesterol. Therefore, the older SR of Taylor et al. 2013 was included to complement Yebyo et al. 2019, after expert consultation with a cardiologist. The applied search strategy in these two SRs was used for an update search on recently published RCTs. This search was also used to develop a search strategy for long-term outcomes in non-randomised studies. The latter search was also built on the search conducted by the Swiss Medical Board[25]; i.e. starting the search in 2013.

Figure 2. PRISMA flowchart systematic reviews on statins for primary prevention of CVD

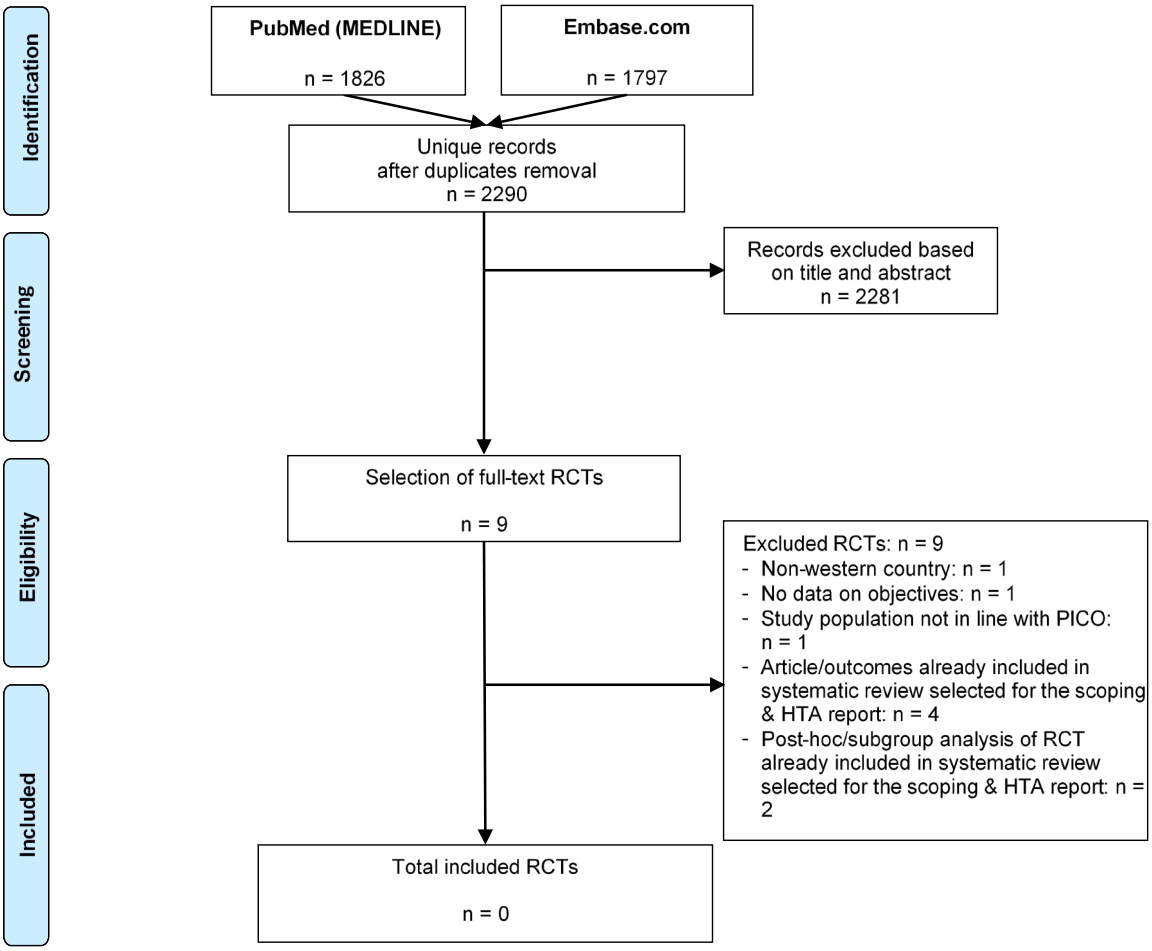


Date of search: 22 May 2019
* 18 of the 19 RCTs included in the Chou, 2016 review were included in Yebyo, 2019 or Taylor, 2013; one RCT was not covered and will be excluded by our criterion for the inclusion of Western countries only: Heljić B, Velija-Asimi Z, Kulić M. The statins in prevention of coronary heart diseases in type 2 diabetics. Bosn J Basic Med Sci. 2009;9(1):71-76; † Kim BH, Cho KI, Jang JS, Park YH, Je HG. Efficacy and safety of statins for primary prevention of cardiovascular events in women and men: Systemic review and up-to-date meta-analysis. Experimental and Clinical Cardiology. 2014;20(1):1222-7. ‡ Three reviews in older populations (Ponce, 2019; Teng, 2015; Savarese, 2013) were excluded after a detailed check. There is almost complete overlap in the included RCTs in these three reviews and all RCTs, except one less recent RCT published in 2003, are covered in the included reviews of Yebyo, 2019 and Taylor, 2013.

Search step II: Update search for RCTs based on the included systematic reviews

In total, 2,290 unique records were identified in PubMed (MEDLINE) and Embase.com for the second search step (Figure 3). Of those, 2,281 records were excluded based on their title and abstract, resulting in nine RCTs selected to be screened in full text. After applying the inclusion and exclusion criteria, all nine RCTs were excluded, because of the following reasons: non-western country (n=1), no data on objectives (n=1), study population not in line with our PICO (n=1), the RCT or outcomes reported in the RCT were already reported in the SRs included in our scoping and HTA report (i.e. in Yebyo et al. 2019[26] or Taylor et al. 2013[2]) (n=4), and post-hoc or subgroup analysis of an RCT already included in the two SRs included in our scoping and HTA report (n=2)[2,26].

Figure 3. PRISMA flowchart RCTs on statins for primary prevention of CVD

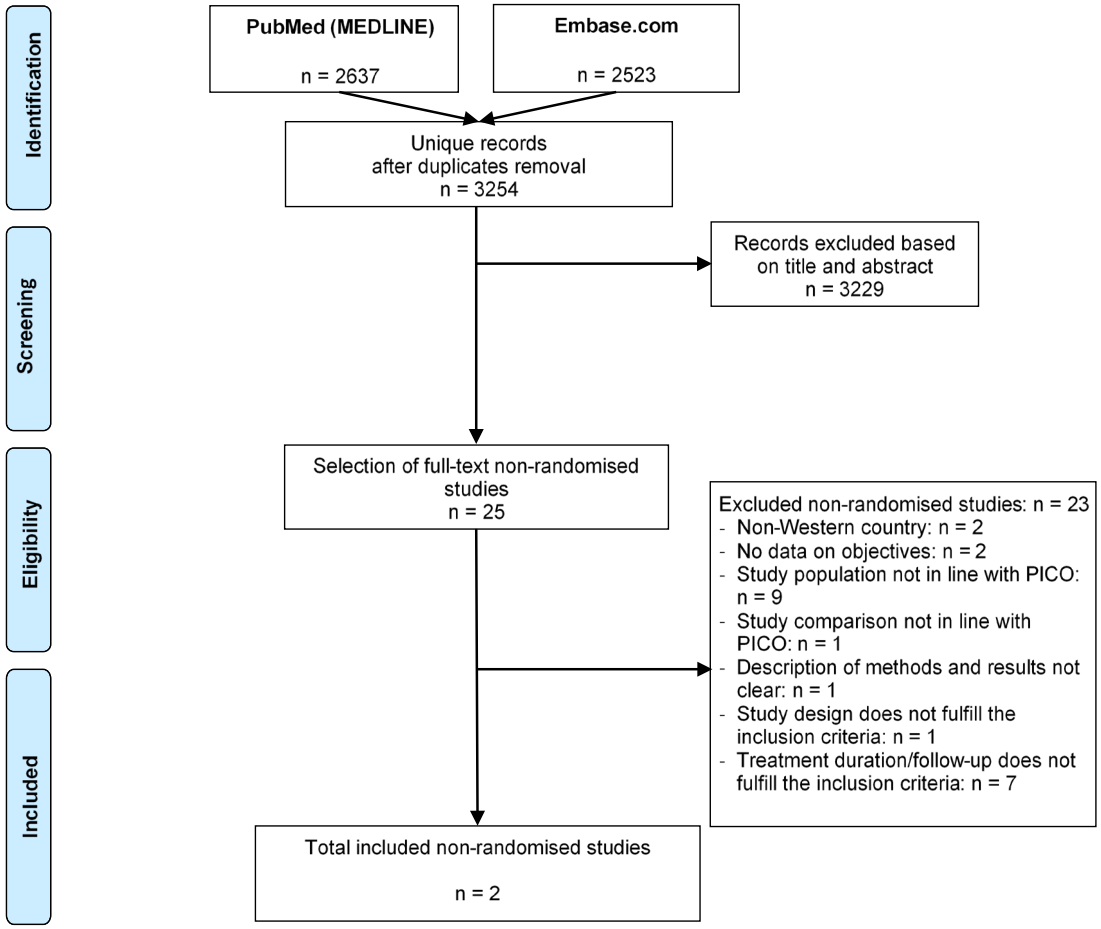


Date of search: 9 July 2019

Search step III: Search for long-term outcomes in non-randomised studies

For the third search step 3,254 unique records were identified in PubMed (MEDLINE) and Embase.com (Figure 4). Of those, 3,229 records were excluded based on their title and abstract, resulting in 25 non-randomised studies selected to be screened in full-text, and two non-randomised studies were finally included. The main reasons for exclusion were study population not in line with our PICO (n=9 studies), and treatment duration or follow-up did not fulfil our inclusion criteria (n=7 studies). A complete overview of the reasons for exclusion is enclosed in the PRISMA flow chart.

Figure 4. PRISMA flowchart non-randomised studies on statins for primary prevention of CVD



Date of search: 9 July 2019

7.2.3 Study characteristics table

Systematic reviews

In the first search step, two high quality SRs were included, which used meta-analyses for the data synthesis.[2,26] The study characteristics of these SRs are outlined in Table 7.2 and the details of the quality assessment are reported in Table 7.3. The most recent SR of Yebyo et al. 2019 was conducted by the

University of Zürich and searched for existing SRs and individual RCTs that compared statins with a placebo or another statin, which were published until January 2018. The SR of Taylor et al. 2013 is an update review of the Cochrane Collaboration, which searched for scientific literature up to January 2012 on the effects of statins in people with no history of CVD. Yebyo et al. included 40 RCTs, of which 33 RCTs compared statins as a class with placebo and 7 RCTs compared two individual statins.[26] In Taylor et al. 18 RCTs comparing statins with placebo or usual care were included.[2] These RCTs provided data on the efficacy and safety outcomes; more details on the included RCTs are described in the next section.

Table 7.2. Study characteristics of the included systematic reviews on primary prevention of CVD

First author	Year	Review objective	Data sources Search period Language	Exclusion criteria	Study population (summary description)	Intervention	Comparator	Included RCTs on primary prevention
Yebyo[26]	2019	To estimate the effectiveness and safety of statins as a class (and of individual statins) for primary prevention of CVD	- SRs and update search individual RCTs - PubMed SRs published between Jan 2013-Nov 2016; update search to Jan 2018 English	- No outcome of interest reported - RCTs that included patients with clinically different risk profile from that of a primary prevention population - RCTs comparing a statin with another active drug or a statin combined with an active drug - ≥10% of patients with history of CVD of total sample size - If cases were disbalanced between statin and placebo arms when <10% of patients with history of CVD of total sample size	Persons without history of any CVD events at baseline *Age (median; IQR)* 58.3 years; 46-76 *Sex (% male, median; IQR)* 61%; 48-77 *Ethnicity (% Caucasian, median; IQR)* 92%; 83-95 *Risk groups (median %; IQR)* - Type 2 diabetes: 14%; 3-95 - Hypertension: 42%; 27-84 - Smoker: 28%; 17-45	Statins (simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, rosuvastatin)	- Placebo - Another statin	- n=40 RCTs; of which n=33 placebo-controlled trials - n=94,283 participants Included RCTs dated from Jan 1985 to Nov 2016
Taylor[2]	2013	To assess the effects, both harms and benefits, of statins in people with no history of CVD	- Built on previous reviews of Bartlett 2005, Ebrahim 1999, Ward 2007 (searches conducted in 2007 were updated) - Cochrane Central Register of Controlled Trials (2011, Issue 4) - MEDLINE OVID (1950-Dec 2011) - EMBASE OVID (1980-Jan 2012) To Jan 2012	- No RCT - Treatment duration <1 year - Follow-up <6 months - RCTs in which statins were used to treat or control chronic conditions - >10% had a history of CVD (including previous angina, MI, and/or stroke)	Adults ≥18 years with no restrictions on total, LDL or HDL cholesterol levels *Age (mean; range)* 57 years; 28-97 *Sex (% male, mean)* 60.3% *Ethnicity (% Caucasian, mean)* 85.9% *Risk groups* - Excluding 4 RCTs that solely recruited patients with diabetes, 1-20% of the patients had diabetes - Excluding 2 RCTs that solely recruited patients with hypertension, 15-67% of	Statins* (pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, cerivastatin)	- Placebo - Usual care	- n=18 RCTs - n=19 trial arms - n=56,934 participants Included RCTs dated from 1994 to 2008

First author	Year	Review objective	Data sources Search period Language	Exclusion criteria	Study population (summary description)	Intervention	Comparator	Included RCTs on primary prevention
			All languages		the patients had hypertension - Smoker: range 10-45%			

Keys: CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high density lipoprotein, LDL = low density lipoprotein, MI = myocardial infarction, QALY = Quality-adjusted life year, RCT = randomised controlled trial, SR = systematic reviews.
* Drug treatments and other interventions were accepted provided they were given to both arms of the intervention groups and adjuvant treatments with one additional drug where a patient developed excessively high lipids during the trial were accepted.

Table 7.3. Quality of the included systematic reviews (assessed with the AMSTAR-2 checklist)[27]

	Yebyo, 2019	Taylor, 2013
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Partial yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Yes
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Partial yes
9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	Yes
OVERALL QUALITY REVIEW	**High quality review**	**High quality review**

Keys: AMSTAR = A MeaSurement Tool to Assess systematic Reviews, PICO = Patient Intervention Comparator Outcome, RoB = risk of bias.

RCTs included in the systematic reviews

In total 40 RCTs were included in the SR of Yebyo et al. 2019[26], of which 33 RCTs compared statins as a class with placebo and 7 RCTs studied the efficacy of two individual statins. These latter RCTs were

out of scope for this HTA. Taylor et al. 2013[2] included 18 RCTs comparing statins as a class with placebo; 5 of the 18 RCTs were not included in the SR of Yebyo et al. The study characteristics of the RCTs included and as reported in these two SRs are outlined in Table 7.5. Yebyo et al. included two publications on the WOSCOPS trial, we presented only the baseline data of the most recent publication of the WOSCOPS trial, resulting in a total of 37 RCTs. The RCTs were published between 1997 and 2017 and the sample size ranged from 47 to 17,802. Most frequently studied statins were pravastatin and atorvastatin. The mean age of the study participants ranged from 49 to 69 years and the percentage of males varied from 0 to 100 percent. The overall quality of the RCTs as assessed in the SRs was good in 12 RCTs, fair in 11 RCTs, and poor in 14 RCTs. The risk of bias is further detailed in Table 7.6.

CVD risk groups

In the SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2] no stratified results are reported for different CVD risk groups (i.e. Yebyo et al. only conducted a sensitivity analysis in which RCTs with a high proportion of diabetes mellitus cases were excluded). Therefore, we checked the individual RCTs for data on CVD risk scores. Only six RCTs reported CVD risk scores for the study population, but three different scoring systems were used and these had no overlap in the definition of and/or stratification in risk groups (see Table 7.4). The risk scores were mostly used for baseline characteristics of the study population and not for stratification of efficacy or safety outcomes, and therefore no results were available stratified for people with low, medium, or (very) high CVD risk.

Table 7.4. CVD risk scores reported in the RCTs included in the systematic reviews of Yebyo, 2019 and Taylor, 2013

Trial name	First author	Year	Included in Yebyo or Taylor	CVD risk score	Description CVD risk score	Risk group	Percentage of patients in risk group
No trial name (Heljić, 2009)[53]	Heljić[53]	2009	Y	CRP	CRP as atherosclerosis marker for primary prevention of major CVD events	- Low risk: <1 mg/cm^3 - Mild risk: 1-3 mg/cm^3 - High risk: >3 mg/cm^3	- Low risk: 0% - Mild risk: 34% - High risk: 66%
CELL A/CELL B	Lindholm[48]	1996	T	Framingham risk score	10-year risk prediction of CVD with prespecified predictors	- Low risk: ≤10% - Intermediate risk: 10-20% - High risk: ≥20%	NR; only mean scores reported
JUPITER	Ridker[57]	2008	Y/T				Low risk: 100%
METEOR	Crouse[63]	2007	Y/T				- ≤10%: 50% - >10%: 50%
COMETS	Stalenhoef[50]	2005	Y	NCEP ATP III risk score	10-year risk assessment based on LDL, total, and HDL cholesterol in combination with major risk factors that modify LDL cholesterol	- Low risk: 0-1 risk factor - Medium risk: ≥2 risk factors & 10-year CHD risk ≤20% - High risk: CHD or CHD-risk equivalent or 10-year CHD risk >20%	- Low risk: 1.2-1.3% - Medium risk: 70.1-72.1% - High risk: 26.7-28.7%
No trial name	Jacobsen[56]	1995	Y	NCEP ATP II risk score	Risk assessment based on LDL cholesterol in combination with major risk factors that modify LDL cholesterol	- Low risk: LDL-C >4.9 mmol/l - Medium risk: LDL-C<4.1 mmol/l with ≥2 risk factors - High risk: previous CAD	- Low risk: 75-78% - Medium risk: 22% - High risk: 0-3%

Keys: CAD = coronary artery disease, CELL = Cost Effectiveness of Lipid Lowering Study, COMETS = COmparative study with rosuvastatin in subjects with METabolic Syndrome, CVD = cardiovascular disease, CRP = c-reactive protein, JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Using Rosuvastatin, METEOR = Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin, NCEP ATP = National Cholesterol Education Program Adult Treatment Panel, NR = not reported, T = Taylor et al. 2013; Y = Yebyo et al. 2018.

Update search for RCTs

With our update search for RCTs based on the search strategies of the SRs of Yebyo et al., 2019 and Taylor et al., 2013, no new RCTs were found on statin therapy for primary prevention of CVD events and mortality.

Non-randomised studies

In our third search step on long-term outcomes in non-randomised studies, two studies were included that provide additional data on the effectiveness and safety outcomes.[33,34] An overview of the study characteristics is included in Table 7.7. Ramos et al. 2018 conducted a retrospective cohort study in Spain with data collected from the database of the Catalan primary care system.[33] In 46,864 people aged 75 years or more without clinically recognised atherosclerotic CVD and with and without type 2 diabetes, they assessed whether statin treatment was associated with a reduction in atherosclerotic CVD and mortality. Izzo et al. 2013 evaluated the risk of incident diabetes in relation to statin prescription in an Italian cohort study including 4,750 hypertensive non-diabetic outpatients, of which 676 patients used statins.[34] Both studies are high quality studies (see Table 7.8).

Table 7.5. Study characteristics of the RCTs included in the systematic reviews of Yebyo, 2019 and Taylor, 2013 (as reported in these reviews)

RCT	Included in Yebyo or Taylor	Publication year	Number of partici-pants	Intervention and dose (mg/day)	Duration (year)	Mean age (years)	Male (%)	White (%)	Black (%)	Mean BMI (kg/m^2)	Smoker (%)	Diabetes Mellitus type 2 (%)	Hypertension (%)	History of CVD (%)	TC (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Sponsor
ACAPS[35]	Y/T	1994	919	Lova (20→40)	3.0	62.0	50	92.1	NR	25.9	56.4	2.3	28.8	0	235.3	155.6	52	G
AFCAPS/TexCAPS[36]	Y/T	1998	6211	Lova (20→40)	5.2	58.0	85	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	I
ALLHAT-LLT[37]	Y	2017	2141	Prava (40)	6.0	68.8	53.1	39.9	35	NR	25.1	51.2	NR	0	225.6	148	47	G
ASCOT-LLA[38]	Y	2003	10305	Atorva (10)	3.3	63.0	81	94.6	NR	28.6	33.2	24.5	100	0	212.6	131.5	50.2	I
ASCOT-LLA_post[39]	Y	2011	4432	Atorva (10)	8	64.3	87.3	88.3	NR	28.9	25.3	28.8	100	0	212.6	131.4	50.2	I
ASPEN[40]	Y/T	2006	1905	Atorva (10)	4.3	60.0	62	84	6.7	28.9	12.5	100	55	4.5	194	113.5	47	I
ASTRONOMER[41]	Y	2010	269	Rosuva (40)	4.0	58.0	62	98.2	NR	28.1	48.4	0	0	0	204.9	123.7	61.8	I
– (Bak, 1998)[42]	Y	1998	215	Prava (20)	0.5	55.9	100	NR	NR	27.1	36.4	NR	NR	0	282.2	201.1	42.5	I
– (Bays, 2004)[43]	Y	2004	770	Simva (10)	0.2	55.4	48.3	88.1	3.4	28.5	NR	4.4	27.6	0	261.6	177.7	52	I
BCAPS[44]	Y	2001	793	Fluva (40)	3.0	61.9	93	NR	NR	25.6	28.9	3.3	13	4.6	235.8	162.4	54.1	I
– (Bone, 2007)[45]	Y/T	2007	604	Atorva (10→40)	1.0	46.0	0	63.1	NR	NR	7.2	0	NR	0	157.7	56.5	24.3	I
CAIUS[46]	T	1996	305	Prava (10)	3.0	55	53	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	I
CARDS[47]	Y/T	2004	2838	Atorva (10)	4.0	62.0	68	94.5	NR	28.8	65.5	100	84	0	208.8	116	54.1	I
CELL A/CELL B[48]	T	1996	227	Prava (10→40)	1.5	49	85	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	I
CERDIA[49]	T	2004	250	Simva (20)	2.0	NR*	NR*	NR*	NR*	NR*	NR*	100	NR*	NR*	NR*	NR*	NR*	I
COMETS[50]	Y	2005	236	Atorva (10→20) vs. Rosuva (10→20)	0.2	57.5	64.2	97.2	NR	30.7	NR	NR	NR	0	251.3	170.1	46.4	I
– (Derosa, 2003)[51]	T	2003	47	Fluva (80)	1.0	51	46	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	NR*	I
– (Gentile, 2000)[52]	Y	2000	165	Atorva (10) vs. Lova (20) vs. Prava (20) vs. Simva (10)	0.5	59.0	67.4	NR	NR	28.7	NR	100	NR	0	NR	NR	NR	G
– (Heljić, 2009)[53]	Y	2009	95	Simva (40)	1.0	61.0	42	NR	NR	31.6	NR	100	NR	0	243.2	167.8	38.6	I
HOPE-3[54]	Y	2016	12705	Rosuva (10)	6.0	66.0	54	20.1	1.8	27.1	27.8	5.8	38	0	201.4	127.8	44.8	I
HYRIM[55]	Y/T	2005	285	Fluva (40)	4.0	57.0	100	NR	NR	29.2	57.9	NR	100	0	228.1	146.9	54.1	I
– (Jacobsen, 1995)[56]	Y	1995	245	Prava (20)	0.2	56.5	67.6	0	100	28.3	NR	NR	41.2	0	282.2	208.8	46.4	I
JUPITER[57]	Y/T	2008	17802	Rosuva (20)	2.2	66.0	61	71.3	12.5	28.3	15.8	NR	NR	0	185.5	108	49	I
KAPS[58]	Y/T	1995	447	Prava (40)	3.0	58.0	100	NR	NR	NR	26.2	2.5	33.1	7.6	224	189	46	I
– (Kerzner, 2003)[59]	Y	2003	284	Prava (10→40)	0.2	57.0	40	91.5	4.5	NR	14	5.5	31	6.5	266.8	NR	54.1	I
– (Lewis, 2007)[60]	Y	2007	320	Prava (80)	0.5	49.8	51.8	89.3	4.9	30.9	NR	NR	NR	0	219	139.4	47.8	I
MEGA[61]	Y/T	2006	7832	Prava (10→20)	5.3	58.0	31	NR	NR	23.8	20.5	21	42	0	243.6	158.5	58	I
– (Melani, 2003)[62]	Y	2003	270	Prava (10→40)	0.2	54.3	48.5	82.5	7.5	NR	15	5	27	5.5	262.9	177.9	54.1	I

METEOR[63]	Y/T	2007	984	Rosuva (40)	2.0	57.0	60	94.5	NR	27.1	4.5	0.1	20.5	0	229.5	154.5	49.5	I
─ (Mohler, 2003)[64]	Y	2003	354	Atorva (10, 80)	1.0	68.5	77.2	93.3	6	26.9	40.7	17.3	100	0	215	150	46	I
MRC/BHF Heart Protection[65]	T	2007	3982	Simva (40)	5.3	NR*	NR*	NR*	NR*	NR*	NR*	100	NR*	NR*	NR*	NR*	NR*	I
─ (Muldoon, 2004)[66]	Y	2004	308	Simva (10→40)	0.5	54	42	86	NR	NR	NR	0	0	0	262.6	181	51.3	G
PHYLLIS[67]	Y/T	2004	253	Prava (40)	2.6	58.3	40.3	NR	NR	NR	20.1	NR	100	0	262.9	181.7	54.1	I
PMSG-Diabetes[68]	Y	1994	325	Prava (10→20)	0.3	58.3	50.7	NR	NR	27.1	NR	100	NR	0	251.3	166.2	42.5	I
PREVEND-IT[69]	Y/T	2004	864	Prava (40)	3.8	52.0	65	96	NR	26	40	2.6	NR	3.4	224.3	154.6	38.6	I
RCASS[70]	Y	2009	203	Simva (20)	2.0	62.8	59.5	NR	NR	24.5	25.5	90.5	68.9	0	224.3	150.8	46.4	I/G
WOSCOPS[71]	Y/T	2017	6595	Atorva (40)	20.0	55.0	100	NR	NR	26	79.5	1	15.5	5	272	192	44	I

Keys: Atorva = atorvastatin, CVD = cardiovascular disease, G = government, Fluva = fluvastatin, HDL-C = high-density lipoprotein cholesterol, I = industry, LDL-C = low-density lipoprotein cholesterol, Lova = lovastatin, NR = not reported, Prava = pravastatin, Rosuva = rosuvastatin, Simva = simvastatin, TC = total cholesterol. Keys trial names: ACAPS = Asymptomatic Carotid Artery Progression Study, AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study, ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ANDROMEDA = A raNdomized Double-blind study to compare Rosuvastatin and atOrvastatin in patiEnts with type II DiAbetes, ARIES = African American Rosuvastatin Investigation of Efficacy and Safety, ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm, ASPEN = Atorvastatin for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus, ASTRONOMER = Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin, BCAPS = Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study, CAIUS = Carotid Atherosclerosis Italian Ultrasound Study, CARDS = Collaborative Atorvastatin Diabetes Study, CELL = Cost Effectiveness of Lipid Lowering Study, CERDIA = abbreviation not found (RCT on the effect of long-term statin therapy on silent myocardial ischemia in type 2 diabetic patients), COMETS = COmparative study with rosuvastatin in subjects with METabolic Syndrome, CORALL = COmpare the effect of RSV with Atorvastatin on apoB/apoA1 ratio in patients with type 2 diabetes meLLitus and dyslipidaemia, DISCOVERY = Direct Statin Comparison of LDL-C Values: An Evaluation of Rosuva-statin Therapy Compared with Atorvastatin, HOPE-3 = Heart Outcomes Prevention Evaluation, HYRIM = Hypertension High Risk Management, JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Using Rosuvastatin, KAPS = Kuopio Atherosclerosis Prevention Study, MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, METEOR = Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin, MRC/BHF = Medical Research Council/British Heart Foundation, PHYLLIS = Plaque Hypertension Lipid-Lowering Italian Study, PMSG = Pravastatin Multinational Study Group for Cardiac Risk Patients, PREVEND-IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial, RCASS = Regression of Cerebral Artery Stenosis Study, QLMG = Quality of Life Multicenter Group, URANUS = Use of Rosuvastatin vs. Atorvastatin iN type 2 diabetes mellitUS, WOSCOPS = West of Scotland Coronary Prevention Study; → Shows titration of the dose; * Not reported in the tables with characteristics of included studies in the review of Taylor, 2013.

Table 7.6. Risk of bias and quality of the RCTs included in the systematic reviews of Yebyo, 2019 and Taylor, 2013 (as assessed in these reviews)

RCT	Included in Yebyo or Taylor	Risk of bias						
		Random sequence	Allocation concealment	Blinding	Reporting bias	Incomplete outcome data*	Other bias	Overall quality†
ACAPS[35]	Y/T							Fair
AFCAPS/TexCAPS[36]	Y/T							Fair
ALLHAT-LLT[37]	Y							Poor
ASCOT-LLA[38]	Y							Good
ASCOT-LLA post[39]	Y							Good
ASPEN [40]	Y/T							Fair
ASTRONOMER[41]	Y							Good
— (Bak, 1998)[42]	Y							Good
— (Bays, 2004)[43]	Y							Poor
BCAPS[44]	Y							Fair
— (Bone, 2007)[45]	Y/T							Fair
CAIUS[46]	T							*Fair*
CARDS[47]	Y/T							Good
CELL A/CELL B[48]	T							*Poor*
CERDIA[49]	T							*Poor*
COMETS[50]	Y							Poor
— (Derosa, 2003)[51]	T							*Fair*
— (Gentile, 2000)[52]	Y							Poor
— (Helji, 2009)[53]	Y							Poor
HOPE-3[54]	Y							Good
HYRIM[55]	Y/T							Poor
— (Jacobsen,	Y							Fair
JUPITER[57]	Y/T							Good
KAPS[58]	Y/T							Good
— (Kerzner, 2003)[59]	Y							Poor
— (Lewis, 2007)[60]	Y							Poor
MEGA[61]	Y/T							Poor
— (Melani, 2003)[62]	Y							Fair
METEOR[63]	Y/T							Good
— (Mohler, 2003)[64]	Y							Poor
MRC/BHF Heart Protection[65]	T							*Poor*
— (Muldoon, 2004)[66]	Y							Fair
PHYLLIS[67]	Y/T							Good
PMSG-Diabetes[68]	Y							Poor
PREVEND-IT[69]	Y/T							Good
RCASS[70]	Y							Good
WOSCOPS[71]	Y/T							Fair

Keys trial names: ACAPS = Asymptomatic Carotid Artery Progression Study, AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study, ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ANDROMEDA = A raNdomized Double-blind study to compare Rosuvastatin and atOrvastatin in patiEnts with type II DiAbetes, ARIES = African American Rosuvastatin Investigation of Efficacy and Safety, ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm, ASPEN = Atorvastatin for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus, ASTRONOMER = Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin, BCAPS = Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study, CAIUS = Carotid Atherosclerosis Italian Ultrasound

Study, CARDS = Collaborative Atorvastatin Diabetes Study, CELL = Cost Effectiveness of Lipid Lowering Study, CERDIA = abbreviation not found (RCT on the effect of long-term statin therapy on silent myocardial ischemia in type 2 diabetic patients), COMETS = COmparative study with rosuvastatin in subjects with METabolic Syndrome, CORALL = COmpare the effect of RSV with Atorvastatin on apoB/apoA1 ratio in patients with type 2 diabetes meLLitus and dyslipidaemia, DISCOVERY = Direct Statin Comparison of LDL-C Values: An Evaluation of Rosuva-statin Therapy Compared with Atorvastatin, HOPE-3 = Heart Outcomes Prevention Evaluation, HYRIM = Hypertension High Risk Management, JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Using Rosuvastatin, KAPS = Kuopio Atherosclerosis Prevention Study, MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, METEOR = Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin, MRC/BHF = Medical Research Council/British Heart Foundation, PHYLLIS = Plaque Hypertension Lipid-Lowering Italian Study, PMSG = Pravastatin Multinational Study Group for Cardiac Risk Patients, PREVEND-IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial, RCASS = Regression of Cerebral Artery Stenosis Study, QLMG = Quality of Life Multicenter Group, URANUS = Use of Rosuvastatin vs. Atorvastatin iN type 2 diabetes mellitUS, WOSCOPS = West of Scotland Coronary Prevention Study. Low risk of bias according to the Cochrane Risk of bias tool; Moderate or unclear risk of bias according to the Cochrane Risk of bias tool; High risk of bias according to the Cochrane Risk of bias tool; Not reported in the review; * Only reported in the review of Taylor, 2013 and not taken into account in the overall quality; † Yebyo, 2019 summarised the risk of bias values for each of the domains and interpreted the overall quality of a RCT as: (a) Good quality: all criteria met (i.e. low for each domain) using the Cochrane risk of bias tool; (b) Fair quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; (c) Poor quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results. We also applied this to the RCTs reported only in Taylor, 2013; the overall quality is therefore written in Italic.

Table 7.7. Study characteristics of the included non-randomised studies on primary prevention in CVD

First author	Year	Country	Study design Study period, Follow-up period	Study population	Exclusion criteria	Intervention	Compari-son	Sample size
Izzo[34]	2013	Italy	Prospective cohort study (Campania Salute Network) Study period NR Follow-up (mean ± SD): 55.8 ± 42.5 mo	Non-diabetic hypertensive patients without CVD* *Age (mean±SD) in y* - Total: 58.6±9.0 - Statins: 62.5±7.3 - No statins: 57.9±9.1 *Sex (% female)* - Total: 42.3 - Statins: 49 - No statins: 41.2 *CVD risk score* NR	- <12 months of follow-up - Prevalent diabetes at the time of the first visit in the Hypertension Clinic	- Statin use (simvastatin 20 or 40 mg/day, atorvastatin 10 or 20 mg/day, rosuvastatin 10 mg/day) - All patients had received statins over at least 1 year without any sus-pension for the entire year before the end of follow-up	No statin use	Statin users: n=676 Non-users: n=4074
Ramos[33]	2018	Spain	Retrospective co-hort study July 2006-Dec 2015 Follow-up (median; IQR): 7.7 y (7.2-8.0)	People aged ≥75 y registered in the SIDIAP database without CVD† *Age (mean ±SD in y)* - Total: 77±NR - Statins 75-84 y: 78.8±2.7 - No statins 75-84 y: 79.1±2.8 - Statins ≥85 y: 88.5±3.2 - No statins ≥85 y: 88.6±3.2 *Sex (% female)* - Total: 63 - Statins 75-84 y: 65.1 - No statins 75-84 y: 62.8 - Statins ≥85 y: 69.8 - No statins ≥85 y: 69.8 *CVD risk score* NR	- Not at least 1 visit recorded in the electronic medical records during the 1.5 years before the index date - People with a history of CVD - People taking drugs to treat cardiac diseases (ATC code C01) - People with type 1 diabetes and a history of lipid lower-ing treatment (statins or others), cancer, dementia, or paralysis, and those re-ceiving dialysis, living in residential care, or with an organ transplant	- Statin use (simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin) - Only new users = any-one who received statin treatment for the first time ever, or who initi-ated statin treatment with no such pharmacy invoicing recorded dur-ing the previous 18 months - Persons with at least two invoices for statins dur-ing the enrolment period were included	No statin use	*75-84 y without T2DM* Statin new users: n=4802 Statin non-users: n=27114 *≥85 y without T2DM* Statin new users: n=743 Statin non-users: n=6325 *75-84 y with T2DM* Statin new users: n=1756 Statin non-users: n=4885 *≥85 y with T2DM* Statin new users: n=201 Statin non-users: n=1038

Keys: CVD = cardiovascular disease, IQR = interquartile range, NR: not reported, SIDIAP = Spanish Information System for the Development of Research in Primary Care, SD = standard deviation; * CVD was defined as previous myocardial infarction or angina or procedures of coronary revascularisation, stroke or transitory ischemic attack, congestive heart failure or chronic kidney disease more than grade 3 (glomerular filtration rate <30 ml/min/1.73 m^2); † CVD was defined as any of several conditions: symptomatic peripheral arterial disease, ischaemic and haemorrhagic stroke, heart failure, and coronary heart disease, including non-fatal angina, non-fatal myocardial infarction, or cardiac revascularisation.

Table 7.8. Quality of the included non-randomised studies*

	Risk of bias								
	Selection				Comparability	Outcome			Total score
	Repre-senta-tiveness	Selection non-exposed	Ascer-tainment exposure	Outcome not present at start	Adjusted analyses	Assess-ment	Sufficient follow-up	Adequacy follow-up	
Izzo, 2013[34]	a/b	a	a	a	b	a/b	a	b	9 out of 9
Ramos, 2018[33]	a	a	a	a	b	b	a	b	9 out of 9

High quality according to the Newcastle - Ottawa quality assessment scale[30]; * Quality of the non-randomised studies was assessed with the Newcastle - Ottawa quality assessment scale (the meaning of a and b is described in Appendix 15.2). A study can be awarded a maximum of one star for each item within the Selection and Outcome categories; a maximum of two stars can be given for Comparability.

Outcomes reported in the systematic reviews and non-randomised studies

In Table 7.9 an overview is given which outcomes of interest are reported in the selected SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2], and in the two included non-randomised studies[33,34] found with our search for long-term outcomes. The SR of Yebyo et al. does not include all predefined outcomes of interest, therefore, besides the Yebyo et al. SR also the SR of Taylor et al. was included. With the inclusion of these two SRs, all predefined outcomes of interest, except life expectancy, are covered. When outcomes were reported in both SRs, only the most up-to-date data reported in the review of Yebyo et al. was extracted. The two non-randomised studies provided additional data on the effectiveness and safety outcomes.

Table 7.9. PICO outcomes reported in the systematic reviews and non-randomised studies

PICO outcomes‡	Yebyo, 2019	Taylor, 2013	Non-randomised studies
1. All-cause mortality	✓	✓*	✓
2. CVD mortality	✓		
3. Fatal and non-fatal CV events			
a. Fatal CVD (not further specified)		✓	
b. Non-fatal CVD (not further specified)	✓	✓*	
c. Specific fatal CVD events	✓	✓*	
d. Specific non-fatal CVD events	✓	✓*	✓
e. Fatal CHD (not further specified)		✓	
f. Non-fatal CHD (not further specified)		✓	
g. Specific fatal CHD events	✓		
h. Specific non-fatal CHD events	✓		
4. Combined endpoints		✓	✓
5. Change in blood cholesterol concentration			
a. Change in total blood cholesterol concentration		✓	
b. Change in LDL-C blood cholesterol concentration		✓	
6. Treatment-associated adverse events			
a. Arthritis		✓	
b. Cancer	✓	✓*	✓
c. Diabetes mellitus type 2	✓	✓*	✓

d. Headache/nausea	✓		
e. Haemorrhagic stroke		✓	✓
f. Hepatic dysfunction	✓	✓*	✓
g. Myalgia	✓†	✓†	
h. Myopathy		✓	✓
i. Renal dysfunction	✓	✓*	
j. Rhabdomyolysis		✓	
7. Revascularisation		✓	
8. Stop/compliance/adherence of/to statin medication	✓	✓	
9. HRQoL		✓	
10. Life expectancy			

Keys: CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high density lipoprotein, HRQoL = health-related quality of life, LDL = low density lipoprotein, MI = myocardial infarction. * Data on this outcome was not extracted from the review of Taylor, 2013, because more up-to-date data is reported in the review of Yebyo, 2019; † Based on the data extraction for the economic modelling we noticed that Yebyo, 2019 extracted myalgia data for the outcome myopathy, therefore we reformulated this outcome as myalgia and also extracted the myalgia data from Taylor, 2013; ‡ The outcomes are defined in the PICO-Box, see Table 5.1.

7.2.4 Findings efficacy

The results of the two included SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2] on the efficacy of statins in people at risk of CVD are summarised in Figure 5. In Table 7.10 the pooled results and quality of the RCTS reported in these SRs are summarised, including the overall quality of the evidence as assessed with GRADE by Yebyo et al. 2019 (i.e. Taylor et al. 2013 did not apply the GRADE approach to assess the overall quality of evidence). Sixteen efficacy outcomes on CVD events and mortality showed a risk reduction as a result of statin treatment, however this difference was not significant for three of these outcomes (i.e. fatal stroke events, fatal MI events, and non-fatal heart failure events). For the outcome HRQoL limited data was found and no data was reported on the outcome life expectancy. The efficacy results in the SRs were not stratified for people with low, medium, or (very) high CVD risk. Yebyo et al. only conducted a sensitivity analysis in which the RCTs with a high proportion of diabetes mellitus cases were excluded. The exclusion of RCTs with a higher proportion of diabetes mellitus cases did not lead to significant differences in the efficacy outcomes.[26]

Table 7.10. Summary of the pooled results and quality of the RCTs reported in the SRs of Yebyo et al. 2019 & Taylor et al. 2013; including an overall quality of the evidence assessed with GRADE for the efficacy outcomes reported in Yebyo et al. 2019 (as assessed in this review)

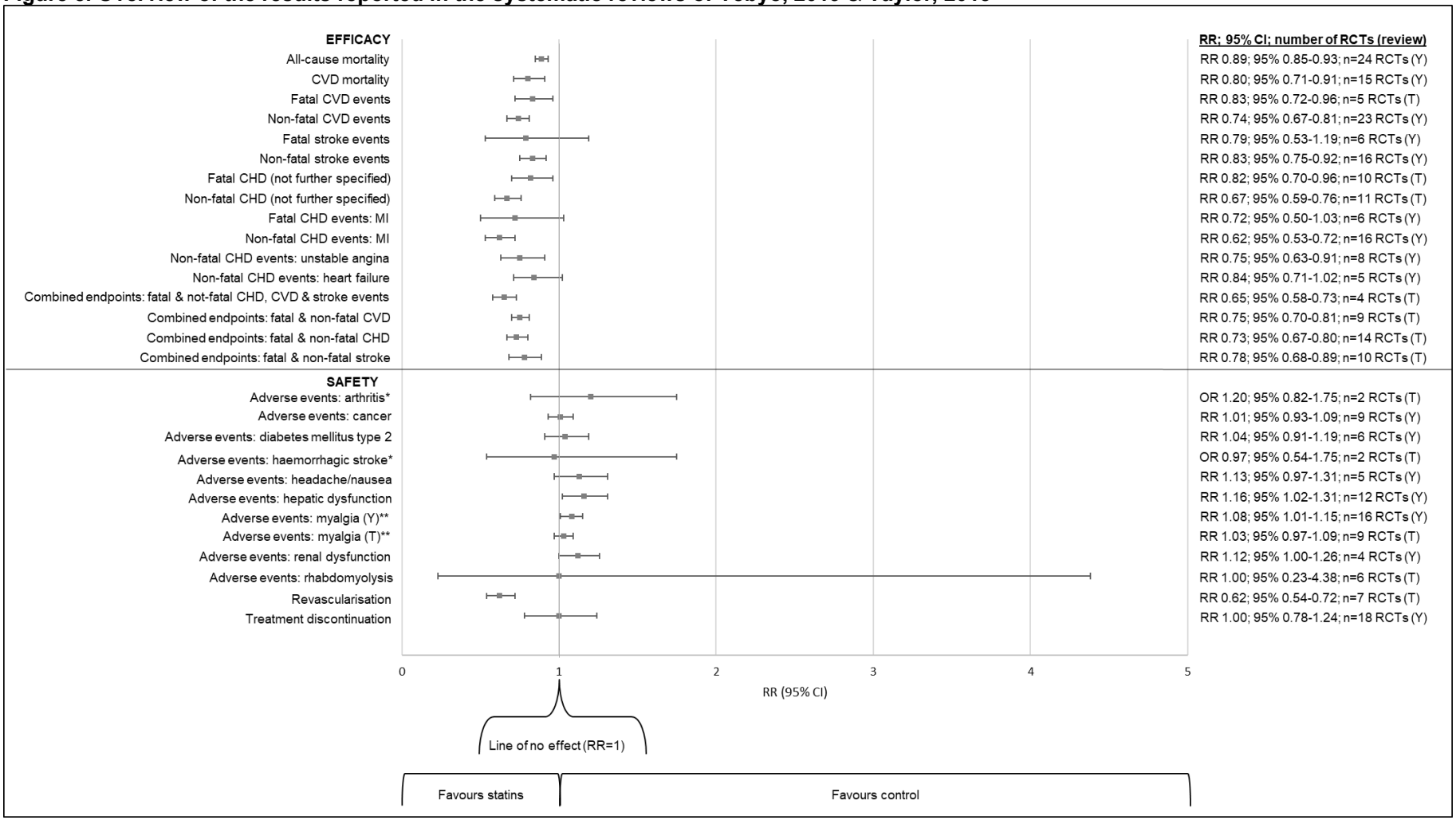
Outcomes	RR (95% CI)	Number of RCTs	Quality of individual RCTs* (Cochrane Risk of bias tool)			Overall quality of the evidence (GRADE)
			Good	Fair	Poor	
All-cause mortality	0.89 (0.85-0.93)	24‖	10[38,39,47,54,57,63,69,70,72,73]	6[35,36,40,45,56,71]	7[37,50,55,60,61,64,68]	Moderate†
CVD mortality	0.80 (0.71-0.91)	15	9[38,39,41,47,54,57,58,69,73]	4[35,36,40,71]	2[37,61]	High

Fatal CVD events	0.83 (0.72-0.96)	5	2[57,69]	2[35,71]	1[61]	NR
Non-fatal CVD events	0.74 (0.67-0.81)	23	NR	NR	NR	Moderate§
Fatal stroke events	0.79 (0.53-1.19)	6	3[38,47,57]	1[71]	2[37,64]	Moderate‡
Non-fatal stroke events	0.83 (0.75-0.92)	16	8[38,41,47,54,57,58,70,73]	4[35,44,66,71]	4[37,53,61,64]	Moderate†
Fatal CHD (not further specified)	0.82 (0.70-0.96)	10	4[47,57,58,69]	5[35,36,40,46,71]	1[61]	NR
Non-fatal CHD (not further specified)	0.67 (0.59-0.76)	11	6[47,57,58,63,67,69]	4[35,40,46,71]	1[61]	NR
Fatal CHD events: MI	0.72 (0.50-1.03)	6	2[47,57]	0	4[37,60,61,64]	Low†‡
Non-fatal CHD events: MI	0.62 (0.53-0.72)	16	9[38,41,47,54,57,58,67,69,73]	2[35,71]	5[37,60,61,64,68]	Moderate§
Non-fatal CHD events: unstable angina	0.75 (0.63-0.91)	8	5[38,41,47,54,57]	1[40]	2[61,64]	High
Non-fatal CHD events: heart failure	0.84 (0.71-1.02)	5	3[38,54,69]	1[71]	1[37]	Moderate‡
Combined endpoints: fatal & non-fatal CHD, CVD, and stroke events	0.65 (0.58-0.73)	4	2[47,57]	1[36]	1[61]	NR
Combined endpoints: fatal and non-fatal CVD	0.75 (0.70-0.81)	9	2[47,69]	3[35,46,71]	4[49,55,61,65]	NR
Combined endpoints: fatal and non-fatal CHD events	0.73 (0.67-0.80)	14	6[47,57,58,63,67,69]	5[35,36,40,46,71]	3[49,55,61]	NR
Combined endpoints: fatal and non-fatal stroke	0.78 (0.68-0.89)	10	5[47,57,58,67,69]	4[35,40,45,71]	1[61]	NR

Keys: CHD = coronary heart disease, CVD = cardiovascular disease, GRADE = Grading of Recommendations Assessment, Development and Evaluation, MI = myocardial infarction, NR = not reported, RCT = randomised controlled trial, RR = risk ratio.

* The risk of bias values for each of the domains of the Cochrane Risk of bias tool were summarised in an overall quality of the individual RCT as: (a) Good quality: all criteria met (i.e. low for each domain) using the Cochrane risk of bias tool; (b) Fair quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; (c) Poor quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results; For details of the risk of bias domains per RCT, see Table 7.6; † Overall quality of the evidence downgraded for limitation in the individual trials base of the risk-of-bias; ‡ Overall quality of the evidence downgraded for precision; § Reason for downgrading the overall level of evidence not reported; ‖Reference and quality of one included RCT in the pooled estimate for this outcome unclear.

Figure 5. Overview of the results reported in the systematic reviews of Yebyo, 2019 & Taylor, 2013



Keys: CHD = coronary heart disease, CI = confidence interval, CVD = cardiovascular disease, HDL = high density lipoprotein, LDL = low density lipoprotein, MI = myocardial infarction, OR = odds ratio, RR = risk ratio, T = Taylor, 2013, Y = Yebyo, 2019. * Based on the data extraction for the economic modelling we noticed that Yebyo, 2019 extracted myalgia data for the outcome myopathy, therefore we reformulated this outcome as myalgia and also extracted the myalgia data from Taylor, 2013; ** This outcome is reported as an odds ratio; OR and RR can be considered similar when the event being assessed is relatively rare in the population.

All-cause mortality

The pooled analysis of Yebyo et al. based on 24 RCTs showed that statins, compared with placebo, significantly reduced the all-cause mortality (RR 0.89; 95% CI 0.85-0.93; moderate quality).[26]

CVD mortality

Yebyo et al. also found a significant reduction in CVD mortality when the statin group was compared with the placebo group (RR 0.80; 95% CI 0.71-0.91; n=15 RCTs; high quality).[26]

Fatal CVD events

Five RCTs included in the SR of Taylor et al. reported a significant risk reduction in fatal CVD events as a result of statin treatment: 17.4% in the statin group versus 20.8% in the placebo group (RR 0.83; 95% CI 0.72-0.96; the quality of 4 out of 5 RCTs was good or fair).[2]

Non-fatal CVD events

The SR of Yebyo et al. reported a significant reduced risk of major cardiovascular events (i.e. a composite outcome of all major cardiovascular events excluding fatal stroke and heart failure) in people at high risk of CVD using statins compared with placebo (RR 0.74; 95% CI 0.67-0.81; n=23 RCTs; moderate quality).[26]

Fatal stroke events

In the Yebyo review no significant effect was found of statin treatment on the outcome fatal stroke (RR 0.79; 95% CI 0.53-1.19; n=6 RCTs; moderate quality).[26]

Non-fatal stroke events

The risk of non-fatal stroke was significantly reduced by statins compared with placebo in the RCTs included in the SR of Yebyo et al. (RR 0.83; 95% CI 0.75-0.92; n=16 RCTs; moderate quality).[26]

Fatal CHD (not further specified)

The pooled analysis of Taylor et al. based on ten RCTs showed that statins resulted in a significant risk reduction in fatal CHD events: 1.1% in the statin group versus 1.3% in the placebo group (RR 0.82; 95% CI 0.70-0.96; the quality of 9 out of 10 RCTs was good or fair).[2]

Non-fatal CHD (not further specified)

The Taylor review found evidence for a significant reduction in non-fatal CHD events in statin users: statin group (1.9%) versus placebo group (2.8%); RR 0.67 (95% CI 0.59-0.76; n=11 RCTs; the quality of 10 out of 11 RCTs was good or fair)).[2]

Fatal CHD events: MI

No significant effect was found for fatal MI in the SR of Yebyo et al. (RR 0.72; 95% CI 0.50-1.03; n=6 RCTs; low quality).[26]

Non-fatal CHD events: MI

Based on 16 RCTs included in the SR of Yebyo et al., it was concluded that statins significantly reduced the risk of non-fatal MI in comparison with placebo (RR 0.62; 95% CI 0.53-0.72; moderate quality).[26]

Non-fatal CHD events: unstable angina

The Yebyo review found evidence for a significant reduction in unstable angina events in statin users compared to placebo (RR 0.75; 95% CI 0.63-0.91; n=8 RCTs; high quality).[26]

Non-fatal CHD events: heart failure

Yebyo et al. did not find a significant effect of statins on non-fatal heart failure events (RR 0.84; 95% CI 0.71-1.02; n=5 RCTs; moderate quality).[26]

Combined endpoints: fatal & non-fatal CHD, CVD, and stroke events

Four RCTs included in the review of Taylor et al. reported a combined endpoint of fatal and non-fatal events for CHD, CVD, and stroke. The treatment of statins led to a significant reduction in this outcome (2.4% in the statins arm versus 3.8% in the placebo arm; RR 0.65; 95% CI 0.58-0.73; the quality of 3 out of 4 RCTs was good or fair).[2]

Combined endpoints: fatal and non-fatal CVD

In total, nine RCTs reporting on the combined endpoint fatal and non-fatal CVD events were included in the Taylor review. The pooled analysis showed a significant reduction in this combined outcome in statin users: 9.3% in the statin group versus 12.2% in the placebo group (RR 0.75; 95% CI 0.70-0.81; the quality of 5 out of 9 RCTs was good or fair).[2]

Combined endpoints: fatal and non-fatal CHD events

In the SR of Taylor et al. 14 RCTs were included which reported on the combined endpoint of fatal and non-fatal CHD events, resulting in a significant risk reduction caused by statins treatment: 3.4% in the statin group versus 4.6% in the placebo group (RR 0.73; 95% CI 0.67-0.80; the quality of 11 out of 14 RCTs was good or fair).[2]

Combined endpoints: fatal and non-fatal stroke

Ten RCTs reported on combined fatal and non-fatal stroke events in the review of Taylor et al. Two of these RCTs were stopped prematurely, because significant reductions in primary composite outcomes

between the intervention and placebo had been observed. A significant reduction in the combined outcome fatal and non-fatal stroke events with the use of statins was found in the pooled analysis: 17% in the statin group versus 22% in the placebo group (RR 0.78; 95% CI 0.68-0.89; the quality of 9 out of 10 RCTs was good or fair).[2]

Change in total blood cholesterol concentration

The RCTs included in the Taylor review demonstrated significant reductions in total cholesterol concentrations as an outcome of statins treatment (net difference -1.05 mmol/L; 95% CI -1.35 to -0.76 mmol/L; n=14 RCTs; the quality of 9 out of 14 RCTs was good or fair). There was marked heterogeneity of effects, but it is likely that the heterogeneity was due to differences in the type of statin and dosage used.[2]

Change in LDL-C blood cholesterol concentration

Statin use resulted in a significant reduction of the LDL cholesterol concentration in 16 RCTs included in the SR of Taylor et al. (net difference -1.00 mmol/L; 95% CI -1.16 to -0.85 mmol/L; n=16 RCTs; the quality of 11 out of 16 RCTs was good or fair). There was marked heterogeneity of effects, but it is likely that this was caused by differences in the type and dosage of statin used.[2]

HRQoL

Taylor et al. 2013 found limited data on the HRQoL of patients. Only one RCT of poor quality was included that reported data on the quality of life, suggesting that the intervention of lifestyle advise plus the statin pravastatin reduced stress and sleeping problems.[2]

Life expectancy

In the SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2] no data were reported on the outcome life expectancy.

7.2.5 Findings effectiveness

Both SRs[2,26] did not report data on the effectiveness of statins for primary prevention of CVD, because all included studies were RCTs which investigated the treatment under specific study conditions. However, the two additionally included non-randomised studies, of which the retrospective Spanish cohort study of Ramos et al. 2018 reported effectiveness data on the outcomes all-cause mortality, atherosclerotic CVD, stroke, and CHD.[33] This cohort study found a significant association between statin use and the effectiveness outcomes in people aged 75-84 years with type 2 diabetes. The results of this non-randomised study are summarised in Appendix 15.4.

All-cause mortality

In people aged 75 years or older without type 2 diabetes statin treatment was not associated with a reduction in all-cause mortality; the hazard ratio (HR) for statin use was 0.98 (95% CI 0.91-1.05) in 75-84 year olds and 1.00 (95% CI 0.90-1.11) in people aged 85+ years.[33] In people with type 2 diabetes statin use was associated with a significant reduction in all-cause mortality, however this effect decreased after the age of 85 years and disappeared in persons aged 90 years or older. The HR for statin use for all-cause mortality was 0.84 (95% CI 0.75-0.94) in 75-84 year olds and 1.05 (95% CI 0.86-1.28) in people aged 85 years or older.[33]

Non-fatal CVD events: atherosclerotic CVD

The effect of statin treatment on atherosclerotic CVD in elderly with and without type 2 diabetes is in line with the association found between statins and all-cause mortality. The results show a lack of association between statin treatment and reduction in atherosclerotic CVD events in people aged 75+ years without type 2 diabetes. The HR for statin use was 0.94 (95% CI 0.86-1.04) in people aged 75-84 years and 1.00 (95% CI 0.80-1.24) in 85+ year olds.[33] In people aged 75-84 years with type 2 diabetes, statins significantly reduced the incidence of atherosclerotic CVD by 24%, however no significant benefits were observed in people aged 85 years or older. The HRs for both groups were respectively 0.76 (95% CI 0.65-0.89) and 0.82 (95% CI 0.53-1.26).[33]

Combined endpoints: fatal and non-fatal stroke

The results for the combined endpoint fatal and non-fatal stroke are in line with the above described effect of statin treatment in older people. A significant association between statin use and stroke was only reported for people aged 75-84 years with type 2 diabetes (HR 0.81; 95% CI 0.66-0.99).[33]

Combined endpoints: CHD (fatal/non-fatal angina, fatal/non-fatal MI, or cardiac revascularisation)

Ramos et al. also reported comparable results for the outcome CHD, which is a composite of fatal and non-fatal angina, fatal and non-fatal MI, or cardiac revascularisation. Statin use was only associated with a significant reduction in CHD for people aged 75-84 years with type 2 diabetes (HR 0.75; 95% CI 0.60-0.94).[33]

7.2.6 Findings safety

The safety results of the two included SRs are summarised in Figure 5. In Table 7.11 the pooled results and quality of the RCTS reported in these SRs are summarised, including the overall quality of the evidence as assessed with GRADE by Yebyo et al. 2019 (i.e. Taylor et al. 2013 did not apply the GRADE approach to assess the overall quality of evidence). For two of the nine reported adverse events statin use resulted in a significant increase in adverse events (i.e. hepatic dysfunction and renal dysfunction). For the adverse event myalgia Yebyo et al. found a significant increase, however the analyses of Taylor et al. did not find a significant association. No significant difference between the statins and placebo group was found for the other six adverse events. Furthermore, the use of statins led to a significant reduction of revascularisation rates and no significant differences were reported for the outcomes treatment discontinuation and compliance to statin medication. The safety results in the SRs were not stratified for people with low, medium, or (very) high CVD risk. Yebyo et al. only conducted a sensitivity analysis in which the data with a high proportion of diabetes mellitus cases were excluded. The exclusion of RCTs with a higher proportion of diabetes mellitus cases did not lead to significant differences in the safety outcomes.[26] The outcomes of the two included non-randomised studies on primary prevention in CVD are reported in Appendix 15.4 and are mostly in line with the results of Yebyo et al. and Taylor et al.

Table 7.11. Summary of the pooled results and quality of the RCTs reported in the SRs of Yebyo et al. 2019 & Taylor et al. 2013; including an overall quality of the evidence assessed with GRADE for the safety outcomes reported in Yebyo et al. (as assessed in this review)

Outcomes	RR (95% CI)	Number of RCTs	Quality of individual RCTs* (Cochrane Risk of bias tool)			Overall quality of the evidence (GRADE)
			Good	Fair	Poor	
Adverse events: arthritis	1.20 (0.82-1.75)#	2	1[63]	1[36]	0	NR
Adverse events: cancer	1.01 (0.93-1.09)	9	4[41,54,57,67]	3[36,46,71]	2[37,61]	Low†‖
Adverse events: diabetes mellitus type 2	1.04 (0.91-1.19)	6	3[38,54,57]	2[36,71]	1[61]	Very low†§‖
Adverse events: haemorrhagic stroke	0.97 (0.54-1.75)#	2	1[57]	0	1[61]	NR
Adverse events: headache/nausea	1.13 (0.97-1.31)	5	1[63]	3[36,45,56]	1[68]	Low†‖
Adverse events: hepatic dysfunction	1.16 (1.02-1.31)	12**	5[41,47,57,58,63]	3[36,62,71]	3[53,61,68]	Low†‡
Adverse events: myalgia¶	1.08 (1.01-1.15)	16**	5[42,47,54,57,63]	5[36,45,56,62,71]	5[53,55,60,61,68]	Moderate†
Adverse events: myalgia¶	1.03 (0.97-1.09)	9	4[47,57,58,63]	4[36,40,45,71]	1[49]	NR
Adverse events: renal dysfunction	1.12 (1.00-1.26)	4††	3[38,41,57]	0	0	Moderate†‡
Adverse events: rhabdomyolysis	1.00 (0.23-4.38)	6	3[47,57,63]	2[36,40]	1[61]	NR
Revascularisation	0.62 (0.54-0.72)	7	3[47,57,58]	3[36,46,71]	1[61]	NR
Treatment discontinuation	1.00 (0.78-1.24)	18**	5[41,47,58,63,69]	5[36,56,62,66,71]	7[50,52,53,59,60,64,68]	Very low†§‖
Compliance to statin medication	1.08 (0.98-1.18)	8	4[57,58,63,69]	3[36,45,71]	1[61]	NR

Keys: GRADE = Grading of Recommendations Assessment, Development and Evaluation, NR = not reported, RCT = randomised controlled trial. * The risk of bias values for each of the domains of the Cochrane Risk of bias tool were summarised in an overall quality of the individual RCT as: (a) Good quality: all criteria met (i.e. low for each domain) using the Cochrane risk of bias tool; (b) Fair quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; (c) Poor quality: one criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results; For details of the risk of bias domains per RCT, see Table 7.6; † Overall quality of the evidence downgraded for limitation in the individual trials base of the risk-of-bias; Overall quality of the evidence downgraded for indirectness problem; § Overall quality of the evidence downgraded for inconsistency; ‖ Overall quality of the evidence downgraded for precision; ¶ Based on the data extraction for the economic modelling we noticed that Yebyo et al. 2019 extracted myalgia data for the outcome myopathy, therefore we reformulated this outcome as myalgia and also extracted the myalgia data from Taylor et al. 2013; # This outcome is reported as an odds ratio (OR); OR and RR can be considered as similar when the event being assessed is relatively rare in the population; ** Reference and quality of one included RCT in the pooled estimate for this outcome unclear; †† Inconsistently reported in Yebyo et al. 2019 whether this pooled estimate is based on 3 or 4 RCTs.

Treatment-associated adverse events

Yebyo et al. 2019 concluded that the use of statins in comparison with placebo led to a significant increase of **hepatic dysfunction** (RR 1.16; 95% CI 1.02-1.31; n=12 RCTs; low quality) and **renal dysfunction** (RR 1.12; 95% CI 1.00-1.26; n=4 RCTs; moderate quality).[26] It is important to keep in mind that these outcomes were not always clearly and homogeneously defined and few RCTs used both clinical features and serum biomarkers to define dysfunction.[26] Statin use was not associated with an increased risk of **liver toxicity** in the Spanish retrospective cohort study of people aged 75 years or older.[33]

In the meta-analysis of Yebyo et al. no significant differences between the statin group and the placebo group were found for the adverse events **type 2 diabetes** (RR 1.04; 95% CI 0.91-1.19; n=6 RCTs; very low quality), **all cancers** (RR 1.01; 95% CI 0.93-1.09; n=9 RCTs; low quality), and **headache and nausea** (RR 1.13; 95% CI 0.97-1.31; n=5 RCTs; low quality).[26] For **type 2 diabetes** similar results were reported in the two included non-randomised studies.[33,34] Ramos et al. also did not find an increased risk of **cancer** associated with statin use in people aged 75+ years.[33]

Based on the data extraction for the economic modelling we noticed that Yebyo et al. 2019 extracted myalgia data for the outcome which they defined as myopathy. We therefore reformulated this outcome as myalgia and also extracted the myalgia data from Taylor et al. 2013. Yebyo et al.[26] reported that statins as a class showed a statistically significant increase of **myalgia** (RR 1.08; 95% CI 1.01-1.15; n=16 RCTs; moderate quality), while Taylor et al.[2] did not find a significant association between statin use and the occurrence of myalgia (RR 1.03; 95% 0.97-1.09; n=9 RCTs; the quality of 8 out of 9 RCTs was good or fair). Data on the adverse event **myopathy** was reported only in the Spanish retrospective cohort study; the incidence rate was low ranging from 0.2-1.1 events per 1000 person-years and statin use was not associated with an increased risk of myopathy.[33]

Furthermore, Taylor et al. did not find evidence of any serious harm caused by statin prescription for three other treatment-associated adverse events: the very rare event **rhabdomyolysis** (RR 1.00; 95% CI 0.23-4.38; n=6 RCTs; the quality of 5 out of 6 RCTs was good or fair), **haemorrhagic stroke** (OR 0.97; 95% CI 0.54-1.75; n=2 RCTs; the quality of 1 out of 2 RCTs was good or fair), and **arthritis** (OR 1.20; 95% CI 0.82-1.75; n=2 RCTs; the quality of 2 out of 2 RCTs was good or fair).[2] The results of Ramos et al. were in line with this and also showed no increased risk of **haemorrhagic stroke** associated with statin use.[33]

Revascularisation

Seven RCTs included in the meta-analysis of Taylor et al. 2013 reported on the need for revascularisation procedures during follow-up: 1.4% in the statin group versus 2.2% in the placebo group underwent either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). The use of statins resulted in a significant reduction of revascularisation rates compared with the control group (RR 0.62; 95% CI 0.54-0.72; the quality of 6 out of 7 RCTs was good or fair).[2]

Treatment discontinuation

Treatment discontinuation events did not significantly differ between the statin and placebo group in the review of Yebyo et al. (RR 1.00; 95% CI 0.78-1.24; 18 RCTs; very low quality).[26]

Compliance to statin medication

No significant difference between the statin use and placebo was reported for the outcome treatment compliance in the Taylor review. In the statin group 77% of the participants and in the placebo group 70% of the participants complied with the treatment (RR 1.08; 95% CI 0.98-1.18; n=8 RCTs; the quality of 7 out of 8 RCTs was good or fair).[2]

Adherence to statin medication

In the SRs of Yebyo et al. 2019[26] and Taylor et al. 2013[2] no data were reported on the outcome treatment adherence.

Summary statement efficacy, effectiveness, and safety

In the clinical review two high quality SRs with relevant data of 37 RCTs were included on the efficacy and safety of statin therapy for primary prevention of CVD in adults. Two high quality non-randomised studies provided additional data on effectiveness and safety. No studies were found on the efficacy of lifestyle adaptations (in combination with statin therapy) for primary prevention of CVD in adults.

Based on the evidence for the efficacy outcomes it can be concluded that statin therapy prescribed for adults without established CVD is effective in the prevention of cardiovascular events and mortality. The available data from non-randomised studies is too scarce to draw conclusions on the effectiveness of statins. In most studies, treatment with statins did not result in an increased risk

of adverse events. Statin use only resulted in a significant risk increase for hepatic dysfunction (low quality of evidence) and renal dysfunction (moderate quality of evidence). However, there are limitations with regard to the definitions of these outcomes in the RCTs. The available evidence for the adverse event myalgia was inconsistent.

Risk scores for CVD were hardly reported in the studies and therefore no stratification of the efficacy, effectiveness, or safety results was available for people with low, medium, or (very) high CVD risk.

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8 Costs, cost-effectiveness, and population-level costs

8.1 Methodology costs, cost-effectiveness, and population-level costs

A systematic literature search was conducted to identify cost-effectiveness studies on primary prevention of CVD with statin therapy. In addition, a de novo cost-effectiveness model was developed to calculate the cost-effectiveness and population-level costs of statin therapy for the Swiss context specifically. In this chapter, the employed methods are further detailed starting with the systematic literature search (Chapters 8.1.1 – 8.1.3), followed by a description of the conceptual cost-effectiveness model, additional searches for model inputs, and cost-effectiveness and population-level cost analyses (Chapter 8.1.4)

8.1.1 Databases and search strategy

PubMed (MEDLINE), Embase.com, and NHS EED databases were searched for peer-reviewed scientific literature. The PICO method was used to specify the research questions. Table 5.1 outlines the utilised PICO for the cost-effectiveness systematic review. Based on expert opinion, a review period of 10 years (2009-2019) was adopted. The most important reason for limiting the search to this time period was because it was expected that recent studies included more mature data due to longer follow-up and would therefore be deemed of higher quality. However, even within this relatively recent time period, it is important to be aware of recent changes in statin prices and the influence of inflation and discount rates on the cost-effectiveness outcomes. Publications in German, English, French, and Dutch were included.

The search terms for the population and intervention of the efficacy, effectiveness, and safety literature search were combined with search terms for economic studies to find economic evaluations. The search terms for economic evaluations were developed together with an information specialist of the Erasmus University Medical Centre and validated extensively with other search terms for economic evaluations and previous SRs of the cost-effectiveness of primary prevention of CVD with statins.

The search for economic evaluations of primary prevention of CVD with statins was executed on 11 July 2019. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract) was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and further manually deleted.

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria is presented in Table 8.1.

Table 8.1. Inclusion and exclusion criteria for cost-effectiveness systematic literature search

	Inclusion	Exclusion
Period publication	• 2009-2019 (10 years; based on expert opinion)	
Study language	• German • English • French • Dutch	All other languages
Country of study	• Western countries*	
Study design/type	Economic evaluations • Cost-utility • Cost-effectiveness • Cost-minimisation • Cost-benefit Resource use measurement	Costing studies
Study quality		• Small sample size (n<20; this criterion is not applicable for model-based studies)
Study population	• Patients without previous cardiovascular events	• Population with previous cardiovascular events
Study intervention	Statins licensed in Switzerland: Atorvastatin (Sortis® and generics), Fluvastatin (Lescol® and generics), Pitavastatin (Livazo®), Pravastatin (Selipran® and generics), Rosuvastatin (Crestor® and generics), Simvastatin (Zocor® and generics)	
Study comparison	Placebo or no treatment and/or adaption for lifestyle (smoking reduction or stop, diet adaptation, physical activity)	Studies comparing statins with other statins or with other cholesterol lowering drugs
Study outcomes	• See outcomes in PICO table (Table 5.1)	

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf);

Quality control

The same quality control measures were put in place in the cost-effectiveness literature search as for the efficacy, effectiveness, and safety literature search.

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers from iMTA. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was more than

5% discrepancy between the two researchers, therefore all titles and abstracts were screened in duplicate. Any conflicts were discussed and amended accordingly.

- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers from iMTA. Again, during screening there was more than 5% discrepancy between the two researchers, therefore all full-text articles were screened in duplicate. Any conflicts were discussed and amended accordingly.

8.1.2 Other sources

Hand search of reference lists SRs

During the full-text screening phase of the efficacy, effectiveness, and safety review and the cost-effectiveness review, reference lists of SRs were checked to find any other studies or SRs that were not captured with our systematic literature search.

HTA websites

Clinical guidelines and technology assessments from the major national HTA agency websites from countries other than Switzerland (e.g. EUnetHTA for Europe[g], NICE[h] from the United Kingdom (UK), IQWIG[i] from Germany, HAS[j] from France, ZiN[k] from the Netherlands, CADTH[l] from Canada, and PBAC[m] from Australia) were searched for documents addressing primary prevention of CVD with statin therapy (i.e. search terms 'statins' in relevant language). This search aimed to check if the published cost-effectiveness studies and guidelines (see other HTA domains) possibly missed relevant evidence on the efficacy, safety, and economic aspects. In addition, these documents provide insight in the stances of other EU HTA agencies on the primary prevention of statins. The initial search yielded the NICE clinical guideline on CVD[n] and

[g] www.eunethta.eu/
[h] www.nice.org.uk
[i] www.iqwig.de/
[j] www.has-sante.fr/
[k] www.zorginstituutnederland.nl/
[l] www.cadth.ca/
[m] www.pbs.gov.au/
[n] https://www.nice.org.uk/guidance/cg181

three SRs on the CADTH webpage.[o,p,q] No missed studies/articles were identified in these guidelines/reviews.

8.1.3 Assessment of quality of evidence

The Consensus Health Economics Checklist (CHEC) checklist was used for the appraisal of the methodological quality of the economic evaluations. The CHEC was preferred over the Drummond checklist, because of the decreasing use of the Drummond checklist in the field[74] and the experienced feasibility of completing the checklists. The CHEC is one of the two most often used checklists in recent studies, the other checklist is CHEERS.[74] The CHEC was chosen over the CHEERS checklist as the CHEC can be used to assess the methodological quality of economic evaluations, while the CHEERS checklist was primarily intended for use as a reporting checklist.

The CHEC is a 19-item checklist[75] with clear questions about the economic evaluation that will give us insight into the general quality of the study for a preliminary critical appraisal of the quality of the included studies. In addition to the CHEC, it was assessed whether statin-specific outcomes were included in the economic evaluations (e.g. treatment adherence and disutility for taking pills every day).

8.1.4 Description of health economic model

Considering the lack of high-quality cost-effectiveness studies in the Swiss context, lack of cost-effectiveness studies using one of the preferred risk scoring systems in Switzerland, and recent changes in prices of statins due to the introduction of generics, a de novo model was developed that incorporated the most recent and (where possible) Switzerland-specific effectiveness, costs, and utility evidence.

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[o] https://www.cadth.ca/discontinuation-statin-therapy-primary-prevention-patients-who-have-achieved-normal-lipid-levels
[p] https://www.cadth.ca/lipid-lowering-agents-stroke-prevention-review-clinical-evidence-safety-and-guidelines
[q] https://www.cadth.ca/clinical-and-economic-review-hmg-coa-reductase-inhibitors-coronary-heart-disease-0

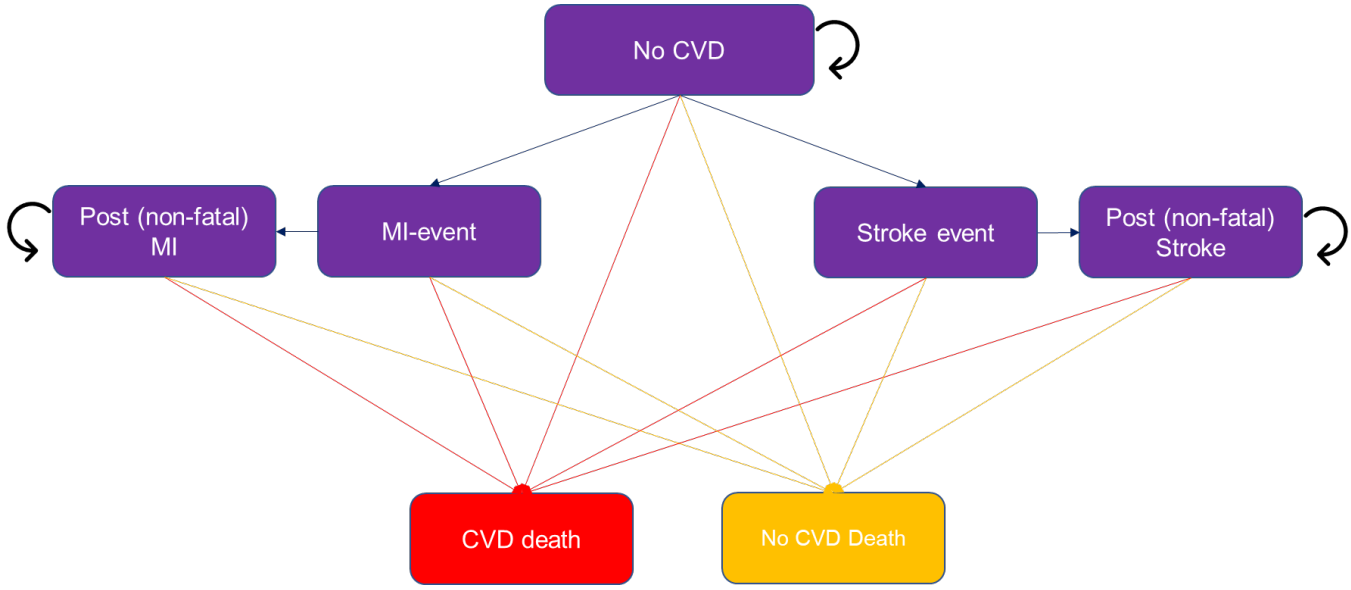
Model structure

A de novo Markov model has been developed to compare the cost-effectiveness of statin therapy for primary prevention of CVD with no statin therapy in adults without established CVD and with low, medium, and (very) high CVD risk. Although the published cost-effectiveness studies did not provide sufficient information to draw firm conclusions on the cost-effectiveness of statin therapy for primary prevention of CVD in Switzerland, the model structures and findings of the published studies were used as a starting point for the development of the cost-effectiveness model.

All studies identified in the cost-effectiveness systematic literature search considered the impact of statins on the occurrence of myocardial infarction and almost every study considered the occurrence of ischemic strokes. The identified systematic reviews of Yebyo et al.[26] and Taylor et al.[2] reported the following CVD events: MI, stroke, unstable angina and heart failure. In addition, the occurrences of unstable angina and coronary revascularisations were often considered. The inclusion of these CVD events in our de novo cost-effectiveness model was discussed with a clinical expert, who advised to include MI, and stroke as the main CVD events. According to the clinical expert unstable angina would be difficult to consider in the economic model because the distinction between unstable angina and MI has changed over time. Therefore, it is possible that studies used different definitions for unstable angina, making it hard to compare study outcomes. Based on the information above and discussion with the FOPH, we included non-fatal MI and non-fatal stroke as CVD events. In addition, all fatal CVD events (including events other than MI and stroke) were taken into account in CVD death. Other non-CVD events resulting in death were included in the 'No CVD death' state.

The conceptual model is presented in Figure 6. The model had a cycle length of 1 year and a lifetime time horizon. The model started with patients without CVD who start statin therapy (intervention arm) or not (comparator arm) and are at risk of non-fatal myocardial infarction (MI), non-fatal stroke, fatal CVD events (including but not limited to fatal MI and stroke), and non-CVD related mortality. Adverse events of statin therapy were not included in the base-case analysis. As the focus of this cost-effectiveness analysis was the use of statins in primary prevention of CVD, the patient's course after the first non-fatal CVD event was not modelled in detail. Instead, the consequences of secondary CVD events were taken into account in the post-CVD event health states (i.e. post MI and post stroke Figure 6), which were associated with an increased mortality risk, costs, and disutility seen amongst post-MI and post-stroke patients.

Figure 6. Conceptual model



As requested by the FOPH, the analyses were performed from a healthcare payer perspective (i.e. including all direct medical costs). Costs were reported in Swiss franc (CHF) and adjusted for inflation to 2019 prices using inflation rates from the Swiss Federal Statistical Office, accessed from the OECD website[r]. Health outcomes were reported in life years (LYs) and quality-adjusted life years (QALYs). In the base-case analysis, costs and effects were discounted with a discount factor of 3%.

The model was programmed in R 3.6.1 using RStudio 1.2.1335 and was based on the state-transition model framework developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup.[76–78]

[r] https://data.oecd.org/

8.1.5 Model inputs

Transition probabilities

The transition probabilities of the CVD events included in the model were based on the predefined AGLA risk score. The baseline AGLA risk score was chosen at the start of the model. To estimate the cost-effectiveness of statins in different subgroups with varying CVD risk, the following baseline AGLA risk scores were included: 1% (low), 5% (low), 10% (medium), 15% (medium), 20% (high), and 25% (very high). In the following years, the AGLA risk score increased due to advancing age. The sex-specific increase in risk due to age was derived from the AGLA risk calculator.[79] In the base-case analysis, it was assumed that other risk factors included in the AGLA risk calculator (i.e. systolic blood pressure, LDL, HDL, triglycerides, smoking status, diabetes mellitus, family history of MI) would remain constant over time.

The AGLA risk score represents the 10-year composite probability of a 'major coronary event', defined as occurrence of sudden cardiac death or a definite fatal or non-fatal MI on the basis of ECG and/or cardiac enzyme changes.[13,79] The definition of a sudden cardiac death was death of a previously apparently well person within one hour of onset of symptoms, providing the cause of death could not be attributed to violence, trauma, or some other potentially lethal condition other than coronary heart disease (CHD).[80] CHD is a synonym for ischemic heart disease or coronary artery disease.[81] According to our conceptual model (Figure 6), non-fatal strokes and deaths due to stroke or other cardiovascular diseases should also be included in the health economic model, in addition to the non-fatal MI and CHD deaths included in the AGLA risk score. Therefore, the relative proportion of non-fatal MI and CHD related deaths was used to disentangle the AGLA risk score into the individual probabilities of non-fatal MI and CHD related death. Subsequently, the relative proportion of non-fatal MI and non-fatal stroke was used to determine the probability of non-fatal stroke corresponding to the AGLA risk score (see the calculation example in Box 1). In addition, the proportion of CHD-related death of all CVD deaths (35%, Table 8.2) was used to determine the total probability of CVD deaths corresponding to the AGLA risk score (see the calculation example in Box 1).

The relative proportion of 'non-fatal MI and CHD deaths' and 'non-fatal MI and non-fatal stroke' was calculated by pooling the incidence rates of these events in the no treatment/placebo arms of the trials included in the systematic review of Yebyo et al.(Table 8.3)[26] These pooled incidences of MI, stroke and CVD death were estimated in a random-effects meta-analysis using inverse variance weighting based on the number of follow-up patient-years using the 'meta' package in R.[82] In case the number of follow-up patient-years was not reported, the mean or median follow-up duration or trial duration was multiplied by the sample size to derive the total number of patient-years. As the reported trial duration is generally longer than the mean

follow-up duration in a trial, the reported trial duration was adjusted using the proportion of the mean/median follow-up duration of the total trial duration in studies that reported both study characteristics. On average the mean/median follow-up duration was 82% of the total trial duration. Based on this analysis, the relative proportion of MI vs. CVD death was 0.559 and the relative proportion of stroke vs. MI was 1.022.

The incidence of CHD death was not available in the systematic review of Yebyo et al. Therefore, the incidence of CVD death of 0.559 was adjusted to the incidence of CHD deaths by dividing it by the proportion of CHD deaths of CVD deaths derived from Eurostat data for Switzerland in 2017 (Table 8.2).[83] For CHD deaths we used the number of deaths caused by ischaemic heart diseases (acute MI and other ischeamic heart diseases) and for other CVD deaths we used the number of deaths caused by other heart diseases, cerebrovascular disease (i.e. including stroke) and other diseases of the circulatory system (Table 8.2).[83] This resulted in a proportion of CHD of CVD deaths of 0.35, i.e. 35% of the CVD deaths were caused by CHD (Table 8.2).[83]

Table 8.2 Standardised death rates in Switzerland in 2017 – diseases of the circulatory system, source: Eurostat[83]

Diseases of the circulatory system	Number of deaths per 100,000 inhabitants	Proportion of total deaths
Ischemic heart disease (including MI)*	191	35%
Other heart disease	144	27%
Cerebrovascular disease (including stroke)	88	16%
Other disease of the circulatory system	118	22%

*Included in the AGLA risk score.

The AGLA risk score provides the 10-year probability on non-fatal MI or CHD death. Therefore, the probabilities of CVD events derived from the AGLA risk score were converted to annual probabilities of the individual CVD events for inclusion in the annual cycles of the model. To convert the resulting 10-year probabilities to annual probabilities, the 10-year probabilities were transformed to rates with the following formula where r is rate and p is probability: $r = -log(1 - p)$. Then the rates were divided by 10 to determine the annual rates. Finally, the annual rates were transformed back to probabilities using the following formula: $p = 1 - e^{(-rt)}$ (see the calculation example Box 1).

Box 1: Example calculation annual probabilities of CVD events per CVD risk subgroup

- AGLA risk score: **10%** (predefined in subgroup definition)
- Incidence of non-fatal MI: **8.5** events per 1000 person-years (Yebyo et al.[3])
- Incidence of CVD death: **6.7** events per 1000 person-years (Yebyo et al.[3])
- Incidence of non-fatal stroke: **8.7** events per 1000 person-years (Yebyo et al.[3])
- Proportion CHD of CVD death: **35%** (EuroStat[83])

Calculation of incidence of CHD deaths

Incidence of CHD deaths = incidence of CVD death * proportion CHD of CVD death = 6.7 / 0.35 = 2.2 events per 1000 person-years

Calculation of individual probabilities of non-fatal MI, non-fatal stroke and CVD deaths

1. **10-year probability of non-fatal MI** in the 10% AGLA risk score group =
   AGLA risk score * (incidence non-fatal MI/(incidence non-fatal MI + CHD death)) =
   10 * (8.5 / (8.5+2.2) = 7.8%

2. **10-year probability of CHD death** in the 10% AGLA risk score group =
   AGLA risk score * (incidence CHD death/(incidence non-fatal MI + CHD death)) =
   10 * (2.2 / (8.5+2.2) = 2.2%

   10-year probability of CVD death in the 10% AGLA risk score group =
   10-year probability of CHD death / proportion CHD of CVD death = 2.2 / 0.35 = 6.2%

3. **10-year probability of stroke** in the 10% AGLA risk score group =
   Non-fatal MI risk (defined in 1) * (incidence non-fatal stroke/non-fatal MI) =
   7.8 * (8.7 / 8.5) = 8.0%

Calculation of annual probabilities from 10-year probabilities

The 10-year MI risk correspond to the following annual probability:

1. 10-year non-fatal MI rate = - log (1-0.076) = 0.0812
2. Annual non-fatal MI rate = 0.0812 / 10 = 0.00812
3. **Annual non-fatal MI probability**= $1 - e^{(-0.00812 * 1)} = 0.00809$

In the same way the annual probabilities on CVD death and non-fatal stroke can be calculated.

The effect of statin treatment was modelled by multiplying the annual probabilities of CVD events with the incidence rate ratio (IRR) of statin versus no statin.(Table 8.3) The relative risks (RR) reported in Yebyo et al. were not used in our model as the outcomes of individual studies were weighted by sample size instead of total number of person-years in their meta-analysis. To consider differences in follow-up duration between the trials, a random-effects meta-analysis using inverse variance weighting based on the number of follow-up patient-years was performed using the 'meta' package in R.[82] The mean number of follow-up patient-years was determined in the same way as described before in the meta-analysis of incidence of CVD events in no treatment/placebo arms of the trials included in Yebyo et al.

The relative proportions of non-fatal MI and CVD death and non-fatal MI and stroke and the RRs of CVD events of statin therapy versus no statin therapy were assumed to be equal across CVD risk groups.

Table 8.3. Outcomes random-effect meta-analyses of incidence rates without statin therapy and IRR statins therapy vs. no statins for non-fatal MI, non-fatal stroke, and CVD death.

	Incidence rate/patient-year without statins (95% CI)	IRR statins therapy vs. no statins (95% CI)	p-value (IRR statins therapy vs. no statins)
Non-fatal MI	0.0085 (0.0130; 0.0145)	0.5858 (0.4679; 0.7334)	<0.0001
Non-fatal stroke	0.0087 (0.0033; 0.0229)	0.7885 (0.6952; 0.8943)	0.0002
CVD death	0.0067 (0.0047; 0.0094)	0.8342 (0.7298; 0.9535)	0.0079

Note: The incidence rates in this table are only used to determine the relative proportion of CVD events that is used in the translation of AGLA risk scores to probabilities of CVD events (see example calculation in Box 1)

Background mortality was based on the all-cause mortality rates derived from Swiss lifetables[s] adjusted for age and sex adjusted proportions of CVD deaths[84] to avoid double counting of CVD deaths.

After a non-fatal MI or stroke, patients have an increased mortality risk mainly due to CVD.[85,86] Therefore, the CVD death rates after non-fatal MI or stroke in the model were multiplied with the standard mortality rates (SMR) reported in studies of Bronnum-Hansen et al. and converted to probabilities (Table 8.4).[85,86] Bronnum-Hansen et al. found a significantly higher SMR in the first year after a non-fatal MI or stroke compared to subsequent years. In subsequent years, the SMR decreased over time but the differences between the time periods were not significant. Therefore, the SMR for the subsequent years in the model was based on the average of SMRs reported for 1-5 years, 5-10 years, and 10-15 years after stroke.

[s] https://www.mortality.org/

Table 8.4. Standard mortality ratios (SMR) after non-fatal MI and stroke based on Bronnum-Hansen et al.[85,86]

	Male SMR (95% CI)	**Female** SMR (95% CI)
First year after MI	4.45 (3.77-5.22)	7.78 (5.98-9.95)
First year after stroke	3.98 (3.50-4.51)	5.62 (5.00-6.30)
Subsequent years after MI	1.93 (1.67-2.24)	2.35 (1.82-3.00)
Subsequent years after stroke	2.41 (2.08-2.78)	2.21 (1.85-2.62)

Treatment adherence

The transition probabilities in the previous paragraph are based on the efficacy of statins in clinical trials. However, in the real-world patients are not fully adherent to statin therapy. Therefore, non-adherence was considered in the base-case analysis of the cost-effectiveness model. was assumed that non-adherence only reduced costs of statin drugs, but not the costs of follow-up and monitoring. In addition, it was assumed that statins would have no effect on CVD risks if treatment adherence was below 20% and would have full effect if treatment adherence was above 80%. A linear reduction in treatment effect was assumed if treatment adherence was between 20% and 80% by increasing the IRR of CVD events when treatment adherence decreased. Real-world treatment adherence was based on a register-based study of statin adherence in Finland[87] who found 69% adherence in the first year of statin therapy and 60% in subsequent years. The impact of full adherence is explored in a scenario analysis. Table 8.5 provides the resulting IRRs for the varying rates of adherence.

Table 8.5 Incidence rate ratios (IRR) of statins therapy vs. no statins for varying rates of adherence

	Full adherence (100%)	**Real world adherence year 1 (69%)**	**Real world adherence >year 1 (60%)**
Non-fatal MI	0.5858	0.6617	0.7239
Non-fatal stroke	0.7885	0.8272	0.8590
CVD death	0.8342	0.8646	0.8895

Cost and resource use inputs

To identify the most recent Swiss cost data available to use as input in the cost-effectiveness model, a comprehensive search for resource use and costs data of primary prevention of cardiovascular events using statins or treatment of cardiovascular events in Switzerland was performed. The search terms, methods, and results of this systematic literature search are provided in Appendix 15.7.

The values of the costs, and resource use were only extracted from the studies that were considered most relevant to inform the input parameters of the cost-effectiveness model. For some of these inputs, other sources were also used such as public databases with specific data for Switzerland.

The following costs and resource use inputs were deemed relevant, and are discussed in further detail below:

- Annual statin drugs acquisition costs.
- Annual costs of monitoring and follow-up of patients using statins.
- Costs of treatment of patients with non-fatal CV events.
- Costs of follow-up of patients with non-fatal CV events.
- Costs of CVD related and non-CVD related deaths (including treatment costs and additional costs associated with the last period before death due to e.g. palliative care).
- Costs of treatment of AE of statins (only in scenario analysis).

Annual statin drugs acquisition costs

Annual statin drugs acquisition costs were calculated by multiplying the per pill drug acquisition costs 365.25 days. Per pill drug acquisition costs were calculated from the annual receipts submitted for reimbursement by the Swiss statutory health insurance for all types of statins available in Switzerland, obtained from: COGE©, Tarifpool ©SASIS AG.[88] These sales data were not disaggregated according to primary or secondary prevention. Therefore, we assume that overall sales pattern would represent the primary prevention sales pattern for statins.

For each formulation (i.e. in terms of the active substance and dosage) and for each brand, the package size (in terms of pill number), annual sales data in terms of CHF and number of packages (2019) were available from Tarifpool: © SASIS AG.[88]

From these detailed level data for each formulation/brand combination, formulation-specific per pill drug acquisition costs and market shares were calculated. Afterwards, overall per pill drug acquisition costs were calculated by taking the weighted average of formulation-specific costs according to their market shares. The formulae used in the calculation of the per pill drug acquisition costs, which were applied to each medication type, are provided in the box below.

This calculation resulted in a per pill price of 0.72 CHF, resulting in annual drug costs of 266.30 CHF per patient per year.

i = formulation i, j = brand j

tablets sold (i,j) = sales in packages (i,j)*package size (i,j)

per pill price (i,j) = sales in CHF(i,j) /# tablets sold (i,j)

tablets sold (i) = $\sum_j$ # tablets sold (i, j)

sales in CHF(i) = $\sum_j$ sales in CHF(i, j)

market share (i, j) = tablets sold (i, j)/ $\sum_i$ tablets sold (i, j)

per pill price = $\sum_i$ per pill price $(i, j) *$ market share (i, j)

Annual costs of monitoring and follow-up of patients with statins

The costs of GP visits were derived from TARMED[t] and the costs for lipid profile tests were derived from Eidgenössische Analysenliste[u].The resource use was based on expert opinion from a Swiss GP.

It was assumed that statin therapy was initiated after consultation with a GP. There are two possible tests to determine whether patients require statin therapy and to control the effect of statin therapy: a direct measurement in the GP practice or a lipid profile test at a laboratory. For both options, the total costs of initiation of statin therapy and follow-up are provided in Table 8.6. In the base-case analysis, it was assumed that 50% of the patients would be prescribed statins based on the direct measurement at the GP practice

[t] https://www.tarmed-browser.ch/de

[u] https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Analysenliste.html

and 50% based on the results of the laboratory analysis (i.e. average of the second and third column in Table 8.6). This assumption was varied in sensitivity analyses.

If patients were prescribed statins based on the direct measurement at the GP practice during the initial visit, we assumed statins would be prescribed during this initial visit.

If patients were prescribed statins based on the results of the lipid profile analysis performed at the laboratory, patients would receive the statin prescriptions after the test results are evaluated. Therefore, additional costs of another GP visit or only a prescription for statins were included (base-case assumption 50%/50%).

In both scenarios, it was assumed that patients had a follow-up visit and test to control the effect of statins six weeks later and an annual follow-up visit at the GP. In subsequent years, it was assumed that patients had an annual follow-up visit at the GP. The total costs of both scenarios are outlined in Table 8.6.

Table 8.6. Costs of GP visits and diagnostic tests related to initiation of statin therapy and annual follow-up visits (in 2019 Swiss Francs)

	Costs visits and diagnostic tests at GP	**Costs visits at GP but diagnostic tests at a laboratory**
Initial GP visit	160.56 CHF	143.81 CHF
Initial diagnostic tests (e.g. lipid profile and other tests)	56.88 CHF	44.1 CHF
GP visit with statin prescription or only statin prescription	*Prescription already provided during first GP visit*	68.41 CHF (GP visit with prescription) / 33.48 CHF (prescription only)
First follow-up GP visit	127.06 CHF	127.06 CHF
First follow-up diagnostic tests	27.02 CHF	34.65 CHF
Annual follow-up GP visit	143.81 CHF	143.81 CHF
Annual follow-up diagnostic tests	27.02 CHF	34.65 CHF
Total costs of first year of statin therapy (including initial GP visit and diagnostic tests, first follow-up visit and diagnostic tests, and annual follow-up GP visit and diagnostic tests)	542.35 CHF	596.49 CHF (GP visit with prescription) / 561.56 CHF (prescription only)
Total costs of subsequent years of statin therapy (including annual follow-up GP visit and annual follow-up diagnostic tests)	170.83 CHF	178.46 CHF

Costs of treatment and follow-up of patients with non-fatal CVD events

The costs of the first year after non-fatal MI or non-fatal stroke and costs in subsequent years after non-fatal MI or non-fatal stroke were derived from Gasche et al. who reported these costs for patients with acute coronary syndrome in Switzerland.[89] These costs are derived from a previous study from the Winterthur Institute of Health Economics who used different sources to estimate the costs of stroke and MI (e.g. literature analysis, interviews with stakeholders from healthcare providers and health insurers, and patient databases). Their cost estimates include all follow-up costs of an event in the first year and in each subsequent year, respectively. The follow-up costs include inpatient and outpatient costs for acute care and rehabilitation.

Costs of CVD related and non-CVD related death

The healthcare costs associated with a CVD death were derived from Pletscher et al. who reported the costs of several fatal CVD events, including stroke (CHF 9,799) and MI (CHF 7,207).[90] A weighted average of these healthcare costs based on the proportion of MI and stroke observed in placebo arms of trials on statins was used as a proxy for healthcare costs of all CVD deaths (CHF 8,511).

The healthcare costs associated with a non-CVD related death were derived from Brändle et al. who reported costs of all-cause mortality (CHF 4,191).[91]

Adverse event costs

In the scenario analysis including adverse events, in line with De Vries et al.[92], costs of myopathy were assumed to include two GP visits. It was assumed that the costs of each of these GP visits were equal to the costs of the first follow-up visit (127.06 CHF). Costs of rhabdomyolysis were derived from the costs of treatment of rhabdomyolysis in a United States (US) cost study converted to CHF.[93] No relevant cost estimates could be determined for the treatment of renal and hepatic dysfunction, because these events were not always clearly and homogeneously defined in the clinical trials and therefore it was unclear how patients were generally treated for these adverse events.

Table 8.7. Healthcare costs used in the base-case of the economic model (in 2019 CHF).

Costs	Base-case value	Source
Annual costs of statin therapy (including drug acquisition, GP visits and diagnostic tests costs)		SASIS AG and TARMED
First year	827	
Subsequent years	441	
Healthcare costs of CVD events		
Non-fatal MI 1st year	16,923	Gasche et al; adjusted for inflation to 2019 CHF
Non-fatal stroke 1st year	19,828	Gasche et al. [89]; adjusted for inflation to 2019 CHF
Non-fatal MI subsequent years	1,734	Gasche et al. [89]; adjusted for inflation to 2019 CHF
Non-fatal stroke subsequent years	11,967	Gasche et al. [89]; adjusted for inflation to 2019 CHF
CVD death	8,511	Pletscher et al. [90]; adjusted for inflation to 2019 CHF
Healthcare costs of Non-CVD related death	4,191	Brändle et al. [91]; adjusted for inflation to 2019 CHF
Healthcare costs of Adverse events		
Myopathy	254.12[v]	TARMED (2 GP visits, CHF)
Rhabdomyolysis	9,236	Pletcher et al.[93]; converted from US dollars to CHF and adjusted for inflation to 2019 CHF
Hepatic dysfunction	No cost estimates identified	
Renal dysfunction	No cost estimates identified	

[v] https://www.tarmed-browser.ch/de

Note: The stated health state costs were converted to CHF when necessary using exchange rates from the OECD website and adjusted for inflation to 2019 prices using inflation rates from the Swiss Federal Statistical Office accessed from the OECD website.

Utility inputs

To identify the most recent Swiss utility data available to use as input in the cost-effectiveness model, a comprehensive search for baseline utilities for patients without cardiovascular events, disutilities associated with CVD events, disutilities for long-term post-CVD events, disutilities associated with adverse events, and disutility of statin use (i.e. 'taking a pill every day') in Swiss patients was performed. The search terms, methods, and results of this systematic literature search are provided in Appendix 15.8.

The following utilities were included in the model:

- baseline utilities for patients without CVD events.
- disutilities associated with CVD events.
- disutilities associated with adverse events (only included in scenario analysis).

Baseline utilities for patients without CVD events

The utility values in patients without CVD events were based on the study of Perneger et al. (2010) who conducted a mail survey in French-speaking Switzerland which included the EQ-5D instrument and descriptive variables.[94] Perneger et al. estimated a linear regression model where EQ-5D utility was predicted by age and sex: 0.84822 - 0.00208 * (age - 50) - 0.00002 * (age - 50)^2 - 0.02090 if female. This formula was used to calculate age and sex specific utility values.

Disutilities associated with CVD events

The utility decrements for non-fatal CVD events were derived from Nikolic et al. who reported a utility decrement of -0.138 after stroke and -0.063 after MI.[95]

In the base-case analysis, it was assumed that the disutility of experiencing a stroke remains constant during the rest of the patient's lifetime, based on a study of Rivero-Arias et al. where no substantial improvement in utility was observed two years after stroke.[96] In contrast, it was assumed that the disutility of MI would only be applicable in the first year after MI, because Reed et al. showed that the utility of patients after MI recovered to (at least) the utility of the general population after one year.[97]

Disutilities associated with adverse events

Disutilities of adverse events were not identified in our literature search. Therefore, in line with the approach of Slejko et al.[98], the disutilities of adverse events were derived from a US catalog of EQ-5D scores for chronic conditions by CCC or ICD-9 code.[99] For hepatic dysfunction, the disutility of liver failure (ICD-9 573; 0.0567) was used. For renal dysfunction, the disutility of renal failure (ICD-9 586; 0.0603) was used. In line with Slejko et al., this disutility was also used for rhabdomyolysis. For myopathy, the utility for connective tissue diseases was used (ICD-9 710; 0.0235) based on clinical judgment of the similarity of these health states reported by Slejko et al. The disutilities of adverse events were applied for one cycle.

Population and reimbursement policy related inputs for population-level cost analysis

The number of people in every 1-year age group in Switzerland in 2019 was derived from the Human Mortality Database.[100] In the Swiss population-based study of Nanchen et al. (2009)[101], 6.4% of the population had CVD (defined as self-reported diagnosis of angina, myocardial infarction, stroke, peripheral arterial disease, or history of coronary revascularisation). This means that 93.6% of the population is eligible for primary prevention of CVD with statin therapy. The distribution of the CVD risk in the Swiss population without CVD was based on the population in the Olten area reported in Romanens et al. (89% low, 10% intermediate, and 2% high CVD risk).[14] As these numbers add up to 101% instead of 100%, the percentage of patients in the largest CVD risk group (i.e. low risk) was reduced from 89% to 88% to avoid calculating annual healthcare costs for too many people.

8.1.6 Analytical methods

Base-case analysis

The base-case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. This implies that the cost-effectiveness model is run using a lifetime time horizon, real-world adherence and discounting of costs and effects with a discount factor of 3%. Adverse events were not included in the base-case analysis, because there was no clear evidence of increased risk on the four selected adverse events: myopathy, rhabdomyolysis, renal and hepatic dysfunction. Discontinuation due to adverse events was not included in the base-case analysis, because it was assumed based on expert opinion that patients would switch to another type of statin when they experienced an adverse event. In addition, no disutility of ‘taking a pill every day’ was assumed. These assumptions were varied in scenario analyses.

The base-case analysis was performed for 96 subgroups with varying age, sex, and AGLA risk score (Table 8.8).

Table 8.8. Subgroups

Age	Sex	AGLA risk score
40	Male	1% (Low)
45	Female	5% (Low)
50		10% (Medium)
55		15% (Medium)
60		20% (High)
65		25% (Very high)
70		
75		

To show the impact of changing the assumptions and parameter uncertainty on the cost-effectiveness results, scenario and sensitivity analyses were performed. These analyses were performed for 1 of the 96 subgroups (50-year old males with AGLA risk of 1%), but the direction and magnitude of the impact is expected to be similar in other subgroups. The subgroup of 50-year old males with AGLA risk of 1% was chosen because this is a large subgroup that may have a large impact on total costs of statin therapy.

Scenario analyses

Several scenario analyses were performed to explore the impact of structural assumptions on the cost-effectiveness outcomes. An overview of the scenario analyses is provided in Table 8.9 and the scenarios are discussed in more detail below.

Table 8.9. Description of base-case and scenario analyses

	Base-case analysis	Scenario analysis
Time horizon	Lifetime	10 years
Discount rate	3% discount rate for costs and outcomes	No discounting 6% discount rate for costs and outcomes
Increase in CVD risk	Increase in AGLA risk due to ageing	Increase in AGLA risk due to ageing combined with additional increase in risk due to other risk factors included

		in the AGLA risk calculator (i.e. systolic blood pressure, LDL, HDL, triglycerides, smoking status, diabetes mellitus, family history of MI)
Duration disutility of MI	1 year	Lifetime
Duration disutility of stroke	Lifetime	1 year
Adverse events	Not included	Myopathy, rhabdomyolysis, hepatic and renal dysfunction
Discontinuation of statin therapy due to adverse events	Not included	• Constant annual discontinuation rate for the entire time horizon of the model; • Constant annual discontinuation rate for three years (i.e. mean trial duration); • Linear decreasing annual discontinuation rate; • Exponentially decreasing annual discontinuation rate.
Statin therapy adherence	Real-world adherence (69% in year 1, 60% in subsequent years)	Full adherence
Effectiveness of statins in patients above 75 years old	Equal to younger patients	Reduced effectiveness in patients above 75 years old
Disutility of taking a pill	Not included	Utility decrement of statin therapy of 0.001

Time horizon

A scenario analysis with a time horizon of 10 years instead of lifetime was performed to be able to compare results with previous studies that often had a time horizon of 10 years, because the risk scoring system provided CVD risk for the next 10 years.

Discounting

In the base-case analysis, discounting costs and effects with a discount factor of 3% was applied as requested by the FOPH. The impact of no discounting and discounting cost and effects with a discount factor of 6% was assessed in scenario analyses.

Additional increase in CVD risk over time due to other risk factors than age

In the base-case analysis, CVD risk increases over time based on ageing. However, other risk factors of CVD events included in the AGLA risk calculator (i.e. systolic blood pressure, LDL, HDL, triglycerides, smoking status, diabetes mellitus, family history of MI) may also change over time causing a higher increase in CVD risk than modelled in the base-case analysis. In this scenario analysis, the impact of this additional

increase in risk over time is explored by increasing the AGLA risk scores every year from cycle 2 onwards with a certain percentage varying between 1% and 20%.

Duration of disutility of MI and stroke

In the base-case analysis, it was assumed that MI only had impact on utility of patients during the first year after MI based on findings in the literature. To explore the impact of a longer duration of disutility after MI, a scenario analysis with lifetime disutility of MI was performed. In contrast to MI, the impact of stroke on utility seems to be longer and therefore a lifetime disutility was applied in the base-case analysis. The impact of this assumption was also explored in a scenario analysis by only applying the disutility of stroke during the first year after stroke.

Adverse events

In this scenario analysis, patients in both treatment arms could experience adverse events, including myopathy, rhabdomyolysis, hepatic and renal dysfunction. Adverse events were associated with treatment costs and disutilities. The effect of statin treatment was modelled by multiplying the annual probability of each adverse event with the incidence rate ratio (IRR) of statin versus no statin of that specific adverse event. Just as the pooled incidences and IRR of CVD events, the pooled incidences and IRR of adverse events were estimated in random-effects meta-analyses using inverse variance weighting based on the number of follow-up patient-years using the 'meta' package in R.[82] The meta-analyses results are presented in Table 8.10.

No relevant cost estimates could be determined for the treatment of renal and hepatic dysfunction, because these events were not always clearly and homogeneously defined in the clinical trials and therefore it was unclear how patients were generally treated for these adverse events. The costs of these events were therefore not included in this scenario analysis, but sensitivity analyses where these costs varied over a large range (from 0 to 100,000 CHF) were performed to show the impact of this parameter on the cost-effectiveness results.

Table 8.10. Outcomes random-effect meta-analyses of incidence rates without statin therapy and IRR statins therapy vs. no statins for adverse events of statin therapy.

Adverse event	Incidence rate/patient-year without statins (95% CI)	IRR statins therapy vs. no statins (95% CI)	p-value (IRR statins therapy vs. no statins)
Myopathy	0.0026 [0.0009; 0.0081]	0.8134 [0.4472; 1.4793]	0.4985
Rhabdomyolysis	0.0004 [0.0001; 0.0014]	0.8899 [0.3502; 2.2614]	0.8064
Hepatic dysfunction	0.0038 [0.0020; 0.0073]	1.1363 [0.9296; 1.3890]	0.2123
Renal dysfunction	0.0012 [0.0002; 0.0060]	1.0992 [0.6916; 1.7471]	0.6985

Statin discontinuation due to adverse events

In this scenario analysis, a proportion of the patients discontinued statin therapy. After discontinuation, the probabilities of non-fatal MI, non-fatal stroke, or fatal CVD events in these patients were equal to the probabilities in the no treatment arm and patients did not have any statin therapy costs.

Several statin discontinuation scenario analyses were performed:

- Constant annual discontinuation rate for the entire time horizon of the model.
- Constant annual discontinuation rate for three years (mean trial duration).
- Linear decreasing annual discontinuation rate.
- Exponentially decreasing annual discontinuation rate.

The probability of discontinuation was derived from the pooled estimate of the treatment discontinuation rate due to adverse events in the statin arms of the studies included in Yebyo et al. (0.0558, 95% CI: 0.0345-0.0904). In all statin discontinuation scenarios, the annual discontinuation rate was varied around this estimate based on the 95% CI.

Full statin adherence

In this scenario analysis, the impact of full statin adherence was explored.

Reduced effectiveness of statin therapy in patients above 75 years old

In this scenario analysis, reduced treatment effectiveness was modelled in patients older than 75 years old. The IRRs of statin therapy vs. no therapy on CVD events used in the base-case analysis (Table 8.3) were

increased with 10% (i.e. reducing the effectiveness of statins) based on the difference between all participants and patients older than 75 years in RR per 1 mmol/L reduction in LDL cholesterol reported by Armitage et al.[102]

Disutility of taking a pill

There is reason to believe that the act of taking a pill every day to prevent CVD may be associated with a small disutility in otherwise healthy people. Previous studies therefore added a small disutility of 0.001 to account for this disadvantage of statin therapy in their analysis.[92,103–106] In line with these studies, a scenario analysis was performed including an annual disutility of 0.001 for people on statin therapy.

One-way sensitivity analyses (OWSA)

Parameter uncertainty was first tested using one-way sensitivity analyses (OWSA); model parameters were systematically and independently varied over a plausible range (Table 8.11, e.g. using the 95% confidence interval or a 20% increase/decrease of the parameter value used in the base-case). The ICER was recorded at the upper and lower limits to produce tornado diagrams.

Probabilistic sensitivity analyses (PSA)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) where all parameters to which probability distributions were assigned were varied jointly. For costs and utilities, no data on uncertainty was available, therefore we assumed the standard deviation was 10% of the mean to estimate the gamma and beta parameters required for estimating the distribution. 1,000 Monte Carlo simulations were performed, and the results were recorded. Results were plotted on the cost-effectiveness plane (CE-plane). From these results, a cost-effectiveness acceptability curve (CEAC) was estimated.

Table 8.11. Input parameters base-case and sensitivity analyses

Parameter	Base-case value	Lower limit OWSA	Upper limit OWSA	Source limits OWSA	Distribution in PSA
Relative proportion CHD vs. CVD death	0.353	0.282	0.423	+/- 20%	Beta
Relative proportion MI vs. CVD death	0.783	0.626	0.939	+/- 20%	Lognormal
Relative proportion stroke vs. MI	1.022	0.818	1.227	+/- 20%	Lognormal
IRR non-fatal MI	0.586	0.468	0.733	CI	Lognormal
IRR non-fatal stroke	0.788	0.695	0.894	CI	Lognormal

IRR CVD death	0.834	0.730	0.954	CI	Lognormal
SMR first year after MI in males	4.45	3.77	5.22	CI	Normal
SMR subsequent years after MI in males	1.93	1.67	2.24	CI	Normal
SMR first year after stroke in males	3.98	3.50	4.51	CI	Normal
SMR subsequent years after stroke in males	2.41	2.08	2.78	CI	Normal
SMR first year after MI in females	7.78	5.98	9.95	CI	Normal
SMR subsequent years after MI in females	2.35	1.82	3.00	CI	Normal
SMR first year after stroke in females	5.62	5.00	6.30	CI	Normal
SMR subsequent years after stroke in females	2.21	1.85	2.62	CI	Normal
Treatment adherence, year 1	0.69	0.55	0.83	+/- 20%	Beta
Treatment adherence, beyond year 1	0.60	0.48	0.72	+/- 20%	Beta
Costs of statin pill	0.729	0.583	0.875	+/- 20%	Gamma*
Initial visit at GP with test at GP	160.56	128.45	192.67	+/- 20%	Gamma*
Initial visit at GP with test at laboratory	143.81	115.05	172.57	+/- 20%	Gamma*
Initial test at GP	56.88	45.50	68.26	+/- 20%	Gamma*
Initial test at laboratory	44.1	35.28	52.92	+/- 20%	Gamma*
GP visit with statin prescription after test at laboratory	68.41	54.73	82.09	+/- 20%	Gamma*
Statin prescription after test at laboratory	33.48	26.78	40.18	+/- 20%	Gamma*
First follow-up GP visit	127.06	101.65	152.47	+/- 20%	Gamma*
Annual follow-up visit	143.81	115.05	172.57	+/- 20%	Gamma*
First and annual follow-up test at GP	27.02	21.62	32.42	+/- 20%	Gamma*
First and annual follow-up test at laboratory	34.65	27.72	41.58	+/- 20%	Gamma*
Proportion test at GP or laboratory	0.5	0	1		Uniform

Proportion GP visit with statin prescription vs. only prescription	0.5	0	1		Uniform
Costs of treatment of MI	16,807	13,446	20,168	+/- 20%	Gamma*
Annual costs post-MI	1,722	1,378	2,067	+/- 20%	Gamma*
Costs of treatment of stroke	19,693	15,754	23,632	+/- 20%	Gamma*
Annual costs post-stroke	11,885	9,508	14,262	+/- 20%	Gamma*
Healthcare costs of CVD death	8,511	6,808	10,213	+/- 20%	Gamma*
Healthcare costs of non-CVD related death	4,191	3,352	5,029	+/- 20%	Gamma*
Utility decrement MI	0.063	0.050	0.076	+/- 20%	Beta*
Utility decrement stroke	0.138	0.110	0.166	+/- 20%	Beta*

* The standard deviation was assumed to be 10% of the mean.

Population-level costs analysis

The data required to perform a budget impact analysis (BIA) is illustrated in Figure 7. First, the number of people without CVD in the total Swiss population should be determined. Subsequently, this population needs to be divided in the different CVD risk groups according to the AGLA risk score. Finally, information is required on the current use of statins in every AGLA risk score group.

Figure 7. Required data for budget impact analysis

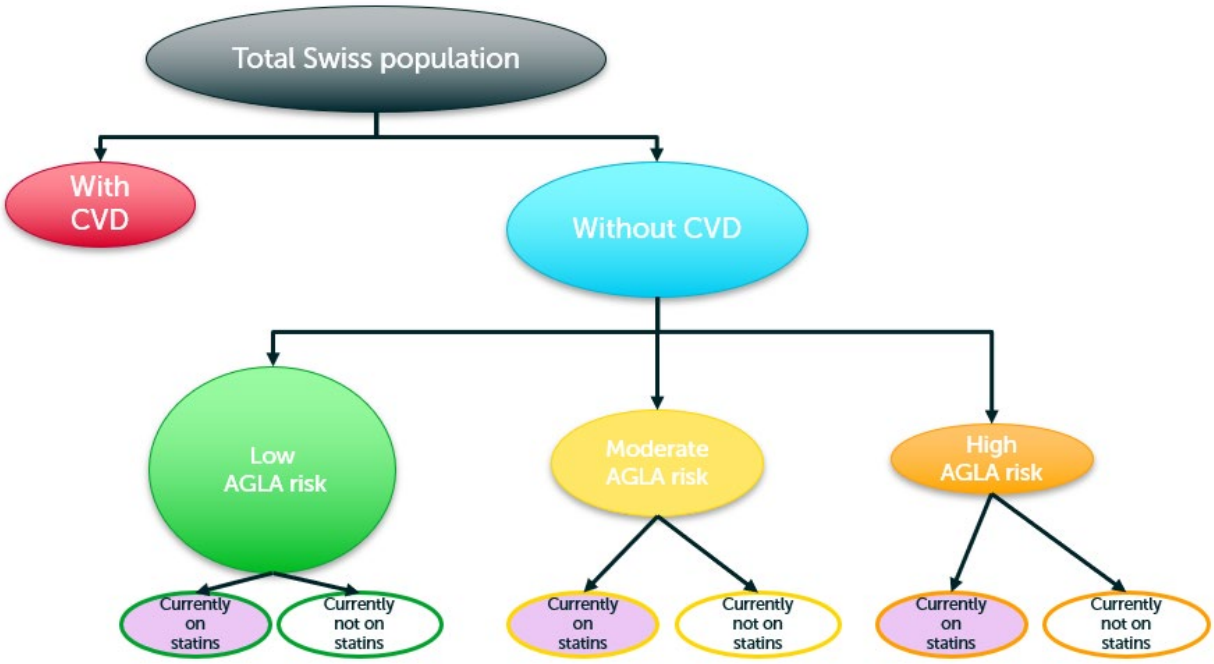


Table 8.12 summarizes the availability of data for the BIA for primary prevention of CVD with statin therapy. There is age- and sex specific data on the size of the total Swiss population. However, there is only non-age and sex-specific data on the prevalence and incidence of CVD and the distribution of AGLA risk in the primary prevention population. Moreover, there is no data on the current use of statins in the primary prevention population.

Table 8.12 Availability of data for budget impact analysis

Parameter	Availability	Assumptions
Size of the total Swiss population	Age and sex specific data available[r]	
Prevalence and incidence of CVD	Data available but not age and sex specific (Nanchen et al.)	Equal for all age and sex groups
Distribution of AGLA risk in primary prevention population (i.e. without CVD)	Data available but not age and sex specific (Romanens et al.)	Equal for all age and sex groups
Proportion of people using statins for primary prevention in every AGLA risk score group	Not available	

As there was no data on the current use of statin therapy for primary prevention of CVD in different CVD risk groups it was not possible to model the budget impact (i.e. the difference in total costs between the

current situation with unrestricted use of statins and restricted reimbursement policies). In addition, the lack of age and sex specific data on the prevalence and incidence of CVD and distribution of AGLA risk in the primary prevention population limited a careful analysis of the budget impact. As an alternative to the budget impact analysis, the maximum population-level annual overall costs of different policies of restricting statin therapy use was calculated. It was assumed that all patients eligible for statin therapy would use statins (i.e. 100% uptake) at the real-world adherence rate assumed in the cost-effectiveness analysis (i.e. 69% in the first year of statin therapy). In this analysis, the same data and assumptions as in the cost-effectiveness analysis were used.

Because the development of CVD risk over time and therefore the probabilities of CVD events in the model are dependent on age and sex, the model was run separately for males and females of all ages between 40 and 75 years and for three CVD risk groups (for the low risk group we assumed an AGLA risk score of 1%, for the intermediate risk group an AGLA risk score of 15%, and for the high risk group an AGLA risk score of 25%). For every subgroup, the annual costs per year derived from the cost-effectiveness model were multiplied with the number of Swiss people in that specific subgroup. Depending on the criteria of the reimbursement policy, the total costs of specific subgroups were summed to determine the country level costs.

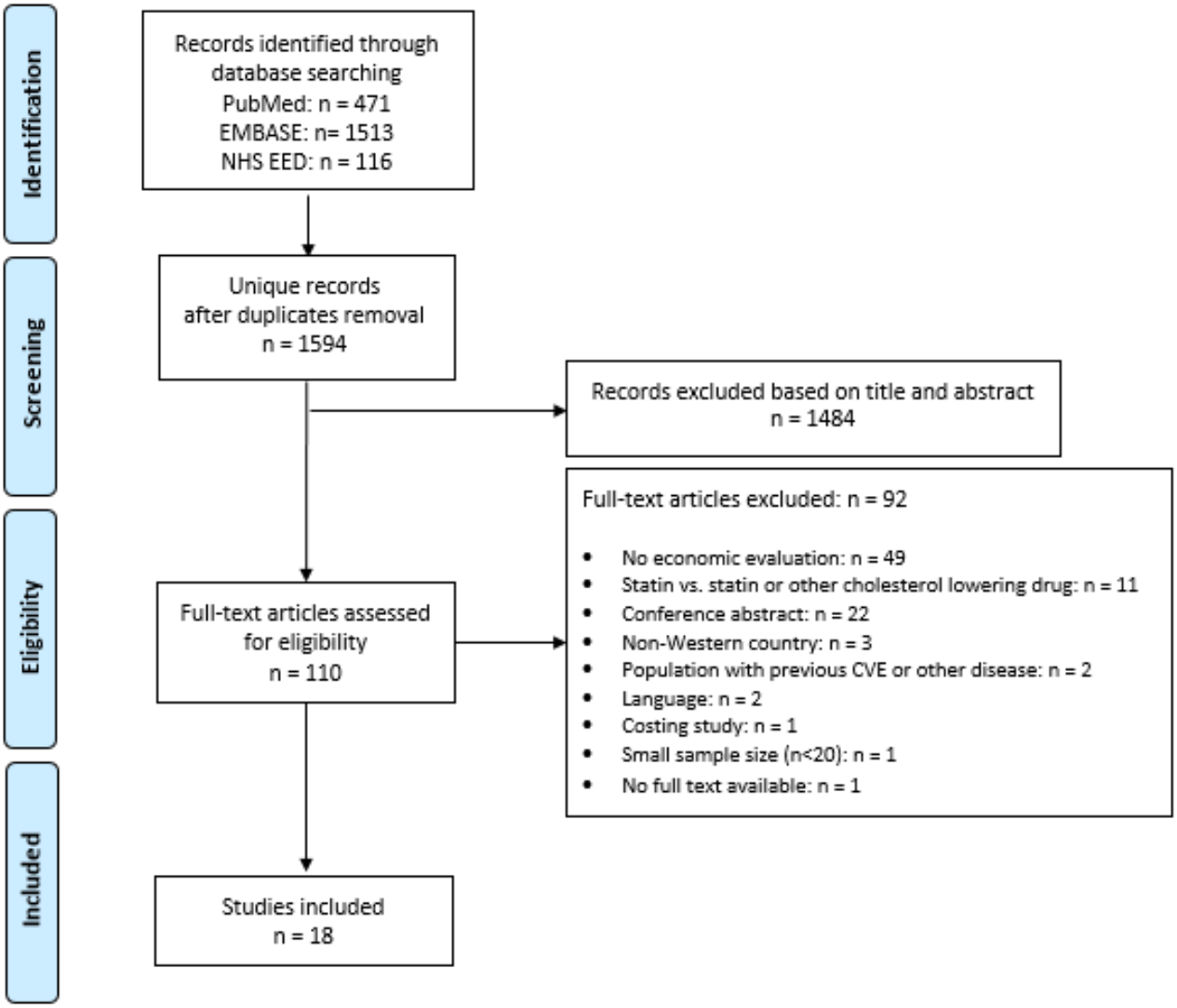
The following reimbursement policies regarding CVD risk were considered: reimbursed for all CVD risks (i.e. high, intermediate and low CVD risk), reimbursed for only high or intermediate CVD risk, and reimbursed for only high CVD risk. In addition, the reimbursement policies were assumed to be restricted for certain starting ages (i.e. the starting age is the age of treatment initiation, people will remain on statins during the rest of their lifetime despite of the age criteria of the reimbursement policy). The options were: no restriction (40-75 years), restricted to starting age between 40 and 59 years, restricted to starting age between 60 and 75 years. Due to the lack of sex specific data, the costs were not reported for males and females separately.

8.2 Results costs, cost-effectiveness and population-level costs

8.2.1 PRISMA flow diagram

In the cost-effectiveness systematic literature search, 1,594 unique records were identified in PubMed (MEDLINE), Embase.com, and NHS EED. Of those, 1,484 records were excluded based on their title and abstract, resulting in 110 articles selected to be screened in full-text, and 18 economic evaluations were finally included. The reasons for exclusion are provided in the PRISMA flow chart in Figure 8.

Figure 8. PRISMA flow diagram cost-effectiveness search



8.2.2 Study characteristics table

Study and model characteristics

The study and model characteristics are presented in Table 8.13 and Table 8.14.

The model structure of the included models was similar. All but one model (Stomberg et al.[107]) include patients without CVD who start statin therapy and are at risk of CVD events. In addition, in some models, patients are also at risk of adverse events related to statin therapy. If patients experience a CVD event, they transition to CVD events health states in which they may have a higher mortality probability and additional costs for secondary prevention therapy.

The study design of all included studies was a cost-utility analysis, expressing outcomes in quality-adjusted life years (QALY) or disability-adjusted life years (DALY). McConnachie et al. was the only cost-utility analysis study that was based on a trial-based economic evaluation; all other included studies were model-based economic evaluations.[108] The study of McConnachie et al. was performed alongside the West of Scotland Coronary Prevention Study (WOSCOPS), which included 6,595 men with hypercholesterolaemia without a history of MI. Most model-based economic evaluations used Markov models (n=13). The other studies were microsimulation models (n=3) or simple calculation models (n=1).

The majority of studies were performed from a healthcare payer perspective (n=15); the other three studies applied a societal perspective. Eight of the studies were performed for the US, seven studies were performed for European countries, two studies for Canada, and one study for Japan. Among the seven European studies, one study was conducted in Switzerland.[109]

The patient populations of interest can be divided into four categories (Table 8.13 and Table 8.14): people from the general population without CVD (without further specifications), people from the general population without CVD but with elevated hs-CRP levels (high-sensitivity C-reactive protein; i.e. a test for CVD risk, higher hs-CRP levels indicate a higher risk of CVD), people from the general population without CVD but with hyperlipidaemia or hypercholesterolaemia, and people with type 2 diabetes.

The types of statins used in the intervention arms differed between the studies. Some studies only considered low, moderate, or high potency statins, whiles others focused on one specific statin. There seems to be an association between the patient population and the specific statin used in the intervention arm. In all five studies on patients with elevated hs-CRP, the statin used in the intervention arm was rosuvastatin because all studies were based on the JUPITER trial. Further, in two out of the three studies on patients

with type 2 diabetes, atorvastatin was the statin used in the intervention arm. Finally, pravastatin was used in both studies on patients with hyperlipidaemia/or hypercholesterolaemia.

The type of comparator(s) used also differed between studies. Eight studies considered 'no statin treatment' as comparator. No statin treatment comparator was defined as 'standard care', which may or may not include lifestyle advice. A further seven studies evaluated statins versus placebo. One study compared statins with no lipid-regulating treatment (defined as no statins or any other lipid-lowering treatment), one study compared various CVD risk thresholds for statin therapy, and one study compared over the counter (OTC) statins with prescription statins. None of the studies compared statin therapy with lifestyle advice only.

Eight of the included studies were sponsored by pharmaceutical companies producing statins.[98,103,107,110–114] The authors of one SR of economic evaluations of statin therapy raised the issue of sponsorship bias in economic evaluations.[115] Catala-Lopez et al. demonstrated an important sponsorship bias in the literature on the cost-effectiveness of statin therapy for prevention of CVD events. Pharmaceutical company-sponsored studies were significantly less likely to reach neutral or unfavourable conclusions than non-pharmaceutical company sponsored studies.[115] In fact, all eight pharmaceutical company sponsored studies concluded that the corresponding statin had a favourable ICER compared to any of the other agents (including competing statins) or placebo.[115]

Table 8.13. Study characteristics

First author	Year	Study population	Cardiovascular risk scoring system used	Cardiovascular risk and risks groups*	Mean age or age groups (in years)	Proportion male/female (%)	Intervention	Comparator	Source effectiveness of statins
General population without CVD									
Aarnio[116]	2015	Adults without CVD	FINRISK	≥5%, ≥10%, ≥15%, ≥20%	45, 50, 55, 60, 65	Subgroup analyses	Statin treatment (distribution of different statins among new Finnish statin users)	No statin treatment	Meta-analysis Taylor et al. 2013[2]
Conly[111]	2011	Adults with low CVD events risk (approximates risk among adults without CVD and diabetes)	Any CVD risk scoring system specifying risk of cardiovascular-related death or nonfatal MI	≥10%, ≥20%	59	NR	Statin treatment with low-potency statins (fluvastatin, lovastatin, pravastatin and simvastatin) or high-potency statins (atorvastatin and rosuvastatin)	No statin treatment	Meta-analysis Tonelli et al. 2011[117]
Greving[104]	2011	Adults without CVD	Any CVD risk scoring system specifying risk of vascular disease (MI or stroke)	≥1%, ≥2.5%, ≥5%, ≥7.5%, ≥10%, ≥15%, ≥20%, ≥25%, ≥30%	45, 55, 65, 75	Subgroup analyses	Low dose statin treatment (costs of 40 mg generic simvastatin)	No statin treatment	Meta-analysis Brugts et al. 2009[118]
Odden[119]	2015	Adults aged 75 years or older	2013 ACC/AHA pooled cohort equations	LDL-C≥4.91 mmol/L (190 mg/dL); LDL-C≥4.14 mmol/L (160 mg/dL); LDL-C≥3.36 mmol/L (130 mg/dL); presence of diabetes; or 10-	75-94	Subgroup analyses	Statin treatment with moderate-dose statins (atorvastatin, simvastatin, pravastatin, lovastatin)	No statin treatment (only secondary prevention)	Cholesterol Treatment Trialists' meta-analysis / PROSPER[120]

				year CVD risk score ≥7.5%					
Pandya[105]	2015	Adults without CVD	2013 ACC/AHA pooled cohort equations	≥30%, ≥20%, ≥15%, ≥10%, ≥7.5%, ≥5%, ≥4%, ≥3%, ≥2%, ≥1%, in addition to treating all patients and no CVD risk–based treatment strategies.	40-75	NR	Statin treatment (simvastatin, atorvastatin, rosuvastatin)	No CVD threshold: eligible for statins through other criteria (history of CVD or diabetes or elevated LDL cholesterol)	Meta-analysis Baigent et al. 2005[121]
Romanens[109]	2017	Adults without CVD	SCORE	≥2.5%, ≥5%, ≥7.5%	40-65	Switzerland: 51/49 Germany: 66/34	Statin treatment	No statin treatment	The effect of statins is assumed to be 1 mmol/l LDL reduction. The impact of a 1 mmol/l LDL reduction was taken from Cholesterol Treatment Trialists' (CTT) Collaborators
Shiffman[106]	2016	Patients without CVD, diabetes or hypercholesterolaemia but at intermediate risk of CVD	Any CVD risk scoring system specifying risk of CVD	5%-7.5%	40-75	NR	Moderate-intensity statin treatment	No statin treatment	NR
Stomberg[107]	2016	Non-institutionalised (non-inpatient) adults (includes outpatients already using statins)	Framingham risk score	<10%, 10%-20%, >20%	>20	NR	Over the counter (OTC) statin treatment	Only prescription use statins	Meta-analysis Baigent et al. 2010[121]
General population without CVD but elevated hs-CRP levels									

Choudhry[103]	2011	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≤10%, >10%	men >50; women >60	NR	Rosuvastatin (20 mg)	Placebo	JUPITER trial[57]
Ohsfeldt[113]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≥10%	67	61/39	Rosuvastatin (20 mg)	Placebo	JUPITER trial[57]
Ohsfeldt[114]	2012	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≥20%	66	60/40	Rosuvastatin (20 mg)	Placebo	JUPITER trial[57]
MacDonald[122]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≤10%, >10%	66	NR	Rosuvastatin (20 mg)	Placebo	JUPITER trial[57]
Slejko[98]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	NA	hs-CRP levels <2.0 mg/L, ≥2.0 mg/L	57	NR	Simvastatin (80 mg, equipotent to rosuvastatin 20 mg)	Placebo	JUPITER trial[57]
General population without CVD with hypercholesterolaemia and/or hyperlipidaemia									
Onishi[123]	2013	Adults with hyperlipidaemia without CVD	JALS-ECC (5-year AMI risk)	Predicted incidence of AMI for four age groups divided by sex and other cardiac risk factors	45, 55, 65, 75	Subgroup analyses	Pravastatin (10 mg)	No statin treatment	Meta-analysis Brugts et al. 2009[118]

McConnachie[108]	2014	Men with hypercholesterolaemia without a history of myocardial infarction	ASSIGN risk score	10.3%, 17.1%, 28.0%	45–54	100/0	Pravastatin (40 mg)	Placebo	WOSCOPS trial[124]
Diabetes type 2 patients									
Annemans[110]	2010	Type 2 diabetes patients without CVD	NA	NA	40-75	68/32	Atorvastatin (10 mg)	No statin treatment	CARDS trial[125]
de Vries[92]	2013	Type 2 diabetes patients without CVD	UKPDS risk engine	Risks groups varied by age group	<45; 45-55, 55-65	49/51	Statin treatment (costs of simvastatin 40 mg)	No lipid-regulating treatment (i.e. no statins or any other lipid-lowering treatment)	Meta-analysis de Vries et al. 2012[126]
Khoury[112]	2009	Type 2 diabetes patients without CVD	NA	NA	61	52/48	Atorvastatin (10 mg)	Placebo	CARDS trial[127]

*10-year CVD risk, unless stated otherwise. Abbreviations: CVD = Cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein

Table 8.14. Model characteristics and main cost-effectiveness findings

First author	Year	Type of model	Perspective, Country	Time horizon, in years (first is base case)	Discount rates (costs/effects)	Main cost-effectiveness findings	Budget impact analysis performed
General population without CVD							
Aarnio[116]	2015	Markov model	Societal, Finland	10; 15	3%/3%	- Statin treatment is more cost-effective among the older patient groups; - Within age groups statin treatment was more cost-effective in higher risk groups; - Statins were less cost-effective in real world adherence scenarios compared to full adherence scenarios; - Statins were cost-effective at lower CVD risk	No

						thresholds in men compared to women; - Treatment adherence has a major impact on cost-effectiveness results of statins; - Statin treatment is more cost-effective when using a longer time horizon; - Statin treatment did not seem to be cost-effective for patients with a 10-year CVD risk of <10% even with the full adherence scenario; - Apart from treatment adherence, cost-effectiveness results were sensitive to monitoring costs in primary prevention, selected time horizon, and the cost of statins.	
Conly[111]	2011	Markov model	Healthcare payer, Canada	Lifetime	5%/5%	- High-potency statins in patients at low CVD risk seem to be cost-effective; - High-potency statins seem to be more cost-effective than low-potency statins.	Yes
Greving[104]	2011	Markov model	Healthcare payer, the Netherlands	10; 20; lifetime	4%/1,5%	- Even at current low costs for generic statin pills, statin treatment seemed not to be cost-effective for low risk primary prevention populations (10-year vascular disease risk <5%) in the Netherlands, when non-adherence was considered; - Statin treatment is more cost-effective among the older patient groups; - Within age groups statin treatment was more cost-effective in higher risk groups; - Statins were cost-effective at lower CVD risk thresholds in men compared to women; - Statin treatment is more cost-effective when using a longer time horizon; - The cost-effectiveness results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.	No
Odden[119]	2015	Markov model	Healthcare payer, USA	10	3%/3%	- Statins are projected to be cost-effective in a population of adults aged 75 to 94 years (all 10-year CVD risk ≥7.5%); - However, even a small increased risk for functional limitation or cognitive impairment due to ageing could offset the cardiovascular benefit; - Statins were more cost-effective in patients with	No

						higher LDL-C levels; - Statins were more cost-effective in younger age groups; - Statins were more cost-effective in men than in women.	
Pandya[105]	2015	Microsimulation model	Healthcare payer, USA	Lifetime	3%/3%	- The use of statins in patients with a 10-year CVD risk threshold of ≥7.5% used in the ACC-AHA guidelines is cost-effective. - Statin treatment was more cost-effective in higher risk groups; - The cost-effectiveness was sensitive to patient preferences for taking a pill daily, changes to statin price, and the risk of statin-induced diabetes.	No
Romanens[109]	2017	Simple calculation model	Healthcare payer, Germany/Switzerland	10; 5	Not substantiated	- The SMB recommendation to use statins only above the 7.5% SCORE risk threshold cannot be derived from the Swiss Medical Board (SMB) model; - Cost-effectiveness of statins is acceptable at a SCORE risk below 5% for statin eligibility; - Statin treatment is more cost-effective when using a longer time horizon.	No
Shiffman[106]	2016	Markov model	Healthcare payer, USA	5	3%/3%	- High-potency statins was the most cost-effective strategy for patients at intermediate CVD risk compared to moderate-potency statins or do-not-treat strategy; - Moderate-potency statins for those in the top decile of LDL-P levels was cost-effective compared to do-not-treat strategy.	No
Stomberg[107]	2016	Markov model	Healthcare payer, USA	10	1%/0%	- OTC statins will be used by patients who meet statin guidelines and are not taking prescription statins, patients who do not meet statin guidelines and are not taking prescription statins, and patients who are using prescription statins and will switch to OTC statins. - With proper labelling and consumer education, it is very likely that OTC statins would be cost-effective.	Yes
General population without CVD but elevated hs-CRP levels							

Choudhry[103]	2011	Markov model	Societal, USA	Lifetime	3%/3%	- Hs-CRP testing and rosuvastatin treatment in patients with hs-CRP≥2.0 mg/l was cost-effective' - Hs-CRP testing and rosuvastatin treatment in patients with hs-CRP≥2.0 mg/l was even more cost-effective in intermediate-risk patients (i.e. FRS≥10%); - If the price of rosuvastatin were reduced to $0.86, treatment of intermediate-risk patients with elevated hs-CRP levels may not only be cost-effective, but also cost-saving.	No
Ohsfeldt[113]	2010	Microsimulation model	Healthcare payer, USA	Lifetime; 20; 10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of ≥10%; - The cost-effectiveness improved with increasing baseline risk of the population; - The cost-effectiveness improved when using a longer time horizon.	No
Ohsfeldt[114]	2012	Microsimulation model	Healthcare payer, Sweden	Lifetime; 20; 10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of ≥20%; - Rosuvastatin remained cost-effective in all patients with elevated hs-CRP regardless of CVD risk; - The cost-effectiveness improved (lower) when using a longer time horizon.	No
MacDonald[122]	2010	Markov model	Healthcare payer, USA	10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of >10%; - In patients with elevated hs-CRP and FRS ≤10%, the cost-effectiveness of rosuvastatin is considered favourable only when this drug's price is less than $2.35 per tablet.	No
Slejko[98]	2010	Markov model	Societal, USA	Lifetime	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP; - Cost-effectiveness varied depending on assumptions of statin cost and age but remained cost-effective.	No
General population without CVD with hypercholesterolaemia							

Onishi[123]	2013	Markov model	Healthcare payer, Japan	Lifetime	3%/3%	- Pravastatin was not cost-effective compared with no-drug therapy. - In all subgroups, the QALY gain was lower in women and resulted in higher ICERs compared with men.	No
McConnachie[108]	2014	Not Applicable (trial-based economic evaluation)	Healthcare payer, Scotland	Follow-up period: 15 years	3.5%/3.5%	- Five years' primary prevention treatment of middle-aged men with a statin significantly reduces healthcare resource utilisation, is cost saving, and increases QALYs. - Treatment of even younger, lower risk individuals than included in this study is likely to be cost-effective.	No
Diabetes type 2 patients							
Annemans[110]	2010	Markov model	Healthcare payer, Belgium	5; lifetime	3%/1.5%	- Use of atorvastatin in patients with diabetes type 2 improves CVD outcomes and is cost saving over a lifetime horizon.	No
de Vries[92]	2013	Markov model	Healthcare payer, the Netherlands	10; 5	4%/1,5%	- With the adherence rates seen in practice, it can be concluded that treating all patients younger than 45 years with type 2 diabetes at diagnosis with statins for primary prevention is not cost-effective. - For patients aged between 45 and 55 years at diagnosis, statin treatment is cost-effective except when the 10-year risk for CHD is as low as 6%. - For the other patients, statin treatment is expected to be cost-effective.	No
Khoury[112]	2009	Markov model	Healthcare payer, Canada	5; 10; 25	5%/ 5%	- Atorvastatin in patients with diabetes type 2 is a cost-effective strategy for the primary prevention of CVD	No

Abbreviations: CHD = Coronary heart disease; CVD = Cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; LDL-C = Low-density lipoprotein cholesterol; LDL-P = Low-density lipoprotein particle number; OTC = over the counter; FRS = Framingham risk score; QALY= quality-adjusted life year; ICER = Incremental cost-effectiveness ratio

Input parameters – costs

Table 8.15 shows which costs were considered in the included studies. In the PICO, three types of healthcare costs were distinguished: prevention-related, CVD-related, and future unrelated healthcare costs.

Regarding prevention-related costs, all studies considered the costs of statins and most studies also considered the costs of monitoring and follow-up of patients using statins for primary prevention of CVD (e.g. laboratory tests and physician visits). The costs of adverse events of statin use were only included in seven studies. The reasons for the lack of adverse events caused by statins in the other studies were because these adverse events are considered rare, incidences were unknown, costs were expected to be low, or adverse events would disappear when patients discontinued statins. CVD-related costs of treatment of non-fatal events were included in all studies, 14 studies included long-term healthcare costs of CVD events (such as long-term follow-up or rehabilitation, and less than half of the studies (n=8) considered costs of fatal events). Finally, none of the studies considered the additional healthcare costs (unrelated to statin treatment or CVD) during the life years gained as a result of statin treatment. Table 8.15 provides an overview of non-health related costs included in the economic evaluations to provide insight in interpreting the cost-effectiveness results. Only three studies considered one or more types of non-healthcare related costs. Non-healthcare related and indirect healthcare-related costs are not considered in the primary perspective of cost assessments in economic evaluations in Switzerland, therefore it is important to note that in the full HTA future unrelated healthcare costs will not be considered.

Input parameters – effectiveness and CVD events

Table 8.16 shows which effectiveness measures and utilities were included. Effectiveness of statin treatment was based on relative risks or hazard ratios of CVD events with statin therapy compared to no statin therapy or placebo derived from meta-analyses or clinical trials (sources provided inTable 8.13).

Adherence to statin treatment was considered in twelve of the 18 studies. Non-adherence was caused by adverse events leading to discontinuation of statin therapy or other non-specified reasons. The effectiveness of statins was assumed to be reduced in patients without full adherence.

Nine of the 18 studies considered adverse events of using statins. Table 8.16 provides an overview of adverse events of statin treatment and CVD events that were included in the economic evaluations. Myopathy and rhabdomyolysis were the most often included adverse events. Myopathy is a disease of

the muscle in which the muscle fibres do not function properly, which results in muscular weakness. Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly, resulting in muscle pain, weakness, vomiting, and confusion. Some studies only included the impact of adverse events on the effect side by applying utility decrements and not on the cost side of the economic evaluation.[104,119]

The CVD events that were considered are provided in Table 8.16. All studies included the impact of statins on the occurrence of MI and almost every study included the occurrence of ischemic strokes. In addition, the occurrences of unstable angina and coronary revascularisations were often included.

The risk of CVD events was calculated by importing the patient characteristics into the underlying risk scoring systems or based on observed event rates in trials or observational cohort studies. In half of the economic evaluations there was variation in the CVD risk scoring system that was used to divide patients into different risk categories (Table 8.13). Only one study used the scoring system recommended by the European Society of Cardiology (ESC): Systematic Coronary Risk Evaluation (SCORE).

In the existing models patients were assigned in a risk group at baseline and only in half of the studies (n=9) the CVD events risk was updated during the time horizon of the model based on age.[92,98,103,104,113,114,116,123] The other parameters in the risk equations were assumed to be constant. In some studies, this can be explained by the fact that the time horizon was equal to the CVD risk period provided by the risk scoring systems (i.e. 10-year CVD risk and 10-year model time horizon). In some studies with longer time horizons, CVD risk was updated every year to account for increasing age.[92,98,103,104,116,123] However, only in the study of Pandya et al. the updated CVD risk was dependent on other parameters included in the risk equations besides age.[105]

Background mortality (i.e. non-CVD related causes of death) was included in most studies. Six of these studies adjusted the general population mortality for deaths due to CVD. In the other studies, double counting of deaths related to CVD may have occurred.

Input parameters – utilities

The utilities without CVD events were dependent on age in seven studies (i.e. utility decreases as age increases). All studies applied disutilities for CVD events, except for Stomberg et al.[107] Stomberg et al. used a mean change in QALYs due to statin use versus no statin use or low-dose versus high-dose statin use derived from a previous cost-effectiveness study to cover utility effects of CVD events.[107]

Most studies applied constant disutilities for CVD events, but in some studies the disutilities were reduced after the first post-event year. In six studies, adverse events were associated with disutilities. Finally, five studies applied a small disutility for taking a pill every day.

Table 8.15. Outcome measures - costs

COSTS	Aarnio 2015	Annemans 2010	Choudry 2011	Conly 2011	De Vries 2013	Greving 2011	Khoury 2009	MacDonald 2010	McConnachie 2014	Odden 2015	Ohsfeldt 2010	Ohsfeldt 2012	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman 2016	Slejko 2010	Stomberg 2016
Prevention-related costs																		
Statin drug costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monitoring and follow-up costs	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓
Adverse event-related treatment costs			✓	✓	✓									✓		✓	✓	✓
CVD event-related costs																		
Non-fatal event costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fatal event/death costs	✓				✓	✓		✓			✓	✓		✓		✓		
Long-term costs after CVD event	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓		✓
Future unrelated healthcare costs																		
Future unrelated healthcare costs																		
Non-healthcare costs																		
Travel														✓				
Time														✓				✓
Informal care																		
Productivity	✓													✓				

Abbreviations: CVD = Cardiovascular disease

Table 8.16. Outcome measures - effectiveness and utilities

EFFECTIVENESS AND UTILITIES	Aarnio 2015	Annemans 2010	Choudry 2011	Conly 2011	De Vries 2013	Greving 2011	Khoury 2009	MacDonald 2010	McConnachie, 2010	Odden 2015	Ohsfeldt 2010	Ohsfeldt 2012	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman 2016	Slejko 2010	Stomberg 2016
Adverse events																		
Myopathy			✓		✓	✓				✓				✓			✓	
Rhabdomyolysis			✓	✓	✓	✓								✓		✓	✓	✓
Diabetes			✓	✓										✓		✓		
Myalgia (muscle pain)														✓		✓		✓
Elevated liver enzymes/liver toxicity/failure			✓	✓													✓	
Renal disease			✓															
Haemorrhagic stroke										✓								
Cardiovascular events																		
Myocardial infarction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Angina pectoris/unstable angina		✓	✓	✓			✓	✓		✓	✓	✓		✓			✓	
Coronary revascularisation		✓	✓	✓			✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Heart failure									✓									
Cardiac arrest (resuscitated)														✓				
Ischemic stroke		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Pulmonary embolism											✓	✓						

Venous thromboembolism			✓								✓	✓					
Background mortality																	
Non-CVD related deaths	✓*	✓*	✓*	✓	✓	✓	✓*	✓	✓*		✓*	✓	✓	✓			✓	
Utilities																	
Baseline utility age-dependent	✓		✓			✓			✓		✓	✓				✓	✓	
CVD events disutilities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Long-term post-CVD events disutility	✓			✓							✓	✓						
Adverse events disutilities			✓	✓						✓						✓	✓	✓
Statin use disutility (‘taking a pill every day’)			✓		✓	✓								✓		✓		
Treatment adherence																		
Treatment adherence	✓	✓		✓	✓	✓	✓				✓	✓		✓		✓	✓	✓

*Background mortality adjusted for CVD-related deaths. Abbreviations: CVD = cardiovascular disease

8.2.3 Findings of the cost-effectiveness systematic literature search

The main cost-effectiveness findings of the identified studies are summarised in Table 8.14. Except for Onishi et al.[123], all studies concluded that statin use for primary prevention of CVD was cost-effective in some CVD risk groups. However, the cost-effectiveness results were difficult to compare between studies, because they all used different risk scoring systems and/or patient populations. In general, statin treatment for primary prevention of CVD was more cost-effective among higher CVD risk groups. In addition, cost-effectiveness results were more favourable for older age groups and in men compared to women.

All of the five studies that examined the cost-effectiveness of statin use for primary prevention of CVD in patients with normal LDL-C levels but elevated hs-CRP levels concluded that rosuvastatin was cost-effective compared to no statin treatment.[98,103,113,114,122] They also agreed that rosuvastatin was even more cost-effective in patients with a 10-year CVD risk score (Framingham risk score) of more than 10%.

The three studies focusing on the use of statins for primary prevention of CVD in diabetes type 2-patients agreed that statins were cost-effective compared to no treatment in this patient population.[92,110,112] However, de Vries et al. noted that with real-world adherence rates, prescribing statins to diabetes type 2-patients younger than 45 years would not be cost-effective.[92]

Multiple studies concluded that treatment adherence had a major impact on cost-effectiveness results of statin use in primary prevention.[92,104,111,112,116] When real-world adherence was taken into account, the ICERs were higher than in full adherence scenarios. In addition, the costs of statins and disutility of taking a pill every day influenced the cost-effectiveness results.

Finally, the chosen time horizon of the economic evaluation had a large influence on the results.[104,109,113,116] Statins were more likely to be cost-effective when longer (especially lifetime) time horizons were applied. Only two of the included studies performed a budget impact analysis. In their study, Conly et al. predicted statin expenditures in Canada for low risk patients using various definitions of low risk, these included: a) patients aged 40+ years without heart disease, diabetes, or stroke who are not currently on a statin, b) men aged 50+ years and women aged 60+ years without heart disease, diabetes, or stroke who are not currently on a statin, and c) men aged 50+ years and women aged 60+ years without heart disease, diabetes, or stroke and either hypertensive or smoker who are not currently on a statin.[111] Additional scenarios were included considering treatment regardless of LDL-C levels, only if LDL-C > 2.5 mmol/L, and only if LDL-C > 4.5 mmol/L. Conly et al. concluded that in their most unlikely scenario (all patients aged 40+ years without heart disease, diabetes, or stroke who are not currently on a statin) the eligible population would increase by 11.6 million people which results in an increased

expenditure of statins of $9.17 billion annually. However, the budget impact analysis did not take into account potential savings from averted cardiovascular events, or additional costs related to life years gained due to statin use.[111]

Stomberg et al. estimated the budget impact of OTC statins under the 2013 American College of Cardiology/ American Heart Association Guidelines.[107] The analysis by Stomberg et al. includes three groups of OTC statin people: a) previously untreated patients who meet statin guidelines, b) previously untreated patients who do not meet statin guidelines, and c) previous prescription statin users who take up OTC statin treatment. They estimate an increase in total costs to the health system by approximately $12.6 billion. This budget impact analysis did not account for differences in compliance rates between OTC and prescription settings.

Quality appraisal

Table 8.17 shows the quality appraisal of the included studies using the CHEC checklist. The studies scored well on the items regarding the study design. Although a lifetime horizon is generally preferred due to the (potentially) lifetime effect of statins on CVD morbidity and mortality, some studies applied a shorter time horizon as the CVD risk was determined for 10 years. Therefore, only studies with a time horizon shorter than 10 years were penalised on this item.

The studies were not scored for the questions with regards to included costs and outcomes (question 7-12), because this requires an in-depth analysis to determine which costs should be included and what the optimal measurement and valuation methods are. Instead we provided an overview of included costs and outcomes in Table 8.15 and Table 8.16.

The included studies also performed well regarding reporting and interpreting the results; all studies performed incremental analyses and their conclusions followed from the reported data. Further, almost all studies discounted both costs and effects and most studies subjected all important uncertain variables to sensitivity analyses. However, almost half of the studies did not discuss generalisability of the results and only one study discussed ethical and distributional issues. Furthermore, in eight studies at least some of the authors were sponsored by pharmaceutical companies. Overall, study quality was deemed moderate to good with only a few areas lacking such as generalisability of results and the fact that almost half of the studies was sponsored by the pharmaceutical industry in some form.

Table 8.17. Critical appraisal using the CHEC checklist[75]

			Aarnio 2015	Annemans 2010	Choudry 2011	Conly 2011	DeVries 2013	Greving 2011	Khoury 2009	MacDonald 2010	McConnachie 2014	Odden 2015	Ohsfeldt 2010	Ohsfeldt 2012	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman 2016	Slejko 2010	Stomberg 2016
Study design	**1**	Is the study population clearly described?	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	2	Are competing alternatives clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
	3	Is a well-defined research question posed in answerable form?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	4	Is the economic study design appropriate to the stated objective?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
	5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
	6	Is the actual perspective chosen appropriate?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Costs	**7**	Are all important and relevant costs for each alternative identified?	More information in Table 8.15																	
	8	Are all costs measured appropriately in physical units?	-																	
	9	Are costs valued appropriately?	-																	
Outcomes	**10**	Are all important and relevant outcomes for each alternative identified?	More information in Table 8.16																	
	11	Are all outcomes measured appropriately?	-																	
	12	Are outcomes valued appropriately?	-																	
Interpretation and results	**13**	Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	14	Are all future costs and outcomes discounted appropriately?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
	15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?			✓	✓	✓	✓	✓	✓			✓	✓		✓		✓	✓	✓
	16	Do the conclusions follow from the data reported?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	✓	✓	✓		✓		✓		✓	✓		✓	✓			✓	✓	
	18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	✓			✓	✓	✓		✓	✓	✓			✓	✓	✓			
	19	Are ethical and distributional issues discussed appropriately?					✓													

8.2.4 Findings of the de novo cost-effectiveness model

This paragraph describes the results of the cost-effectiveness analyses performed with the de novo cost-effectiveness model specifically developed for this study.

Base-case analysis

Table 8.18, Table 8.19, and Table 8.20 show the incremental cost-effectiveness ratios (ICERs), incremental QALYs, and incremental costs respectively of statin therapy versus no statin therapy in all age, sex, and AGLA risk subgroups. The ICER represents the difference in costs of statin therapy and no statin therapy divided by the differences in QALYs. This means that a negative ICER can be the result of a reduction in costs and increase in QALYs or an increase in costs and reduction in QALYs. All negative ICERs in this study (Table 8.18) are caused by higher lifetime QALYs (Table 8.19) and lower total lifetime healthcare costs (Table 8.20) for statin therapy (i.e. statin therapy is cost saving and increases QALYs). In general, the ICER was higher in older age groups, males, and lower AGLA risk score groups. The ICER was higher in older age groups because due to the lifetime time horizon of the model there was less time to enjoy the benefits of statins (i.e. prevention of CVD events) than in younger age groups. There are several reasons for the higher ICERs in males than females: 1) the increase in CVD risk over time is higher in females, 2) the increase in mortality risk after stroke and MI (SMR) is higher in females, and 3) females have a higher life expectancy. Consequently, the incremental benefits of preventing CVD event with statins are higher in females. Finally, the ICERs were higher in lower AGLA risk groups because in these subgroups less CVD events are prevented that can offset the costs of statin therapy than in higher AGLA risk groups.

Table 8.18. Incremental cost-effectiveness ratios (ICER) in CHF per QALY of base-case analysis in all subgroups

Age	AGLA risk					
	1%	5%	10%	15%	20%	25%
Males						
40	39,514	4,518	1,088	-105	-748	-1,154
45	59,300	5,798	925	-466	-1,134	-1,542
50	88,152	8,291	890	-913	-1,652	-2,055
55	114,080	12,185	1,318	-1,297	-2,268	-2,714
60	157,037	18,288	2,694	-1,317	-2,832	-3,472
65	204,759	26,356	5,466	-580	-2,999	-4,115
70	274,366	38,398	10,214	1,565	-2,243	-4,208
75	381,012	59,023	19,420	6,692	677	-2,658
Females						
40	14,133	2,757	471	-722	-1,214	-1,573
45	21,095	3,023	383	-702	-1,320	-1,985
50	35,175	3,114	108	-1,009	-1,653	-2,075
55	61,885	4,348	-370	-1,584	-2,176	-2,563
60	91,027	7,992	-400	-2,322	-2,993	-3,327
65	139,794	15,349	1,200	-2,500	-3,811	-4,345
70	217,042	28,403	5,726	-907	-3,668	-4,963
75	344,412	51,832	16,038	4,660	-634	-3,512

Red: ICER > 150,000 CHF/QALY, Orange: ICER > 100,000 CHF/QALY, Yellow: ICER > 50,000 CHF/QALY, Green (light): < 50,000 CHF/QALY, Green (dark): Cost saving. These negative ICERs were all caused by lower total life-time healthcare costs and higher lifetime QALYs for statin therapy (i.e. statin therapy dominates no statin therapy).

Table 8.19 Incremental QALYs of base-case analysis in all subgroups

Age	AGLA risk					
	1%	5%	10%	15%	20%	25%
Males						
40	0.173	0.443	0.552	0.603	0.634	0.654
45	0.124	0.376	0.501	0.563	0.599	0.622
50	0.087	0.309	0.443	0.513	0.555	0.581
55	0.066	0.247	0.379	0.455	0.502	0.532
60	0.046	0.190	0.311	0.388	0.439	0.474
65	0.033	0.142	0.244	0.317	0.369	0.406
70	0.022	0.101	0.181	0.243	0.292	0.330
75	0.014	0.065	0.121	0.169	0.210	0.244
Females						
40	0.323	0.526	0.600	0.653	0.675	0.691
45	0.246	0.480	0.565	0.608	0.636	0.676
50	0.172	0.429	0.525	0.571	0.602	0.624
55	0.111	0.358	0.477	0.532	0.564	0.586
60	0.076	0.277	0.410	0.480	0.519	0.544
65	0.049	0.199	0.324	0.405	0.456	0.490
70	0.030	0.132	0.233	0.310	0.367	0.410
75	0.017	0.079	0.147	0.206	0.256	0.298

Table 8.20 Incremental costs (in CHF) of base-case analysis in all subgroups

Age	AGLA risk					
	1%	5%	10%	15%	20%	25%
Males						
40	6,828	2,001	600	-63	-474	-754
45	7,373	2,181	464	-262	-679	-960
50	7,660	2,561	394	-469	-917	-1,195
55	7,481	3,011	500	-590	-1,138	-1,444
60	7,191	3,469	838	-511	-1,244	-1,645
65	6,672	3,747	1,331	-184	-1,106	-1,671
70	6,030	3,876	1,845	381	-655	-1,390
75	5,266	3,846	2,352	1,131	142	-649
Females						
40	4,571	1,450	282	-471	-819	-1,087
45	5,190	1,452	216	-427	-840	-1,341
50	6,064	1,337	57	-576	-995	-1,296
55	6,845	1,557	-176	-842	-1,226	-1,502
60	6,953	2,214	-164	-1,114	-1,552	-1,809
65	6,837	3,053	389	-1,013	-1,739	-2,128
70	6,423	3,745	1,336	-281	-1,347	-2,033
75	5,761	4,099	2,364	960	-162	-1,047

Table 8.21 shows the full results of one of the subgroups that will be considered in scenario analyses: 50-year old males with an AGLA risk of 1% at baseline. In this subgroup, statins prevented 21 MIs and 10 strokes per 1000 people. On average, a person on statin therapy gained 0.09 QALYs and the healthcare costs were CHF 7,660 higher compared to a person without statin therapy, resulting in an ICER of CHF 88,152/QALY.

Table 8.21. Full results of base-case analysis in 50-year old males with baseline AGLA risk of 1%

Therapy	MI	Stroke	LYs (undis-counted)	QALYs (dis-counted)	Costs (CHF, discounted)	ICER (CHF/QALY)
No statins	0.080	0.082	34.62	17.18	34,474	NA
Statins	0.060	0.072	34.89	17.27	42,134	NA
Incremental	0.021	0.010	0.10	0.09	7,660	88,152

Scenario analyses

Table 8.22 presents the results of the scenario analyses of one of the subgroups: 50-year old males with an AGLA risk of 1% at baseline. The time horizon, discount rate, disutility of taking a pill, and adherence to statin therapy had the largest impact on the cost-effectiveness results. The results of the scenario analyses are discussed in more detail below.

Table 8.22. Results of scenario analyses in 50-year old males with baseline AGLA risk of 1%

Scenario	ΔCosts (in CHF)	ΔQALYs	ICER	% change from base case ICER
Base case	7,660	0.09	88,152	0%
Time horizon 10 years	4,348	0.00	951,429	979%
No discounting	10,576	0.22	48,220	-45%
Discount rate 6%	5,859	0.04	150,481	71%
Additional AGLA risk increase 5%	7,560	0.09	83,379	-5%
Lifetime disutility after MI	7,660	0.09	81,899	-7%
1-year disutility after stroke	7,660	0.08	95,402	8%
Adverse events	7,650	0.086	88,575	0%
Constant annual discontinuation lifetime	4,319	0.04	110,899	26%
Constant annual discontinuation 3 years	6,650	0.074	89,646	2%
Linear decreasing annual discontinuation	4,732	0.045	104,717	19%
Exponential decreasing annual discontinuation	6,624	0.073	90,649	3%
Full adherence	6,607	0.13	50,719	-42%
Reduced effectiveness age >75 years	7,934	0.074	106,807	21%
Disutility of taking a pill	7,660	0.07	116,874	33%

Time horizon

Limiting the time horizon to 10 years instead of lifetime increased the ICER substantially because the benefits of using statins for primary prevention of CVD often occur beyond 10 years. In other words, the increase in healthcare costs of using statins is not offset by the benefits of preventing CVD events in the first 10 years.

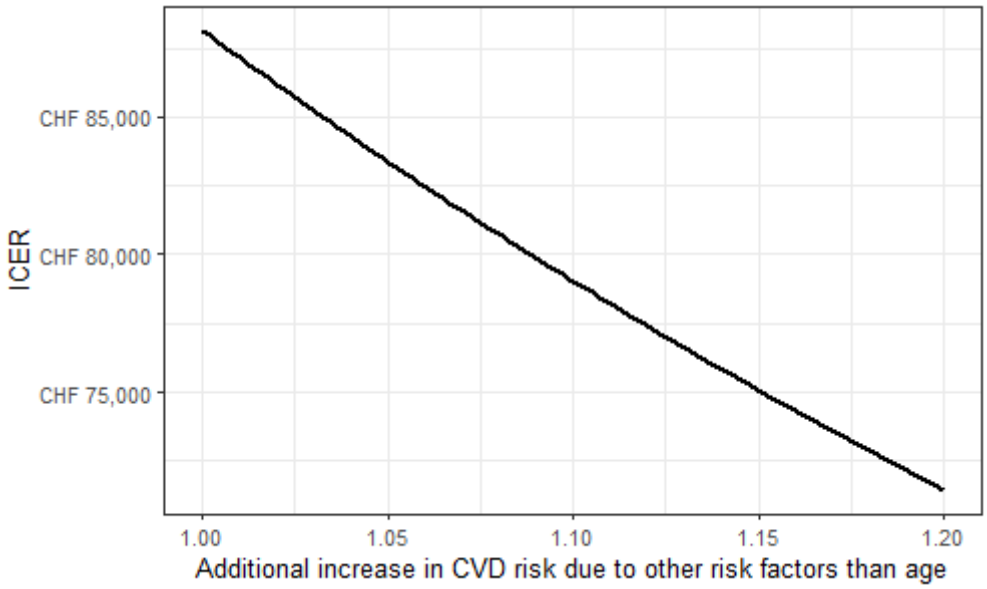
Discounting

As CVD risk increases over time due to ageing, the benefits of using statins increase over time. However, due to discounting costs and benefits in the future are valued less than present costs and benefits. Therefore, the ICER decreases if discounting is not applied and the ICER increases if a higher discount rate is used.

Additional increase in CVD risk over time due to other risk factors than age

The results in Table 8.22 showed that an additional increase of 5% in CVD risk over time due to other risk factors included in the AGLA risk calculator (i.e. systolic blood pressure, LDL, HDL, triglycerides, smoking status, diabetes mellitus, family history of MI) than age lowers the ICER with 5%. Figure 9 shows the impact of varying the assumed annual additional increase in CVD risk between 0% (risk adjustment factor is 1) and 20% (risk adjustment factor is 1.20). If the additional increase in CVD risk over time is larger, statin therapy will prevent more CVD events and therefore the ICER decreases.

Figure 9. Impact of the assumed annual additional increase in CVD risk over time due to other risk factors than age



Disutilities after MI and stroke

Changing the assumptions on the duration of impact on utility of MI and stroke only has a limited effect on the ICER. If the disutility for MI is increased from one year in the base-case to lifetime in the scenario analysis, the ICER decreases with 7% because the benefits of preventing a MI with statin therapy are larger. In contrast, if the disutility of stroke is decreased from lifetime in the base-case to one-year in the scenario analysis, the ICER increases with 8% because the benefits of preventing a stroke with statin therapy are smaller.

Adverse events

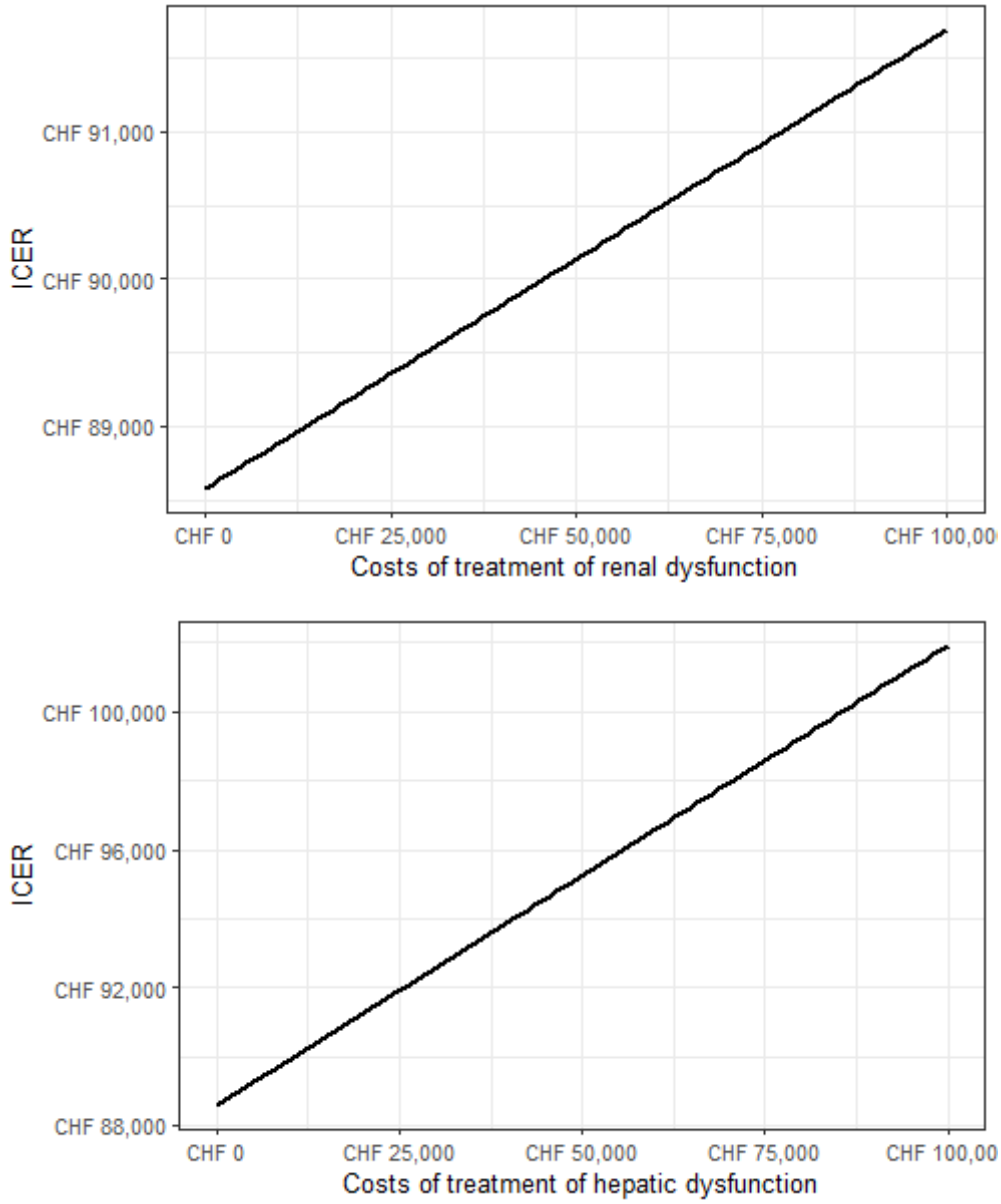
The results of the scenario analyses including adverse events are presented in Table 8.23. Without including the costs of treatment of renal and hepatic dysfunction, the impact on the cost-effectiveness results is very small.

Figure 10 shows the impact of varying the costs of treatment of renal and hepatic dysfunction between 0 and 100,000 CHF on the ICER. If the costs of treatment of renal dysfunction or hepatic dysfunction were assumed to be 100,000 CHF, the ICER increased with 3.5% to 91,697 CHF or with 11.6% to 101,931 CHF, respectively.

Table 8.23. Full results of scenario analysis with adverse events

Therapy	MI	Stroke	LYs	QALYs	Costs	ICER
No statins	0.080	0.082	34.62	17.17	34,559	NA
Statins	0.060	0.072	34.89	17.26	42,209	NA
Incremental	0.021	0.010	0.27	0.09	7,650	88,575

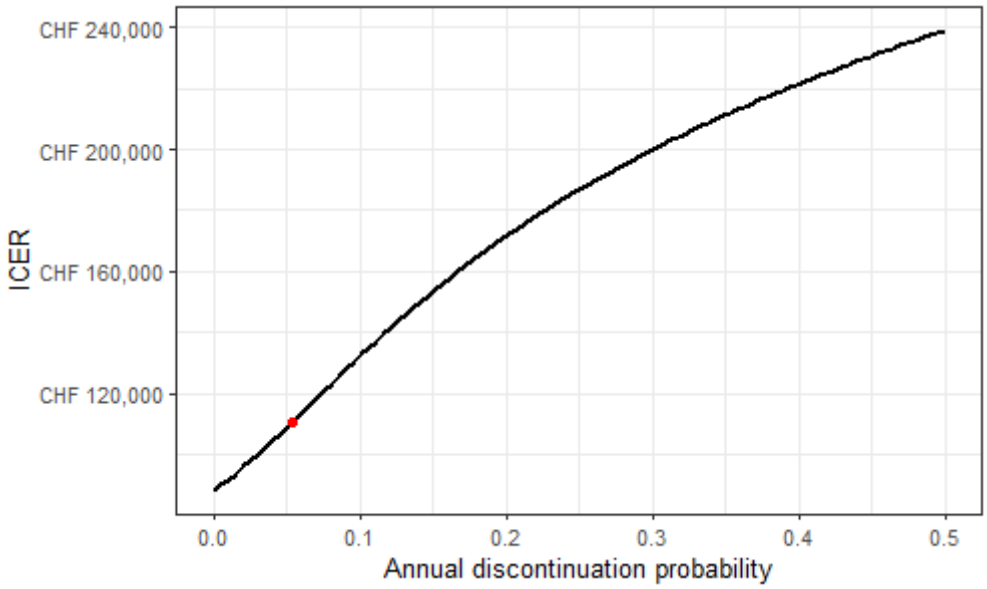
Figure 10. Impact of varying treatment costs of renal and hepatic dysfunction on the ICER



Statin discontinuation due to adverse events

Four scenarios with varying assumptions on statin discontinuation due to adverse events were performed (see results in Table 8.22). A constant annual discontinuation probability during the entire lifetime of the patient had the highest impact on the ICER. Figure 11 shows the impact of varying the annual discontinuation probability in this scenario analysis (red dot represents the probability that was used in the constant annual discontinuation lifetime scenario in Table 8.22: 0.0558). If there is a higher annual probability that patients will stop statin therapy (i.e. discontinuation), the ICER increases.

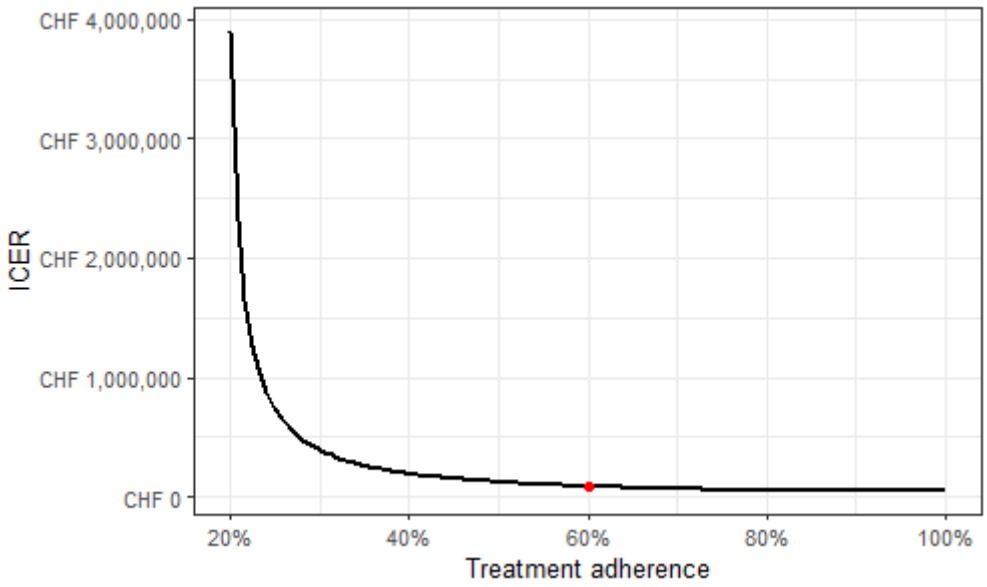
Figure 11. Sensitivity analysis of annual discontinuation probability in constant annual discontinuation scenario analysis



Statin adherence

In the base-case, a treatment adherence of 69% in the first year and 60% in subsequent years was assumed. Table 8.22 shows the cost-effectiveness results when patients are fully adherent to statin therapy. In Figure **12** the impact of varying treatment adherence in subsequent years from 20% to 100% is illustrated. The red dot represents the base case assumption of 60%. The figure illustrates that higher treatment adherence estimates results in lower ICERs.

Figure 12. Sensitivity analysis of treatment adherence



Reduced effectiveness age >75 years

Reduced treatment effectiveness in patients older than 75 years old, reduces the benefits of statin therapy and therefore the ICER increases.

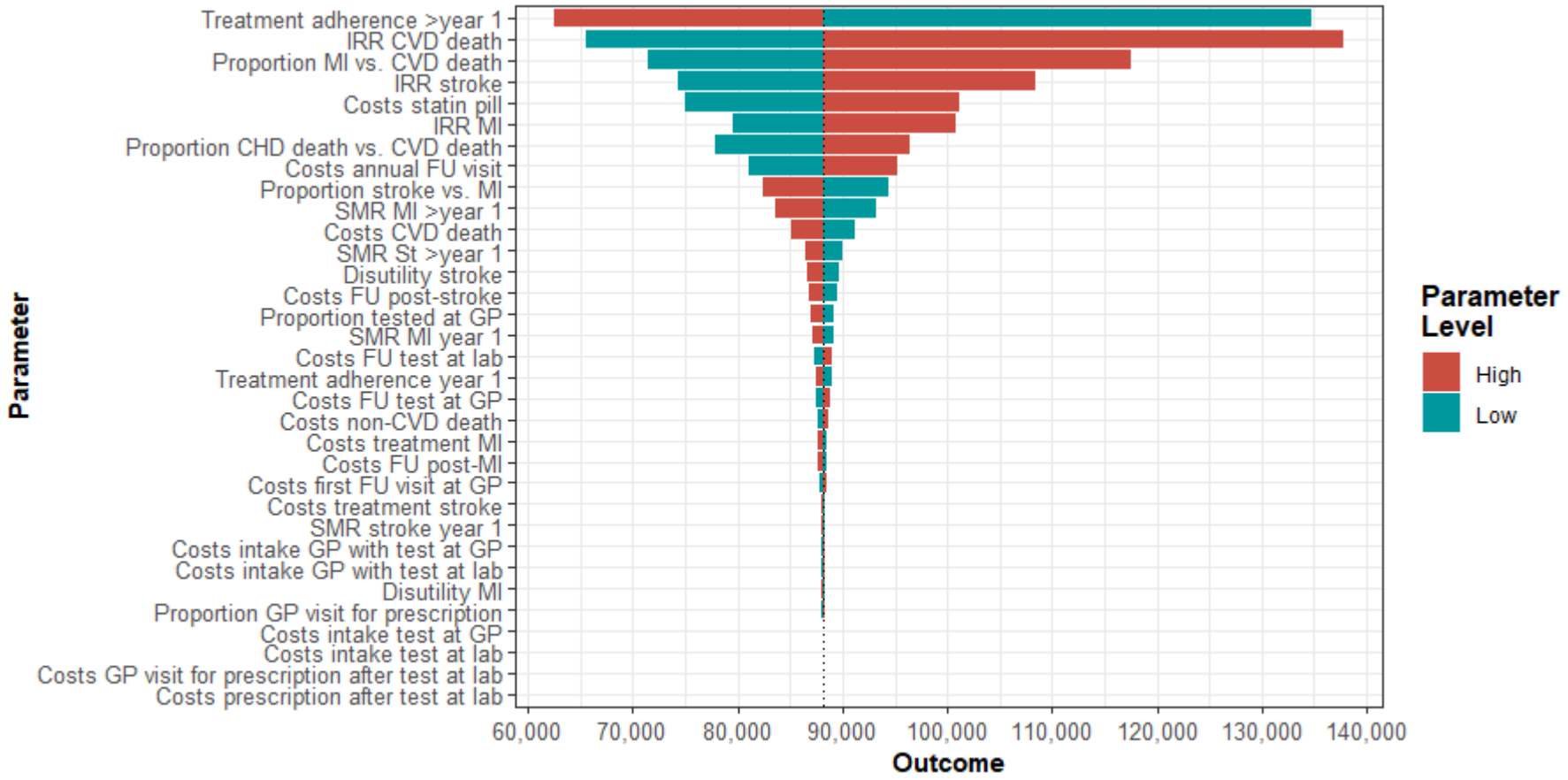
Disutility of taking a pill

When a small disutility of 0.001 is included to take into account for the disadvantage of statin therapy to take a pill every day, the benefits of statin therapy are reduced and therefore the ICER increases. As this disutility is applied during the patient's whole lifetime, the impact on the ICER is considerable.

One-way sensitivity analyses (OWSA)

The results of the OWSA for the subgroup of 50-year old males with baseline AGLA risk of 1% are illustrated in the tornado diagram in Figure 13 and the detailed results are presented in Table 8.24 . The effect of statins in reducing CVD events for statins versus no statins (i.e. IRR CVD death, IRR stroke, and IRR MI), the treatment adherence in subsequent years, the proportion of MI versus CVD death, and the costs of a statin pill and GP visit had the largest impact on the ICER. In addition, OWSA were performed for the scenario analysis including adverse events. The results of this analysis are presented in Appendix 15.9. The effect of statins in reducing CVD events (i.e. IRRs) had the largest impact on the cost-effectiveness results, followed by the incidence of the adverse events without statins. Disutility and costs of adverse events only had a minor impact on the cost-effectiveness results.

Figure 13. Tornado diagram of one-way sensitivity analyses base-case scenario



Outcome is incremental cost-effectiveness ratio (ICER). Abbreviations: IRR: incidence rate ratio. CVD: cardiovascular disease. MI: myocardial infarction. FU: follow-up. SMR: standard mortality ratio. St: stroke. GP: general practitioner.

Table 8.24. Outcomes one-way sensitivity analyses base-case scenario

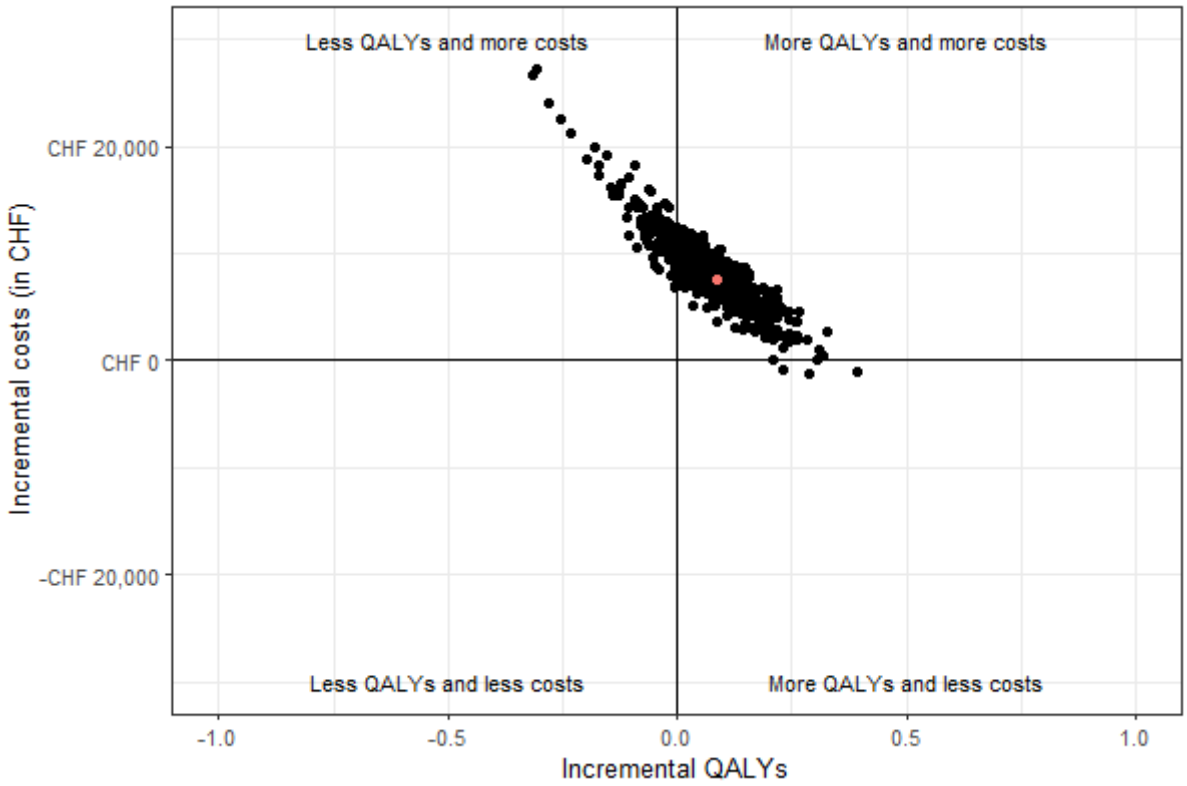
Parameter	Parameter value low	ICER value low	Parameter value high	ICER value high	Absolute difference	Relative difference (%)
Treatment adherence >year 1	0.48	135,752	0.72	62,763	72,990	53.77
IRR CVD death	0.73	65,827	0.95	138,801	72,974	110.86
Proportion MI vs. CVD death	0.63	71,709	0.94	118,371	46,662	65.07
IRR stroke	0.70	74,624	0.89	109,019	34,395	46.09
Costs statin pill	0.58	75,406	0.87	101,744	26,337	34.93
IRR MI	0.47	79,965	0.73	101,397	21,432	26.80
Proportion CHD death vs. CVD death	0.28	78,217	0.42	96,998	18,781	24.01
Costs annual FU visit	115.05	81,463	172.57	95,686	14,223	17.46
Proportion stroke vs. MI	0.82	94,953	1.23	82,873	12,080	12.72
SMR MI >year 1	1.67	93,649	2.24	83,990	9,659	10.31
Costs CVD death	6808.80	91,644	10213.20	85,506	6,138	6.70
SMR St >year 1	2.08	90,406	2.78	86,892	3,514	3.89
Disutility stroke	0.11	90,104	0.17	87,097	3,007	3.34
Costs FU post-stroke	9508.00	89,892	14262.00	87,258	2,634	2.93
Proportion tested at GP	0.00	89,686	1.00	87,463	2,223	2.48
SMR MI year 1	3.77	89,529	5.22	87,542	1,986	2.22
Costs FU test at lab	27.72	87,678	41.58	89,472	1,794	2.05
Treatment adherence year 1	0.55	89,517	0.83	87,835	1,681	1.88
Costs FU test at GP	21.62	87,876	32.42	89,274	1,399	1.59
Costs non-CVD death	3352.80	88,067	5029.20	89,082	1,015	1.15
Costs treatment MI	13445.60	88,998	20168.40	88,152	846	0.95
Costs FU post-MI	1377.60	88,995	2066.40	88,155	840	0.94
Costs first FU visit at GP	101.65	88,281	152.47	88,869	588	0.67
Costs treatment stroke	15754.40	88,815	23631.60	88,335	479	0.54
SMR stroke year 1	3.50	88,797	4.51	88,335	461	0.52
Costs intake GP with test at GP	128.45	88,389	192.67	88,761	372	0.42
Costs intake GP with test at lab	115.05	88,408	172.57	88,741	333	0.38

Disutility MI	0.05	88,716	0.08	88,435	281	0.32
Proportion GP visit for prescription	0.00	88,474	1.00	88,676	202	0.23
Costs intake test at GP	45.50	88,509	68.26	88,641	132	0.15

Probabilistic sensitivity analyses (PSA)

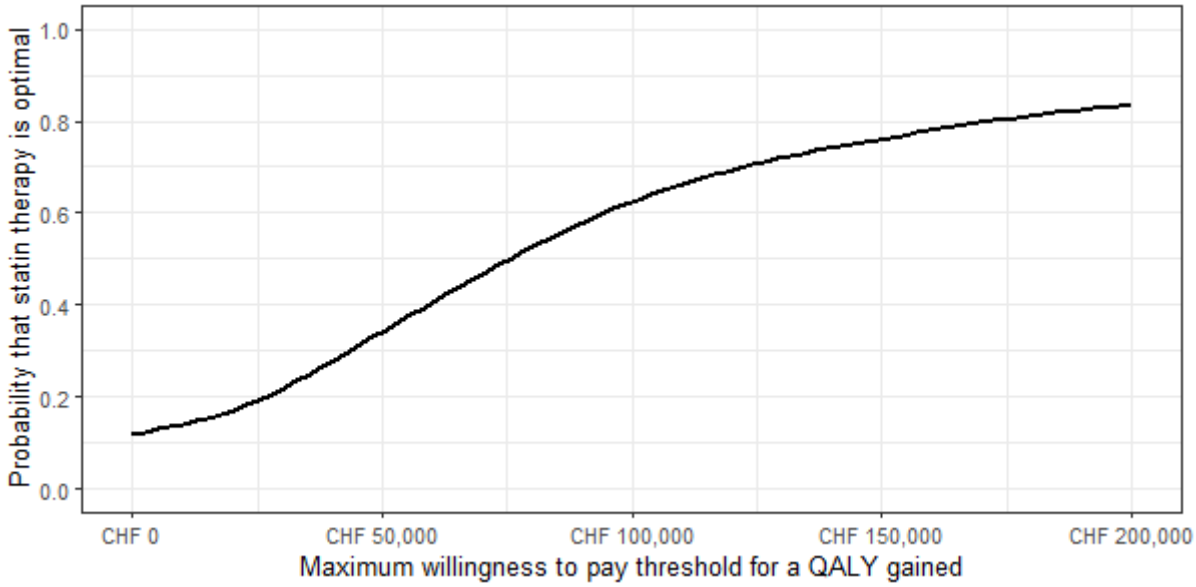
The results of the PSA for the subgroup of 50-year old males with baseline AGLA risk of 1% are presented in the cost-effectiveness plane (Figure 14) and cost-effectiveness acceptability curve (CEAC, Figure 15). The mean incremental costs and QALYs of the PSA iterations were 8,060 CHF and 0.08 QALYs, resulting in an ICER of 104,637 CHF/QALY. The difference between the deterministic and probabilistic ICER can be explained by the use of lognormal distributions for the relative proportions and IRRs of CVD events. The cost-effectiveness plane shows that there is uncertainty about whether statins are cost-saving or cost-increasing and whether more or less QALYs are gained. The red dot represents the deterministic ICER.

Figure 14. Cost-effectiveness plane



The cost-effectiveness acceptability curve shows the probability that statin therapy is optimal is 33.4% at a willingness-to-pay threshold per QALY of 50,000 CHF and 62.7% at a willingness-to-pay threshold per QALY of 100,000 CHF.

Figure 15. Cost-effectiveness acceptability curve



8.2.5 Findings population-level cost analysis

As mentioned before, the budget impact compared to current unrestricted use could not be estimated because of lack of data on the current use of statins in Switzerland. Instead of the budget impact, the annual population-level costs of the different statin therapy reimbursement policies were calculated. Table 8.25 shows the total healthcare costs (including all costs specified in paragraph 8.1.5) for different reimbursement policies based on CVD risk and age assuming all eligible patients will start using statin therapy with real-world treatment adherence of 69%.

Table 8.25 Total annual healthcare costs of different reimbursement policies of statins

Reimbursement policy	Number of people using statins	Total annual healthcare costs (in CHF)
All risks/40-75 years	2,182,953	933,539,742
All CVD risks/40-59 years	1,396,312	610,307,353
All CVD risks/60-75 years	786,641	350,019,450
Moderate or high CVD risk/40-75 years	261,954	83,446,885
Moderate or high CVD risk/40-59 years	167,557	54,913,191
Moderate or high CVD risk/60-75 years	94,397	31,748,142
High CVD risk/40-75 years	43,659	11,194,795
High CVD risk/40-59 years	27,926	7,412,580
High CVD risk/60-75 years	15,733	4,317,956

Eighteen economic evaluations of statin therapy were identified in the systematic literature search. Considering the lack of high-quality cost-effectiveness studies in the Swiss context, lack of cost-effectiveness studies using one of the preferred risk scoring systems in Switzerland, and changes in prices of statins due to the introduction of generics, a de novo model was developed that incorporated the most recent and (where possible) Switzerland-specific effectiveness, costs, and utility evidence.

This de novo model showed that from a healthcare payer perspective, applying a lifetime time horizon with discounting, assuming real-world treatment adherence and no discontinuation due to adverse events, the cost-effectiveness of statin therapy for primary prevention of CVD compared to no statin therapy varied substantially across subgroups. ICERs were lower in subgroups with higher CVD risk, younger age, and female sex. The ICER was above 100,000 CHF/QALY in males with a starting age of 55 years or higher and females with a starting age of 65 years or higher with an AGLA risk of 1%. The ICER was between 50,000 and 100,000 CHF/QALY in males with a starting age between 45-55 years with an AGLA risk of 1%, males with a starting age of 75 years with an AGLA risk of 5%, females with a starting age between 55-65 years with an AGLA risk of 1%, and females with a starting age of 75 years with an AGLA risk of 5%. For all other subgroups, the ICER was below 50,000 CHF/QALY. Moreover, statin therapy was even more effective and cost-saving in males with a starting age between 40-65 with an AGLA risk of 15%, males with a starting age between 40-70 years with an AGLA risk of 20% and males with a starting age between 40-75 years with an AGLA risk of 25%, females with a starting age between 40-70 years with an AGLA risk of 15%, and females with a starting age between 40-70 years with an AGLA risk of 20% or 25%.

The various scenario analyses and sensitivity analyses showed the influence of specific assumptions and parameters on the outcomes. A shorter time horizon, applying a higher discount factor, and including a disutility of taking a pill increased the ICERs significantly. The effectiveness of statins in reducing CVD events, the proportion of MI versus CVD deaths, and the costs of statin therapy were important parameters that introduced uncertainty about the cost-effectiveness of statin therapy. The PSA showed that the uncertainty was relatively large around the ICER estimate.

Due to a lack of data on the current use of statins for primary prevention of CVD in various CVD risk groups in Switzerland, the budget impact of restricted reimbursement policies compared to

the current unrestricted use of statin therapy in Switzerland could not be determined. Instead, the maximum population-level annual healthcare costs of reimbursement policies were estimated. Reimbursing statins for all patients above 40 years old, regardless of CVD risk, and assuming 100% uptake and real-world adherence to statin therapy was associated with annual healthcare costs of 934 million CHF. The annual healthcare costs decreased when the reimbursement policy was restricted to certain age groups and CVD risks, with annual healthcare costs of around 4 million CHF in the most restricted reimbursement policy where statin therapies were only reimbursed for people between 60 and 75 years old at high CVD risk.

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9 Legal, social and ethical issues

9.1 Methodology legal, social and ethical issues search

9.1.1 Databases and search strategy

Two literature search strategies were created for the legal issues and the social and ethical issues, separately. The legal and social and ethical search strategies and the results are detailed below.

Legal issues search

A search filter for legal evidence was added to the 'Patient population' and 'Intervention' search terms that were used in the efficacy, effectiveness, and safety search and cost-effectiveness search in PubMed (MEDLINE) and Embase.com (see Appendix 15.5).

Social and ethical issues search

Following the recommendations in the HTA Core Model Version 3.0[128], modified search filters from Droste et al. 2010[129] were embedded to the clinical search strings regarding CVD and statins (see Appendix 15.6).

The same inclusion and exclusion criteria were used for these searches (see Table 9.1).

Table 9.1. **Inclusion and exclusion criteria other HTA domain searches**

	Inclusion	**Exclusion**
Period publication	No restriction on period of publication: because other HTA domain issues might be identified in earlier publications.	
Study language	• German • English • French • Dutch	All other languages
Country of study	• Western countries*	
Study population	Patients without previous cardiovascular events	Patients with previous cardiovascular events
Study intervention	Statins licensed in Switzerland: Atorvastatin (Sortis® and generics), Fluvastatin (Lescol® and generics), Pitavastatin (Livazo®), Pravastatin (Selipran® and generics), Rosuvastatin (Crestor® and generics), Simvastatin (Zocor® and generics)	Other interventions

The same quality control measures were put in place in the other HTA domains literature searches as for the efficacy, effectiveness, and safety and cost-effectiveness literature searches.

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers from iMTA. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was more than 5% discrepancy between the two researchers, therefore all titles and abstracts were screened in duplicate. Any conflicts were discussed and amended accordingly.
- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers from iMTA. Again, during screening there was more than 5% discrepancy between the two researchers, therefore all full-text articles were screened in duplicate. Any conflicts were discussed and amended accordingly.

9.1.2 Other sources

For legal aspects, a search in the Swiss legislation database[w] (in German, English, French languages; for all legal product types; for both national and international law documents; for both in force and not in force legislations) was conducted to find any relevant legislation documents associated with statin therapy, from 1848 until 2019. The terms “statins” and “cardiovascular disease”, and their German and French translations were entered.

The legal documents from the search in the Swiss legislation database did not include any information related to statin therapy.

9.1.3 Assessment of quality of evidence

Not applicable.

9.1.4 Methodology data analysis legal, social and ethical issues

The summary of the findings related to the legal, social, and ethical domains are provided narratively. No statistical tests were applied to the literature search output of the above-mentioned domains.

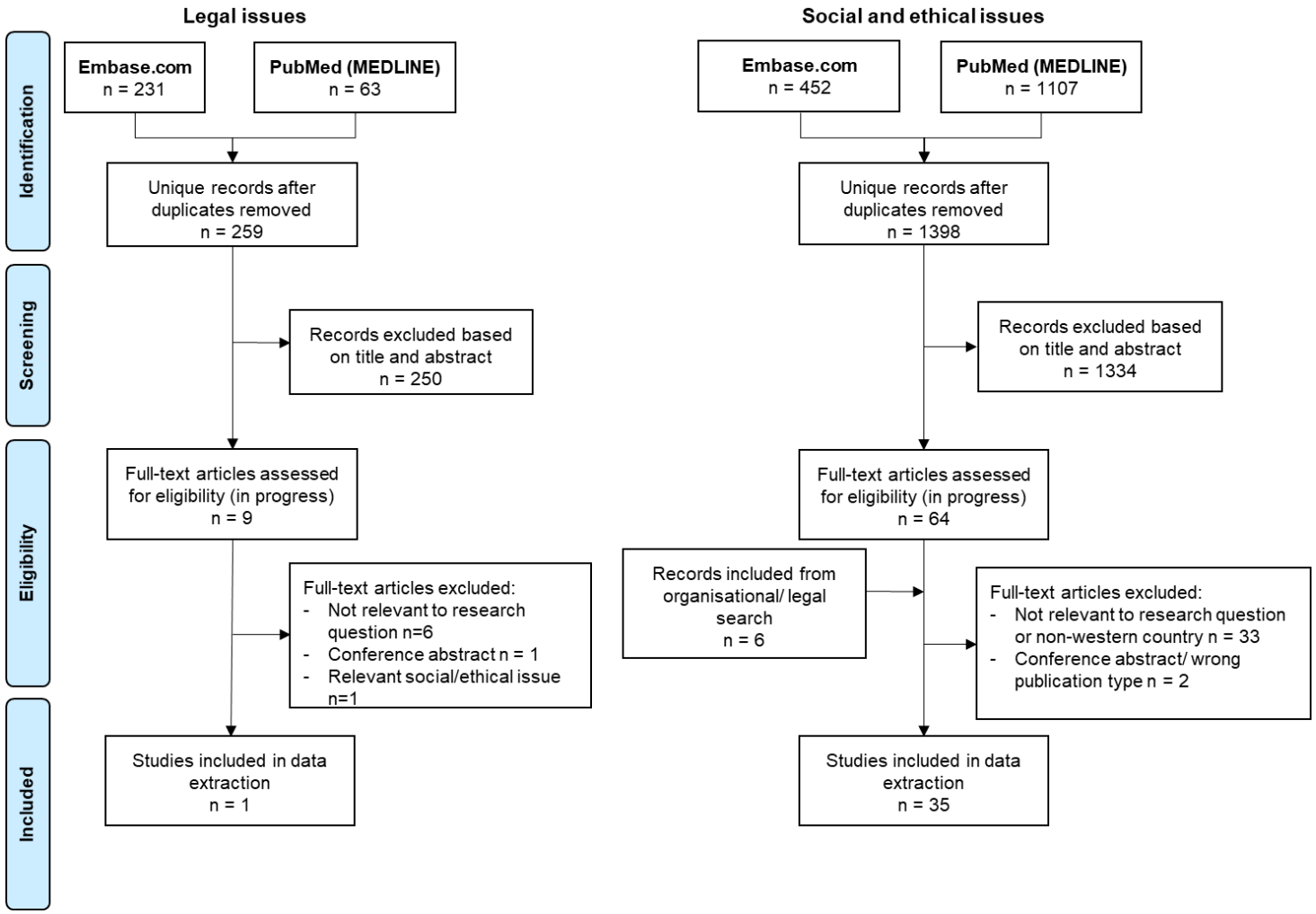
[w] https://www.admin.ch/opc/search/search.php?lang=en

9.2 Results legal, social and ethical issues

9.2.1 PRISMA flow diagram

The legal issues search yielded *63 hits* in PubMed and *231 hits* in Embase.com (search performed on 12-2-2020).and the social and ethical issues search yielded *452 hits* in PubMed and *1,107 hits* in Embase.com (search performed on 20-2-2020). The full details on these searches is displayed in Figure 16.

Figure 16. PRISMA flow diagram legal, social and ethical issues search



9.2.2 Evidence table

Not applicable.

9.2.3 Findings legal issues

From the systematic literature search outlined above and from the search performed in the Swiss legislative database, no relevant articles were identified that concerned healthcare rationing for statin therapy in primary prevention of CVD specifically.

We identified one study on the role of regulators in approving the use of statins.[130] Jefferson et al. argue that regulators across the world approved statins for the primary prevention of CVD despite the important debate on whether benefits outweigh their harms.[130] They examined the regulators knowledge, access and independent assessment of the presented data in 32 European countries. Only a few countries were able to consistently defend their decision-making. Moreover, only a few countries had done an independent scrutiny of the presented safety data. The main reason for not performing an independent analysis of safety data was the lack of pre- and post-marketing harm-related data. This data was either inaccessible or (low-middle level) adverse events were excluded from the benefit/harm analysis because of vague definitions.

9.2.4 Findings social issues

Findings on the social domain regarding the use of statins for primary prevention of CVD focused on three main issues: adherence to statin therapy and its determinants, the disutility of daily intake of a statin pill, and patient preferences and shared decision-making.

Adherence to statin therapy

Fourteen articles examined the demographic and socioeconomic determinants of (real-world) adherence to statin therapy. The most relevant determinants included self-perceived risk, income, sex, ethnicity, age and comorbidities. The list of relevant factors associated with adherence are provided in Table 9.2. We also identified several studies which discussed the impact of changes to patient co-payments for statins. These studies will be discussed in the 'Organisational issues' section in Chapter 0.2.2.

Table 9.2. Factors associated with adherence to statin therapy across articles

Factors analysed	First author and publication year	General direction of effect
Socioeconomic factors		
Income	Aarnio 2016[131], Wallach-Kildermoes 2013[132], Chan 2010[41], Lemstra 2012[133], Mann 2010[134]	Income up, adherence up

Co-payment	Chan 2010[41], Fung 2018[135], Lemstra 2012[133]	Co-payment up, adherence down
Demographic and other factors		
Sex	Aarnio 2016[131], Wallach-Kildermoes 2013[132], Chan 2010[41], Cicero 2014[136], Lewey 2013[137], Mann 2010[134], Karalis 2016[138], Lavikrainen 2016[139], Moreno-Arellano 2018[140]	Women are on average less adherent than men.
Age	Wallach-Kildermoes 2013[132] and 2012[141], Chan 2010[41], Cicero 2014[136], Mann 2010[134]	Highest adherence between 50-65, bell-shaped effect
Ethnicity	Mann 2010[134], Lewey 2013[137], Chan 2010[41]	Non-white patients are on average more likely to be non-adherent
Perceived risk	Fung 2018[135]	Perceived risk up, adherence up
Comorbidities	Lemstra 2012[133], Cicero 2014[136], Mann 2013[137], Chan 2010[41]	On average patients with comorbidities are more adherent
Other		
Media coverage	Bezin 2016[142], Matthews 2016[143]	Media controversy/negative coverage, adherence down

Socioeconomic status

In general, individuals with lower income or socioeconomic status were less likely to adhere to statin therapy, which was especially the case for individuals using statins for primary prevention.[41,131–134] The influence of socioeconomic status on adherence was found to be significant among male but not among female populations in two studies that analysed Scandinavian populations.[131,132]

Sex

Several studies examined the association between sex and adherence.[41,131,132,134,136–140] All except one article[136] found that females are on average less adherent to statins. The magnitude of the association varied, but the trend seems to be (almost) universal. This negative association between the female sex and statin adherence may be caused by a higher engagement in healthier lifestyles, higher health literacy, and a different health-seeking behaviour of females compared to males.[131] These characteristics may make them less willing to engage in long-term drug treatments like statins. Also, females are more likely to be dissatisfied with their statin medication, to report statin-related adverse events, and to discontinue therapy because of adverse events.[131,132,138] Other explanations include the general misconception by both patients and physicians that females bear less CVD risk than males, and the fact that females frequently serve as caregivers for family members which in turn has been associated with lower rates of medication adherence.[137]

Age

Age appeared to have a bell-shaped relationship with adherence with the relatively young adults (<45-50 years) and those above 65-70 years of age showing lower rates of adherence compared to middle-aged adults.[132,134] The low adherence rates among the youngest and the oldest groups have led policies and guidelines updates to focus on stimulating the uptake of statins in these subgroups. In Denmark, this resulted in a triplicate in the proportion of individuals in primary prevention in the extremes of the age range.[141] In contrast, Chan et al. found an association of decreasing adherence with age, even in the group of elderly individuals in his sample.[72] An explanation for this could be that their sample did not include a large proportion of adults over 65-70 years.[41]

Ethnicity

Three articles analysed the association between ethnicity and adherence.[41,134,137] Their findings suggest that non-white patients are less likely to be adherent and this is more pronounced for those in primary prevention compared to secondary prevention.[41,134,137] The article by Lewey et al. provides the following potential reasons: non-white patients experience increased barriers to access high-quality care, are less likely to have a consistent relationship with a primary care provider compared with white patients with similar levels of insurance, exhibit overall more mistrust towards the health care system, more often lack knowledge on how to navigate the healthcare system, and may face communication barriers that hinder the understanding of the healthcare provider's instructions.[137]

Perceived risk

The systematic review by Lemstra et al. showed that primary prevention patients were 52% less likely to be adherent compared to secondary prevention patients.[133] This can be explained by the differences in perceived risk of disease between these two groups[135], and is highly associated with the presence of cardiovascular-related comorbidities.[41,133,134,136,137] Due to these low adherence rates, statin therapy for primary prevention of CVD could become ineffective even for the high-risk young individuals.[116]

Statin-related media coverage

Two articles examined the effect of statin-related media coverage on statin utilisation for the primary prevention of CVD. One French study explored the effect of a particular case of controversial media coverage regarding the efficacy of statin therapy continuation among patients in different risk categories.[142] This controversy started in 2013 when a French retired professor of medicine published a book refuting the efficacy of statins for cardiovascular prevention and the subsequent wide broadcast of the book and interviews with the author in a variety of media. Bezin et al. found that after the controversy, low- and middle-risk patients were 40% and 53% more likely to discontinue their therapy in the short-run, respectively.[142] In the UK, a similar situation emerged in October 2013 when two articles published in the BMJ suggested that statin side effects outweigh their benefits in patients at low and middle CVD

risk. The debate peaked and achieved national media coverage.[143] However, the controversy had no significant impact on statin initiation for primary prevention of CVD among high-risk patients compared with before the controversy.[143]

Disutility of taking a pill

In the study by Fontana et al. (2014), the authors weighted the disutility of taking a pill against the expected long-term health gain from statin therapy for primary prevention of CVD.[144] They showed that two thirds of the eligible subjects desired at least one month of life expectancy gain to consider adherence to statin therapy to be worthwhile. Most notably, 12% of the subjects reported to experience extreme disutility and would require more than 10 years of extended life expectancy in order to commit to a long-term statin therapy.

Shared decision making

In primary prevention, physicians are often faced with the dilemma of giving a therapy to a relatively healthy individual in order to prevent future healthcare events, even though this patient could experience harmful events from taking the preventive therapy. Physicians have their own preferences and beliefs regarding statin treatment in primary prevention of CVD and evidence suggests that there is a clear discrepancy between the perceived care and actual care provided by physicians. One study showed that while physicians claim to follow the latest guideline recommendations and assured to give a statin to hypothetical patients in the study, in practice this was not the case. Practitioners with higher belief in statins are more likely to follow the guideline recommendations in real practice.

In addition to disutility of taking a pill every day, patients may question the efficacy of statins and fear the adverse events.[145,146] The balance between benefits and harms is often not easily reduced to a yes/no decision. Patient-centred guidelines regarding cholesterol treatment for the primary prevention of CVD should recognize this and should avoid recommendations based solely on cut-off values and embrace shared decision-making.[145,147–149]

Decisions regarding statin therapy for primary prevention of CVD should always consider a patient's perspective and preferences.[146,147] In order to increase shared decision-making, some articles suggested the use of specific tools to improve communication and empower the patient in the decision-making process.[144,147,149]

Luymes et al. analysed the barriers and enablers encountered between patients and their GPs after an update in cardiovascular prevention guidelines and reimbursement policy which resulted in the exclusion of patients with low CVD risk from the reimbursement scheme in the Netherlands.[150] Patients were generally positive toward deprescribing preventive cardiovascular medication and they relied on the information and expertise of their GP to determine the justification of deprescription. The main barrier for

deprescription was a patient's fear towards the (health) consequences of stopping their statin therapy. The assurance that follow-up care was available and that medication could be restarted if deemed required, facilitated the process and acceptance of deprescription of statins by Dutch patients.[150]

9.2.5 Findings ethical issues

Two ethical issues were identified in the systematic literature search. The first issue was related to health disparities in primary prevention of CVD and statin therapy. Seven articles addressed this issue and one of these compared population-based approaches versus individual-level measures to reduce CVD risk.[151–157] The other issue was related to the quality of evidence used for recommendations for primary prevention of CVD with statins.[158–160]

In the scoping report, it was questioned whether it would be ethical if patients with good adherence to statin therapy that belong to subgroups with low predicted adherence were to be denied reimbursement from statin therapy. In our extended systematic literature search, we did not find any articles that provided additional information on this topic.

Health disparities in statin therapy for the primary prevention of CVD

Health disparities were most frequently associated with differences in socioeconomic status (income and education), ethnicity, and sex.

Socioeconomic status

One study examined the change in cholesterol levels over time after the introduction of statins for primary prevention across different income groups in the US. Using data from the National Health and Nutrition Examination Surveys 1970 and 2004, the article showed that statins were more often adopted by those with higher income which led to widening health disparities that favoured the wealthy.[153] Another US study showed that patients with lower education and income level receive poorer care for the prevention of CVD despite their higher CVD risk.[154] In contrast to these findings in the US, no evidence of socioeconomic inequality in statin use was found in the UK.[157]

Ethnicity

Health disparities also exist among certain ethnic groups whose CVD risk is underestimated by the available risk scores, which is most notably the case for people of South Asian descent.[155] In addition, non-white individuals are systematically prescribed less statins for primary prevention of CVD although they are eligible for statin therapy.[151,152]

Sex

Evidence also suggests that health disparities exist across sexes. Females are less likely to be told or engage in discussions with their doctors about their CVD risk compared with males, making them less likely to receive treatment with statins for primary prevention of CVD.[138,140] This inequality is closely related to the determinants of adherence to statin therapy discussed in Chapter 9.2.4.

Reducing health disparities

Structural measures aimed at reducing risk factors at the socioenvironmental level or whole-population approaches have the potential to reduce socioeconomic inequalities in cardiovascular health. An example of this provided by Capewell et al. is the Norsjo Community Intervention Program in Sweden. This program combined population health and health sector interventions, generating local health promotion collaboration between healthcare providers, grocery stores, schools, and municipal authorities. Individual risk factors screening, and counselling was provided by primary care physicians and community interventions and also included food labelling modifications to encourage adherence to healthy diets. Through this program a 36% reduction in CVD mortality risk was achieved, with disadvantaged groups benefiting the most.[156] In this way, population-based approaches have a strong ethical background as governments should respect, protect, and fulfil their obligations related to public health for everyone.

Questioning the quality of the evidence

There has been great debate about the quality of the evidence used to support the guideline recommendations, especially the ACC/AHA 2013[20], the European Society of Cardiology (ESC) 2019, and the European Atherosclerosis Society (EAS) 2019. These guidelines suggest extended primary prevention to populations considered ‘healthy’ and composed mainly of young individuals. The validity of the findings that support these guidelines is questioned due to the already large and increasing amount of industry-funded studies.[159] The conflicting interests affects the transparency of the results, stimulates publication bias and jeopardises the real-value assessment of new drugs and technologies.[158,159]

Summary statement legal, social and ethical issues

Despite variations across studies, the association between low socioeconomic status or low income and non-adherence seems to be almost universal. Differences in adherence behaviour signals a trend in which females are less likely to be adherent than males and that both younger patients (below 50 years old) and older patients (above 70 years) tend to be less adherent than middle-aged patients (50-70 years). People using statins for primary prevention of CVD tend to have lower adherence rates than people who use statins for secondary prevention for CVD, which is most likely explained by low self-perceived risk of disease.

Several studies found that patients experience disutility of taking a pill each day, especially for primary prevention of disease. Disregarding this disutility and the patients' preferences lies far away from the model of patient-centredness and should therefore be considered.

In addition, physicians are often faced with the dilemma of giving a therapy to a relatively healthy individual in order to prevent future healthcare events, even though this patient could experience harmful events from taking the preventive therapy.

Health disparities due to the introduction of statin therapy for primary prevention of CVD were most frequently associated with differences in income, socioeconomic status, ethnicity, and sex. In general, access to statin therapy seems to be restricted to those better-off in systems without universal health coverage (like the US), which imposes a risk for widening wealth-related inequalities in health outcomes of CVD. No evidence of socioeconomic inequality in statin use was found in the UK, but there were ethnic-related disparities. There was no specific evidence on health disparities in statin therapy in Switzerland available in the literature.

Finally, there has been great debate about the quality of the evidence used to support the guideline recommendations. Policy makers have to be aware of the issues regarding the quality of evidence on which guidelines are based in order to make informed decisions.

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10 Organisational issues

10.1 Methodology organisational issues

10.1.1 Databases and search strategy

For the organisational aspects, a search for studies published listed under the MESH subheadings of “Hydroxymethylglutaryl-CoA Reductase Inhibitors/organisation and administration” or “Hydroxymethylglutaryl-CoA Reductase Inhibitors/supply and distribution” on the PubMed (MEDLINE) website was conducted. The exact search terms were: ("Hydroxymethylglutaryl-CoA Reductase Inhibitors/organisation and administration"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors/supply and distribution"[Mesh]).

In addition, relevant studies on organisational issues were included from the social and ethical search in PubMed and EMBASE due to the use of the term ‘healthcare delivery’ in that search filter.

Table 10.1. Inclusion and exclusion criteria other HTA domains searches

	Inclusion	**Exclusion**
Period publication	No restriction on period of publication: because other HTA domain issues might be identified in earlier publications?	
Study language	• German • English • French • Dutch	All other languages
Country of study	• Western countries*	
Study population	Patients without previous cardiovascular events	Patients with previous cardiovascular events
Study intervention	Statins licensed in Switzerland: Atorvastatin (Sortis® and generics), Fluvastatin (Lescol® and generics), Pitavastatin (Livazo®), Pravastatin (Selipran® and generics), Rosuvastatin (Crestor® and generics), Simvastatin (Zocor® and generics)	Other interventions

10.1.2 Other sources

Not applicable.

10.1.3 Assessment of quality of evidence

Not applicable.

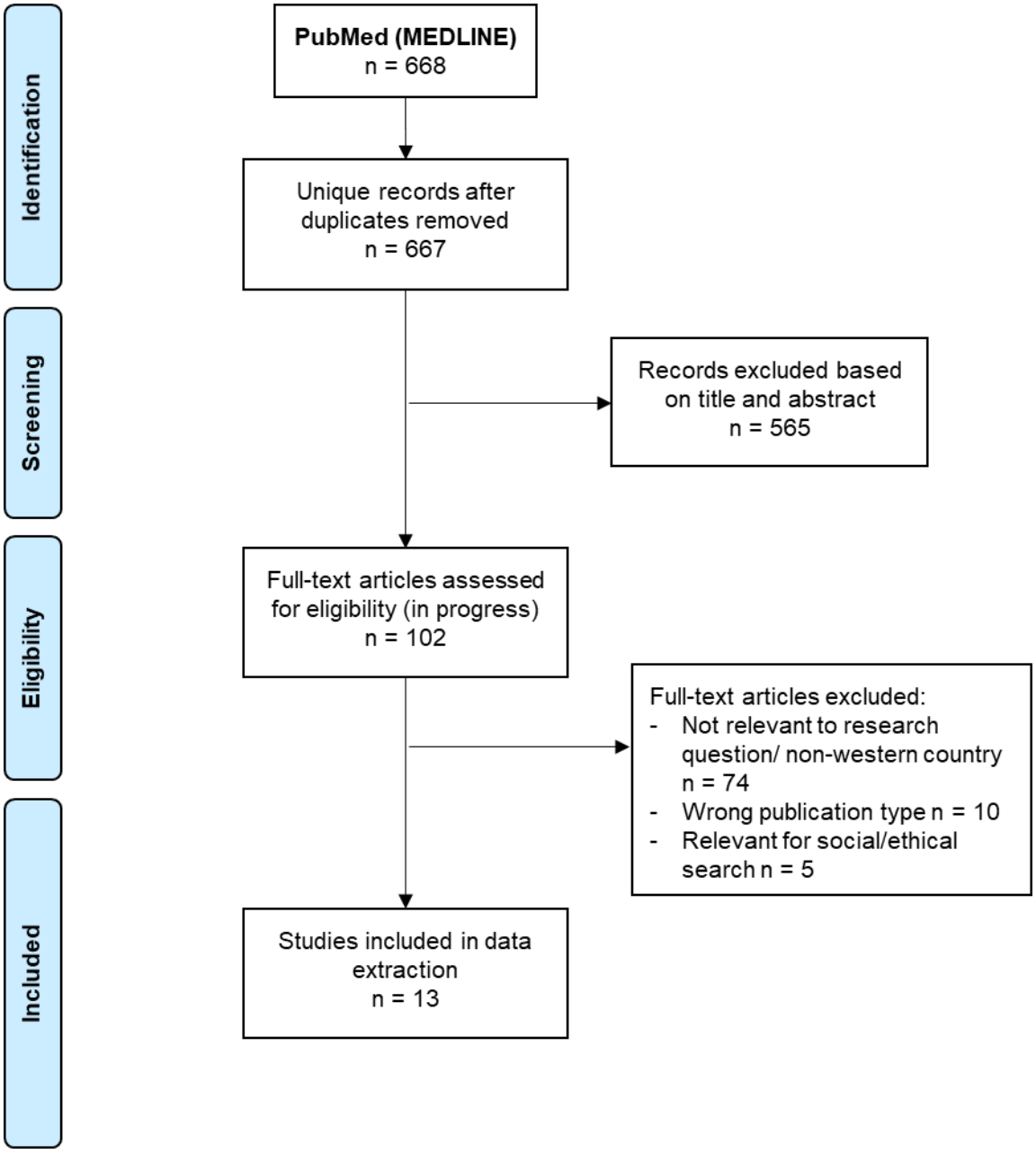
10.1.4 Methodology data analysis organisational issues

The evidence on organisational aspects of the technology was described narratively. No statistical tests were applied to the literature search output of this domain. The title/abstract screening phase and the subsequent selection of the relevant studies was performed by two researchers at iMTA.

10.1.5 PRISMA flow diagram

The search for organisational issues in in the Embase database resulted in *668 hits* (search performed on 12-02-2020). The search is further detailed in Figure 17.

Figure 17. PRISMA flow diagram organisational issues search



10.1.6 Evidence table

Not applicable.

10.2 Findings organisational issues

Of the thirteen studies selected after full text screening, seven examined the impact of supply and distribution factors and co-payment on adherence.[87,161–166] One study reported the impact of statin therapy

in obese patients on healthcare costs of obesity[167]; and five studies analysed the effect of reimbursement policy changes regarding the genericisation of certain statins on prescription, costs, and treatment disruption.[168–172]

10.2.1 Impact of supply and distribution factors on adherence

Supply and distribution factors were analysed in six articles.[87,161–165] The table below summarizes the factors analysed, the definitions and the associated studies.

Table 10.2. Supply and distribution factors analysed

Factors analysed	Definition	First author and publication year
Dispensation delay	Time between prescription and dispensation	Aarnio 2014[87], Abbass et al. 2017[161]
Prescription size	Number of pills supply or days covered after every prescription/dispensation	Batal 2007[162], Ellis 2004[164]
Ordering method	Mail ordering - Medication is received via mail	Pittman 2011[165], Chaudhry 2008[163]

Dispensation delay, small prescription size and traditional in-person ordering were associated with lower statin adherence in different healthcare systems.[87,161–165] These studies included populations of both primary and secondary prevention patients and the effect of these factors was not disaggregated by prevention category.

Aarnio et al. (2014) found that a longer dispensation delay was a predictor for poor adherence to statins. Dispensation delay is influenced by the number of pharmacies in the community, the possibility to receive the medication via post at home and the way prescriptions are refilled and sent to pharmacies.[87,161]

Findings suggests that patients who receive a larger quantity of pills (more than two-month supply) with each refill have higher adherence[162,164] and that mail ordering and mail refill reminders are useful tools to increase adherence.[163,165] These strategies were particularly relevant for the most vulnerable patients and those with limited resources as it may reduce direct and indirect costs related to prescription refilling.[162,163,173]

10.2.2 Impact of changes in co-payment on adherence

In total seven articles identified in the organisational search[87,161–166] and three articles from the social search[41,133,173] examined the effect of co-payments and out-of-pocket expenditures on adherence to statin therapy. All articles found a negative association between higher co-payment and adherence. One article examined the effect of a (publicly-funded) voucher that served as a waiver on the co-payment

costs and was associated with higher adherence rates among the beneficiaries group (including patients on statin therapy for secondary prevention of CVD).[166]

10.2.3 Genericisation of statins

Different strategies to incentivize the prescription of generic statins and their effects on statin expenditure, utilisation and/or adherence were described in the identified studies. These strategies included modification of plan design factors[172], changes on restricted reimbursement national policies[168,169], and demand-side measures.[170] It is important to note that these strategies do not necessarily reflect strategies employed in Switzerland.

Cox et al. studied the effect of moving atorvastatin out of the reimbursement formulary on patient behaviour. Due to the removal of atorvastatin form the reimbursement formulary, the co-payment price changed which stimulated the uptake of statins included in the formulary.[172]

Two studies analysed the impact of restricted reimbursement national policies on statin use and expenditures in the context of publicly funded healthcare systems in Scandinavia.[168,169] Their findings suggest that when genericisation is formally enforced, switching rates can be as high as 60% after the first year[168] generating saving of as much as 20% in the first year.[169]

Enforcing well-designed demand-side measures aimed at stimulating the uptake of generics statins can have a positive effect on statin prescription and use while containing costs at the same time.[170] These demand-side measures include the design of value-based care indicators and quality targets, provision of economic incentives, revision and update of guidelines, education of healthcare providers to stimulate the prescription of low-cost statins and enforcement of all these policies through different regulations.[170]

The genericisation of statins is associated with switching behaviour and, therefore, risk of discontinuation, nonadherence or potentially inappropriate statin use.[168,171,172] One study explored the impact of generic substitution and found that the large majority of patients were switched to equipotent doses and adherence rates were relatively high after switching to a generic equipotent dose after 6 months.[171]

Summary statement organisational issues

There is evidence that supply and distribution factors, like prescription size and delay, as well as the level of co-payments by patients, influence statin adherence and, consequently, health outcomes. Several articles discuss the potential of genericisation of statins and its positive effect on adherence rates and cost containment.

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11 Additional issues

Due to our broad search for legal, social, ethical and organisational issues related to statins, no additional issues were encountered that were not already covered in the previous chapters.

12 Discussion

The present HTA evaluated the efficacy, effectiveness, safety, cost-effectiveness, and population-level costs of statin therapy for prevention of CVD compared to no statin therapy in adults without established CVD (i.e. primary prevention) and with low, medium, and (very) high CVD risk, based on available scientific literature. In this section, the main findings, strengths, and limitations of this HTA are discussed.

Main findings efficacy, effectiveness, and safety

Evidence from RCTs showed that statin therapy prescribed to adults without established CVD is effective in the prevention of cardiovascular events and mortality under study conditions (i.e. efficacy). However, there was limited evidence that these effects can be replicated under real-world circumstances (i.e. effectiveness). The evidence regarding the safety of statins was inconclusive. In their SR, Yebyo et al. found a significant increased risk of renal and hepatic dysfunction, but the quality of this evidence was low or moderate.[26] Findings of the meta-analysis conducted for this HTA report, which in contrast to Yebyo et al. considered differences in follow-up duration between the trials in the meta-analysis, did not show a statistically significant risk of these adverse events when using statins. The occurrence of these adverse events was rare (1 to 4 events per 1,000 statin users per year in the meta-analysis conducted for this report). Although the comparative evidence for safety is inconclusive, the event rate is low. Risk scores for CVD were hardly reported in the studies and therefore no stratification of the efficacy, effectiveness, or safety results was available for people with low, medium, or (very) high CVD risk.

Main findings cost-effectiveness

In addition to the clinical consequences, it is important to assess what the impact of these possible foregone benefits of statin therapy is on people's life expectancy and health-related quality of life and how this relates to the costs of statin therapy. According to a simplified calculation with a 5-year time horizon in the Swiss Medical Board (SMB) report of 2013[25], the ICER of the use of statins for primary prevention was around CHF 210,000 per QALY. The literature was searched for a cost-effectiveness analysis using a comprehensive cost-effectiveness model adopting a lifetime time horizon, incorporating up-to-date Swiss clinical and economic input parameters, and using the most often used CVD risk scoring system in Switzerland (i.e. the AGLA Risk Score) was required. Furthermore, decision makers do not only need a precise point estimate of the cost-effectiveness of statins, but extensive scenario and sensitivity analyses should also give them insight in the uncertainty surrounding this outcome and the ultimate decision being addressed. Such an economic evaluation was not identified in the literature. Therefore, a de novo cost-effectiveness model including the beforementioned characteristics was developed in our HTA.

In the following paragraph, we compared our results with the results of previous cost-effectiveness studies. First, in line with the results from previous cost-effectiveness studies, the results of our cost-effectiveness analyses showed that statin therapy for primary prevention of CVD was especially cost-effective in subgroups with higher CVD risk as more CVD events can be prevented in these subgroups. Second, and in contrast to previous studies, ICERs were higher in older age groups in our cost-effectiveness analyses. This difference is caused by the different time horizons used in the previous studies (often 10 years) and the current study (lifetime). When applying a lifetime horizon, older patients have less time to enjoy the benefits of statins (i.e. prevention of CVD events) than younger patients explaining the higher ICERs in older age groups. Finally, as opposed to findings in previous studies, our study found lower ICERs in females compared to males. There are two reasons for this difference. First, previous studies often only adjusted background mortality for sex, while we also used sex-specific input parameters for increase in CVD risk over time and increased mortality after CVD events (i.e. SMRs). The AGLA risk calculator showed that the increase in CHD risk over time is higher in females compared to males.[79] Furthermore, the probability to die after a stroke or MI was higher in females compared to males.[85] Consequently, the benefits of preventing CVD with statins are higher in females, resulting in lower ICERs compared to males. Second, because we applied a lifetime horizon (in contrast to most previous studies) and females on average have a higher life expectancy than males, females have more time to enjoy the benefits of statin therapy than males.

The scenario analyses performed in our HTA confirm the large impact of treatment adherence and disutility of 'taking a pill every day' on the cost-effectiveness of statins found in previous studies. In addition, we showed that the time horizon and discount rates have a large impact on the cost-effectiveness outcomes. OWSA showed that the parameters for the effect of statins in reducing CVD events for statins versus no statins (i.e. IRR CVD death, IRR stroke, and IRR MI), the proportion of MI versus CVD deaths, the treatment adherence in subsequent years and the costs of a statin pill and GP visit had the largest impact on the ICER. Finally, sensitivity analyses showed that uncertainty around the exact value of the input parameters has a large impact on the uncertainty in the cost-effectiveness results.

Main findings population-level costs

The cost-effectiveness analyses provided information about the balance between costs and benefits per patient, but as the size of lower CVD risk groups is large, it is also important to estimate the impact of theoretically prescribing statin therapies to all these people on the national healthcare budget. Our population-level cost analysis showed that the costs of reimbursing statin therapy in people with all CVD risks (i.e. including low CVD risk) are large, while our cost-effectiveness analyses showed that the number of CVD events that occur without statin therapy in (especially older) people with low CVD risk is limited. However, it should be noted that it is unknown how many people with low CVD risk are currently

using statin therapy for primary prevention of CVD events in Switzerland. Therefore, cost savings resulting from restricting reimbursement of statin to moderate and/or high risk could not be determined in this study.

Main findings other HTA domains

When considering possible restriction of statins to certain subgroups of people, relevant legal, social, ethical, and organisational issues should also be considered. For example, one should consider that changes in reimbursement policy can further increase health disparities between patients based on age, sex, race, and social economic status. In addition, real-world adherence to statins differs greatly from adherence in a clinical setting, especially in case of primary prevention. This should be considered when interpreting the results from the cost-effectiveness analyses.

Strengths

One of the main strengths of this HTA is the systematic search for SRs, RCTs, and non-randomised studies on the efficacy, effectiveness, and safety of primary prevention of CVD with statins in multiple peer-reviewed literature databases. A rigorous methodology, adhering to international methodological standards such as Cochrane and PRISMA, was applied to identify, critically appraise, analyse, and summarise the relevant evidence in order to minimise bias. Data was included on multiple individual as well as composite outcomes and further synthesised with meta-analyses in the two included SRs. Another strength of this HTA is the cost-effectiveness model that was developed specifically for the Swiss context which was an improvement compared to previous studies for numerous reasons, including extending the time horizon from 10 years to lifetime and updating CVD risk over time, using up-to-date and, when possible, Swiss-specific clinical and economic input parameters, based on the AGLA risk scoring system and accompanied with extensive sensitivity analyses. Finally, this HTA provided a comprehensive overview of the scientific literature on relevant legal, social, ethical, and organisational issues regarding primary prevention of CVD events with statin therapy.

Limitations

This HTA has several limitations. First, since a large amount of studies is published on statin therapy for the prevention of CVD events and mortality in adults without established CVD, we chose to include published high-quality SRs instead of individual RCTs. The inclusion of published SRs on efficacy, effectiveness, and safety of primary prevention of CVD with statins with determined data extraction and synthesis is a general limitation, because their choices for objectives, selection criteria, and data synthesis are never fully in line with our HTA scope. Furthermore, identified studies were mostly sponsored by the industry. Second, due to limited available data and other limitations, the health economic model represents a simplification of the complex reality of CVD. The main CVD events (MI, stroke, fatal CVD

events) and its consequences (i.e. revascularization interventions for the treatment of MI) were included in the model, but CVD events such as revascularization for coronary artery disease before the occurrence of a MI or (un)stable angina were not considered. Consequently, the benefits of statin therapy may be higher than reported in this report. Third, the results of this cost-effectiveness analyses in this HTA are not applicable to other risk scoring systems (e.g. SCORE or Framingham) and additional CVD risk factors (such as very high LDL or presence of atherosclerotic plaque) were not taken into account, because CVD risk was solely defined using the AGLA risk scoring system. However, the general conclusion that statins are more cost-effective in high CVD risk groups, younger age groups, and females will also be applicable to settings that use other CVD risk scoring systems. Fourth, statins were evaluated as a class, but since there are differences in efficacy, safety, and drug costs between statins[26] they may not be applicable to individual statins. Finally, the details of secondary events after the first non-fatal CVD event were not modelled explicitly. However, the consequences of a non-fatal CVD event in terms of increased mortality risk, costs, and disutility seen amongst post-MI and post-stroke patients were included in the model.

Evidence gaps

The following evidence gaps were identified during this HTA.

There was no evidence of the efficacy, effectiveness and safety of statin therapy compared to lifestyle adaptations, therefore we could only determine the cost-effectiveness of statin therapy versus no statin therapy.

It is unknown whether the efficacy, effectiveness, and safety of statin therapy versus no statin therapy is equal across CVD risk groups. Due to the lack of data, we assumed that the relative effectiveness and safety of statin therapy compared to no statin therapy was equal for people with low, medium, and (very) high CVD risk, but more research is needed to deny or confirm this assumption.

Another important evidence gap exists regarding the development of the underlying risk factors of CVD (such as blood cholesterol and blood pressure) in the people without established CVD. As a result, CVD risk could only be updated based on age in the cost-effectiveness model. Sensitivity analyses were performed to explore the impact of additional increases in CVD risk due to other risk factors on the cost-effectiveness results.

There was no clear evidence on positive (e.g. dementia reduction) and negative side effects (i.e. the beforementioned adverse events) of statins and/or the treatment costs of these events in Switzerland, therefore they were not included in the base-case analysis.

The scenario and sensitivity analyses showed that statin therapy adherence and disutility of ‘taking a pill every day’ had a significant impact on the cost-effectiveness outcomes, but (real-world) evidence on

these parameters in Switzerland is lacking. In the base-case analysis, treatment adherence was based on a Finnish study as the healthcare system with partly out-of-pocket costs for statins and the 'medical believers' attitude was comparable to Switzerland.

Evidence was lacking on the current use of statins for primary prevention of CVD in various CVD risk groups in Switzerland, therefore the budget impact of restricted reimbursement policies compared to the current unrestricted use of statins in Switzerland could not be determined. Instead, the population-level costs of reimbursement policies assuming all patients will start using statin therapy with real-world adherence was estimated. Due to a lack of age and sex-specific data on the number of patients without CVD, we assumed that the proportion of people eligible for primary prevention of CVD with statin therapy was equal across age and sex groups. However, it is likely that the proportion of patients without CVD is lower in younger and female subgroups. Consequently, we may have underestimated the number of eligible people for primary prevention of CVD in younger age groups and vice versa.

Summary

This HTA report showed that it can be concluded that statins can prevent CVD events without resulting in many adverse events of statins at a reasonable cost especially in subgroups with an AGLA risk score above 1%. However, the evidence of safety, effectiveness of and adherence to statins in the real-world is limited and the cost-effectiveness of statins is highly dependent on model settings and uncertain input parameters. Furthermore, as there is no data on the current use of statins for primary prevention of CVD events in Switzerland, the cost savings of disinvestment in statins for the national healthcare budget are unclear.

13 Conclusions

Sufficient evidence shows that statin therapy prescribed to adults without established CVD is effective in the prevention of cardiovascular events and mortality under study conditions (i.e. efficacy), but there is limited evidence on safety and effectiveness under real-world settings. Risk scores for CVD were hardly reported in the studies and no stratification of the efficacy, effectiveness, or safety results was available for people with low, medium, or (very) high CVD risk.

The health economic analyses were limited by a number of evidence gaps that should be beared in mind when interpreting the results. In summary, from a healthcare payers perspective, applying a lifetime horizon with discounting, and assuming real-world treatment adherence and no discontinuation due to adverse events, statin therapy for primary prevention of CVD seems to be associated with low ICERs compared to no statin therapy in subgroups with an AGLA risk above 1%, especially for those at younger

age and females. ICERs were higher in subgroups with low CVD risk (expressed in AGLA risk), older age and in males. The findings regarding age and sex were in contrast to the findings in previous studies, who found lower ICERs in males and older age groups. This is mainly caused by the application of a lifetime horizon and age- and sex specific increase in CVD risk over time in our study. The various scenario analyses and sensitivity analyses showed that specific assumptions and parameters had a large impact on the outcomes, such as the time horizon, discounting, treatment adherence, effectiveness of statins in reducing CVD events and the costs of statin therapy.

The budget impact of restricted statin reimbursement policies compared to the current unrestricted use of statins in Switzerland could not be determined due to a lack of data on the current use of statins. The annual healthcare costs of reimbursing statin therapy for all patients above 40 years old, regardless of CVD risk, and assuming all eligible people use statins with real-world adherence to statin therapy compared to no reimbursement of statins was 934 million CHF. The annual healthcare costs of statin therapy decreased when reimbursement of statins was restricted to certain age groups and CVD risks.

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15 Appendices

15.1 Search strategy efficacy, effectiveness, and safety

Table I. Search strategy PubMed (MEDLINE) efficacy, effectiveness, and safety

	I. SRs/meta-analyses	II. RCTs	III. Non-randomised studies
CVD	("cardiovascular diseases"[Mesh] OR cardiovascular disease*[tiab] OR cardio-vascular disease*[tiab] OR CVD[tiab] OR CVDs[tiab])	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])	
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])		
Primary prevention	("primary prevention"[Mesh] OR primary[tiab])	("primary prevention"[Mesh] OR primary prevent*[tiab] OR primordial prevent*[tiab] OR risk*[tiab])	
Study design	(((systematic*[tiab] OR comprehensive*[tiab]) AND (bibliographic*[tiab] OR literature[tiab] OR review*[tiab])) OR literature review*[tiab] OR meta-analysis[pt] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab])	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR RCT[tiab] OR RCTs[tiab] OR random*[tiab] OR controlled[tiab] OR control-treated[tiab] OR placebo[tiab] OR cross-over studies[Mesh] OR "single-blind method"[Mesh] OR single-blind*[tiab] OR single-blind*[tiab] OR single-masked[tiab] OR double-blind method[Mesh] OR double-blind*[tiab] OR doubleblind*[tiab] OR double-masked[tiab] OR triple-blind*[tiab] OR triple-blind*[tiab] OR triple-masked[tiab])	(nonrandomized[tiab] OR non-randomized[tiab] OR nonrandomised[tiab] OR non-randomised[tiab] OR quasiexperimental[tiab] OR quasi-experimental[tiab] OR non-equivalent control*[tiab] OR non-equivalent control*[tiab] OR "cohort studies"[Mesh] OR prospective*[tiab] OR retrospective*[tiab] OR follow-up stud*[tiab] OR followup stud*[tiab] OR longitudinal stud*[tiab] OR cohort[tiab] OR "comparative effectiveness research"[Mesh] OR comparative effectiveness[tiab] OR real-world[tiab] OR real-life[tiab] OR “case-control studies”[Mesh] OR case-control[tiab] OR case-control[tiab] OR case-comparison[tiab] OR case-referent[tiab])
Limits	Publication period: 2013 - 22 May 2019	Publication period: 2012 - 9 July 2019	Publication period: 2013 - 9 July 2019
	Language: English	Language: German, English, French, Dutch	
		No animal studies: NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))	
		No case reports and irrelevant publication types: NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt])	
		No reviews and meta-analyses: NOT ("systematic review"[pt] OR review[ti] OR "meta-analysis"[pt] OR meta-analysis[ti])	

Table II. Search strategy Embase.com efficacy, effectiveness, and safety

	I. SRs/meta-analyses	II. RCTs	III. Non-randomised studies
CVD	('cardiovascular disease'/exp OR cardiovascular disease*:ti,ab OR cardio-vascular disease*:ti,ab OR CVD:ti,ab OR CVDs:ti,ab)	('cardiovascular disease'/exp OR CVD:ti,ab OR CVDs:ti,ab OR stroke*:ti,ab OR coronary*:ti,ab OR heart*:ti,ab OR cardio*:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR angina*:ti,ab OR hypertensi*:ti,ab OR 'hyperlipidemia'/exp OR hyperlip*:ti,ab OR triglycerid*:ti,ab OR hypertriglycerid*:ti,ab OR hyperlipoprotein*:ti,ab OR 'cholesterol'/exp OR hypercholesterol*:ti,ab OR cholesterol*:ti,ab OR HDL:ti,ab OR LDL:ti,ab)	
Statins	(statin:ti,ab OR statins:ti,ab OR 'atorvastatin'/exp OR atorvastatin:ti,ab OR atorva:ti,ab OR sortis:ti,ab OR 'fluindostatin'/exp OR fluvastatin:ti,ab OR lescol:ti,ab OR 'pitavastatin'/exp OR pitavastatin:ti,ab OR livazo:ti,ab OR 'pravastatin'/exp OR pravastatin:ti,ab OR selipran:ti,ab OR mevalotin:ti,ab OR 'rosuvastatin'/exp OR rosuvastatin:ti,ab OR crestor:ti,ab OR 'simvastatin'/exp OR simvastatin:ti,ab OR zocor:ti,ab)		
Primary prevention	('primary prevention'/exp OR primary:ti,ab)	('primary prevention'/exp OR "primary prevent*":ti,ab OR "primordial prevent*":ti,ab OR risk*:ti,ab)	
Study design	(((systematic*:ti,ab OR comprehensive*:ti,ab) AND (bibliographic*:ti,ab OR literature:ti,ab OR review*:ti,ab)) OR "literature review*":ti,ab OR 'meta analysis'/exp OR meta-analys*:ti,ab OR meta-analyz*:ti,ab OR meta-analyt*:ti,ab OR metaanalys*:ti,ab OR metaanalyz*:ti,ab OR metaanalyt*:ti,ab)	('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR RCT:ti,ab OR RCTs:ti,ab OR random*:ti,ab OR controlled:ti,ab OR control-treated:ti,ab OR placebo:ti,ab OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR single-blind*:ti,ab OR single-blind*:ti,ab OR single-masked:ti,ab OR 'double blind procedure'/exp OR double-blind*:ti,ab OR doubleblind*:ti,ab OR double-masked:ti,ab OR 'triple blind procedure'/exp OR triple-blind*:ti,ab OR triple-blind*:ti,ab OR triple-masked:ti,ab)	(nonrandomized:ti,ab OR non-randomized:ti,ab OR nonrandomised:ti,ab OR non-randomised:ti,ab OR quasiexperimental:ti,ab OR quasi-experimental:ti,ab OR "non-equivalent control*":ti,ab OR "non-equivalent control*":ti,ab OR 'cohort analysis'/exp OR prospective*:ti,ab OR retrospective*:ti,ab OR "follow-up stud*":ti,ab OR "followup stud*":ti,ab OR "longitudinal stud*":ti,ab OR cohort:ti,ab OR 'comparative effectiveness'/exp OR "comparative effectiveness":ti,ab OR real-world:ti,ab OR real-life:ti,ab OR 'case control study'/exp OR case-control:ti,ab OR casecontrol:ti,ab OR case-comparison:ti,ab OR case-referent:ti,ab)
Limits	Publication period: 2013 - 22 May 2019	Publication period: 2012 - 9 July 2019	Publication period: 2013 - 9 July 2019
	Language: English	Language: German, English, French, Dutch	
		No animal studies: NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)	
		Relevant publication types: ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [note]/lim OR [short survey]/lim)	
		No reviews and meta-analyses: NOT ('systematic review'/exp OR review:ti OR 'meta analysis'/exp OR meta-analysis:ti)	

15.2 Checklists for the assessment of the quality of evidence

AMSTAR 2 checklist for the quality assessment of systematic reviews[27]

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:

- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

Cochrane Collaboration's tool for the quality assessment of RCTs[28] (as applied in the systematic reviews of Yebyo et al. 2019 and Taylor et al. 2013)

Note: Bias is judged per domain as low risk of bias, high risk of bias, or unclear risk of bias.

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Newcastle - Ottawa quality assessment scale for the quality assessment of cohort studies[30]

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users e.g. nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g. surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

15.3 Excluded studies during full-text selection efficacy, effectiveness, and safety search

Table I. Excluded SRs during full-text selection efficacy, effectiveness, and safety search

Reference	Reason for exclusion
Byrne P, Cullinan J, Smith A, Smith SM. Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. BMJ open. 2019;9(4):e023085.	Review which was reported in the review protocol, but is excluded in the scoping & HTA report based on narrative data synthesis
Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016;316(19):2008-2024.	Review which was reported in the review protocol, but is excluded in the scoping & HTA report based on most RCTs were covered in the reviews of Yebyo, 2019/Taylor, 2013 (see Table II for study characteristics and Table III for a comparison of the review results)
De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol. 2014;78(4):684-98.	No data on objectives
Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet (London, England). 2015;385(9976):1397-405.	Comparator not in line with PICO
He Y, Li X, Gasevic D, Brunt E, McLachlan F, Millenson M, et al. Statins and Multiple Noncardiovascular Outcomes: Umbrella Review of Meta-analyses of Observational Studies and Randomized Controlled Trials. Annals of internal medicine. 2018;169(8):543-53.	No data on objectives
Kristensen ML, Christensen PM, Hallas J. The effect of statins on average survival in randomised trials, an analysis of end point postponement. BMJ open. 2015;5(9):e007118.	Review which was reported in the review protocol, but is excluded in the scoping & HTA report based on no outcome of interest reported
Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis. The Lancet Haematology. 2017;4(2):e83-e93.	Systematic review on one specific disease
Li M, Wang X, Li X, Chen H, Hu Y, Zhang X, et al. Statins for the Primary Prevention of Coronary Heart Disease. BioMed research international. 2019;2019.	Systematic review on one specific disease
Lowe RN, Vande Griend JP, Saseen JJ. Statins for the primary prevention of cardiovascular disease in the elderly. The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists. 2015;30(1):20-30.	Lacking review methodology
Martin-Ruiz E, Olry-de-Labry-Lima A, Ocaña-Riola R, Epstein D. Systematic Review of the Effect of Adherence to Statin Treatment on Critical Cardiovascular Events and Mortality in Primary Prevention. Journal of cardiovascular pharmacology and therapeutics. 2018;23(3):200-15.	No data on objectives
Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. European journal of preventive cardiology. 2013;20(4):641-57.	Review which was reported in the review protocol, but is excluded in the scoping & HTA report based on same outcomes reported and less recent review compared to Yebyo, 2019/Taylor, 2013 (see Table II for study characteristics and Table III for a comparison of the review results)
Nunes JP. Statins in primary prevention: impact on mortality. A meta-analysis study. Minerva cardioangiologica. 2017;65(5):531-8.	Lacking review methodology
Ponce OJ, Larrea-Mantilla L, Hemmingsen B, Serrano V, Rodriguez-Gutierrez R, Spencer-Bonilla G, et al. Lipid-Lowering Agents in Older Individuals: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. The Journal of clinical endocrinology and metabolism. 2019;104(5):1585-94.	Population of older persons only
Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data	Meta-analysis includes primary and secondary prevention trials

from major randomized trials. European heart journal. 2015;36(24):1536-46.	
Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary Prevention With Statin Therapy in the Elderly: New Meta-Analyses From the Contemporary JUPITER and HOPE-3 Randomized Trials. Circulation. 2017;135(20):1979-81.	Non-pertinent publication type
Savarese G, Gotto AM, Jr., Paolillo S, D'Amore C, Losco T, Musella F, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. Journal of the American College of Cardiology. 2013;62(22):2090-9.	Population of older persons only
Swiss Medical Board. Statine zur Primärprävention kardiovaskulärer Erkrankungen. Zollikon, 2013.	Review which was reported in the review protocol, but is excluded in the scoping & HTA report based on narrative data synthesis
Teng M, Lin L, Zhao YJ, Khoo AL, Davis BR, Yong QW, et al. Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis. Drugs & aging. 2015;32(8):649-61.	Population of older persons only
Wang W, Zhang B. Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. PloS one. 2014;9(3):e92388.	Meta-analysis includes primary and secondary prevention trials
Waters DD. Meta-analyses of statin trials: clear benefit for primary prevention in the elderly. Journal of the American College of Cardiology. 2013;62(22):2100-1.	Non-pertinent publication type

Table II. Study characteristics of two excluded SRs (Chou et al. 2016 and Naci et al. 2013) on primary prevention in CVD

Reference	SR objective	Data sources, search period, language, data synthesis	Exclusion criteria	Study population	Intervention	Comparator	Included studies on primary prevention
Chou, 2016[31]	To systematically review benefits and harms of statins for prevention of CVD to inform the US Preventive Services Task Force	- Cochrane Central Register of Controlled Trials (from 1991) - Cochrane Database of Systematic Reviews (from 2005) - Ovid MEDLINE the Cochrane Central Register of Controlled Trials (from 1991) - Cochrane Database of Systematic Reviews (from 2005) - Ovid MEDLINE (from 1946) to June 2016 English Meta-analysis	- Populations in age group <40 years or with a prior CVD-related event - Not original study - Outcomes not all-cause mortality, coronary heart disease, stroke-related morbidity or mortality, or harms of treatment (including muscle injury, cognitive loss, incident diabetes, and hepatic injury) - No RCT, except large cohort and case-control studies of statin use vs. nonuse for diabetes incidence - Wrong study design for key question - Studies not on statin treatment adjusted to achieve target LDL-C levels vs. fixed-dose or other treatment strategies - Studies that not evaluated effects of statin therapy intensity on benefits and harm - Comparison is not placebo or no statin (except type of studies mentioned above) - Intervention not statin therapy (except type of studies mentioned above) - Abstract only	Adults 40 years and older without prior CVD events *Age* (*range of mean age)*: 51-66 y *Sex:* NR *Ethnicity*: NR *Risk group* - Presence of dyslipidemia: n=6 - Early cerebrovascular disease: n=3 - Diabetes: n=4 - Hypertension: n=2 - Mild to moderate aortic stenosis: n=1 - Microalbuminuria: n=1 - Elevated CRP level (≥20 mg/L): n=1 - At least 1 of a number of risk factors (elevated waist-to-hip ratio, dyslipidemia, dysglycemia, and mild renal dysfunction): n=1	Statins (lovastatin; atorvastatin; rosuvastatin; cerivastatin, switch to simvastatin; pravastatin; simvastatin; fluvastatin)	- Placebo - Standard lipid control with diet only	- n=19 RCTs - n=71,344 participants - Duration of follow-up ranged from 6 mo-6 y Included studies dated from 1994 to 2016 6 RCTs were of good quality, 11 of fair quality and 1 of poor quality (n=1 NR)
Naci, 2013[32]	To evaluate the effect of statins on major coronary events and all-cause mortality across all populations, in addition to secondary and primary prevention of CVD separately. To	- MEDLINE - EMBASE - Cochrane Database of Systematic Reviews - Cochrane Central Register of Controlled Trials (studies published between 1 January 1985 and 1 January 2011)	- No open-label and double-blind RCT - ≤50 participants per trial arm - Lasted ≤4 weeks - Did not report major coronary events or all-cause mortality - RCTs conducted in patients with renal insufficiency - Combination therapy - Not used in CVD	Adults without coronary heart disease at baseline Age (range of mean age): 55.1-67.1 y *Sex:* NR *Ethnicity*: NR *Risk group* NR	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	- Placebo - Usual care - Diet - Simvastatin - Pravastatin - Atorvastatin	- n=19 studies: n=12 double blinded, n=1 not blinded, n-4 open label, n=2 NR - n=67,927 participants Included studies dated from 1989 to 2008

	compare the effectiveness of different statins head-to-head in these patient populations taking into account dose differences across the included set of RCTs	All languages Network meta-analysis					Overall quality of included trials was rated as moderate

Abbreviations: CVD = cardiovascular disease, LDL-C = low density lipoprotein cholesterol, mo = months; NR = not reported, RCT = randomised controlled trial US = United States, y = years

Table III. Comparison of the results and conclusions of two excluded SRs (Chou et al. 2016 and Naci et al. 2013) with the two included SRs (Yebyo et al. 2019 and Taylor et al. 2013) to check if the review outcomes are in line

	Yebyo, 2019[26]	**Taylor, 2013**[2]	**Chou, 2016**[31]	**Naci, 2013**[32]
SR results	Statins as a class showed statistically significant risk reductions on (RR; 95% CI): - **Non-fatal MI** (0.62; 0.53-0.72) - **CVD mortality** (0.80; 0.71-0.91) - **All-cause mortality** (0.89; 0.85-0.93) - **Non-fatal stroke** (0.83; 0.75-0.92) - **Unstable angina** (0.75; 0.63-0.91) - **Composite major cardiovascular events** (0.74; 0.67-0.81) Statins increased statistically significantly relative risks of (RR; 95% CI): - **Myopathy** (1.08; 1.01-1.15) - **Renal dysfunction** (1.12; 1.00-1.26) - **Hepatic dysfunction** (1.16; 1.02-1.31)	Reduced by statins (RR; 95% CI): - **All-cause mortality** (OR 0.86; 0.79-0.94) - **Combined fatal and non-fatal CVD** (0.75; 0.70-0.81) - **Combined fatal and non-fatal CHD events** (0.73; 0.67-0.80) - **Combined fatal and non-fatal stroke** (0.78; 0.68-0.89) - **Revascularisation rates** (0.62; 0.54-0.72) - Total cholesterol and LDL cholesterol were reduced in all RCTs, but there was evidence of heterogeneity of effects - There was no evidence of any **serious harm** caused by statin prescription	Statin therapy was associated with decreased risk of (RR; 95% CI): - **All-cause mortality** (0.86; 0.80-0.93] - **Cardiovascular mortality** (0.69; 0.54-0.88) - **Stroke** (0.71; 0.62-0.82) - **Myocardial infarction** (0.64; 0.57-0.71) - **Composite cardiovascular outcomes** (0.70; 0.63-0.78) Statins were not associated with increased risk of (RR; 95% CI): - **Serious adverse events** (0.99; 0.94-1.04) - **Myalgias** (0.96; 0.79-1.16) - **Liver-related harms** (1.10; 0.90-1.35) - **Diabetes** (1.05; 0.91-1.20)	In primary prevention, statins significantly reduced (OR; 95% CI): - **Deaths** (0.91; 0.83-0.99) - **Major coronary events** (0.69; 0.61-0.79)
SR conclusion	All statins showed statistically significant risk reduction of CVD and all-cause mortality in primary prevention populations while increasing the risk for some harm risks	Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins	In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events	Statins significantly reduce the incidence of all-cause mortality and major coronary events as compared to control

Table IV. Excluded RCTs during full-text selection efficacy, effectiveness, and safety search

Reference	Reason for exclusion
Choi SH, Lim S, Hong ES, Seo JA, Park CY, Noh JH, et al. PROPIT: A PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with metabolic syndrome. Clinical endocrinology. 2015;82(5):670-7.	Non-western country
Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation. 2016;133(11):1073-80.	Article/outcomes already included in SR selected for the scoping & HTA report
Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. The Lancet. 2017;389(10088):2473-81.	Article/outcomes already included in SR selected for the scoping & HTA report
Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, et al. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. JAMA internal medicine. 2017;177(7):955-65.	Article/outcomes already included in SR selected for the scoping & HTA report
Huesch MD. Serious Adverse Events Among SPRINT Trial Participants Taking Statins at Baseline. Drugs in R&D. 2017;17(4):623-9.	No data on objectives
Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PloS one. 2013;8(9):e72642.	Study population not in line with PICO
Nishimura R, Sone H, Nakagami T, Tajima N. Importance of high-density lipoprotein cholesterol control during pravastatin treatment in hypercholesterolemic Japanese with type 2 diabetes mellitus: a post hoc analysis of MEGA study. Diabetes research and clinical practice. 2013;100(2):e31-3.	Post-hoc/subgroup analysis of RCT already included in SR selected for the scoping & HTA report
Ridker PM, Mora S, Rose L. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. European heart journal. 2016;37(17):1373-9.	Post-hoc/subgroup analysis of RCT already included in SR selected for the scoping & HTA report
Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. The New England journal of medicine. 2016;374(21):2021-31.	Article/outcomes already included in SR selected for the scoping & HTA report

Table V. Excluded non-randomised studies during full-text selection efficacy, effectiveness, and safety search

Reference	Reason for exclusion
Alperovitch A, Kurth T, Bertrand M, Ancelin ML, Helmer C, Debette S, et al. Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study. BMJ (Clinical research ed). 2015;350:h2335.	Treatment duration/follow-up does not fulfill the inclusion criteria
Asberg S, Eriksson M. Statin therapy and the risk of intracerebral haemorrhage: a nationwide observational study. International journal of stroke : official journal of the International Stroke Society. 2015;10 Suppl A100:46-9.	Treatment duration/follow-up does not fulfill the inclusion criteria
Ashrani AA, Barsoum MK, Crusan DJ, Petterson TM, Bailey KR, Heit JA. Is lipid lowering therapy an independent risk factor for venous thromboembolism? A population-based case-control study. Thrombosis research. 2015;135(6):1110-6.	Study comparison not in line with PICO
Baptista LC, Verissimo MT, Martins RA. Statin combined with exercise training is more effective to improve functional status in dyslipidemic older adults. Scandinavian journal of medicine & science in sports. 2018;28(12):2659-67.	Study population not in line with PICO
Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. Journal of the American College of Cardiology. 2016;68(3):252-60.	Treatment duration/follow-up does not fulfill the inclusion criteria
Bezin J, Moore N, Mansiaux Y, Steg PG, Pariente A. Real-Life Benefits of Statins for Cardiovascular Prevention in Elderly Subjects: A Population-Based Cohort Study. The American journal of medicine. 2019;132(6):740-	Treatment duration/follow-up does not fulfill the inclusion criteria

8.e7.	
Ble A, Hughes PM, Delgado J, Masoli JA, Bowman K, Zirk-Sadowski J, et al. Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12 156 Typical Older Patients: A Quasi-Experimental Study. The journals of gerontology Series A, Biological sciences and medical sciences. 2017;72(2):243-50.	Study population not in line with PICO
Daida H, Teramoto T, Kitagawa Y, Matsushita Y, Sugihara M. The relationship between low-density lipoprotein cholesterol levels and the incidence of cardiovascular disease in high-risk patients treated with pravastatin: main results of the APPROACH-J study. International heart journal. 2014;55(1):39-47.	Study design does not fulfill the inclusion criteria
Garcia-Gil M, Comas-Cufi M, Blanch J, Marti R, Ponjoan A, Alves-Cabratosa L, et al. Effectiveness of Statins as Primary Prevention in People With Different Cardiovascular Risk: A Population-Based Cohort Study. Clinical pharmacology and therapeutics. 2018;104(4):719-32.	Treatment duration/follow-up does not fulfill the inclusion criteria
Hayashi T, Kubota K, Kawashima S, Sone H, Watanabe H, Ohrui T, et al. Efficacy of HMG-CoA reductase inhibitors in the prevention of cerebrovascular attack in 1016 patients older than 75 years among 4014 type 2 diabetic individuals. International journal of cardiology. 2014;177(3):860-6.	Description of methods and results not clear
Hung RK, Al-Mallah MH, Qadi MA, Shaya GE, Blumenthal RS, Nasir K, et al. Cardiorespiratory fitness attenuates risk for major adverse cardiac events in hyperlipidemic men and women independent of statin therapy: The Henry Ford ExercIse Testing Project. American heart journal. 2015;170(2):390-9.	No data on objectives
Jones M, Tett S, Peeters GMEE, Mishra GD, Dobson A. New-Onset Diabetes After Statin Exposure in Elderly Women: The Australian Longitudinal Study on Women's Health. Drugs and Aging. 2017;34(3):203-9.	Study population not in line with PICO
Kim K, Lee CJ, Shim CY, Kim JS, Kim BK, Park S, et al. Statin and clinical outcomes of primary prevention in individuals aged >75years: The SCOPE-75 study. Atherosclerosis. 2019;284:31-6.	Non-Western country
Kokkinos P, Faselis C, Myers J, Kokkinos JP, Doumas M, Pittaras A, et al. Statin therapy, fitness, and mortality risk in middle-aged hypertensive male veterans. American journal of hypertension. 2014;27(3):422-30.	Study population not in line with PICO
Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet (London, England). 2013;381(9864):394-9.	Study population not in line with PICO
Lassila R, Jula A, Pitkaniemi J, Haukka J. The association of statin use with reduced incidence of venous thromboembolism: a population-based cohort study. BMJ open. 2014;4(11):e005862.	Treatment duration/follow-up does not fulfill the inclusion criteria
Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, et al. Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring. Journal of the American College of Cardiology. 2018;72(25):3233-42.	Treatment duration/follow-up does not fulfill the inclusion criteria
Orkaby AR, Gaziano JM, Djousse L, Driver JA. Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men. Journal of the American Geriatrics Society. 2017;65(11):2362-8.	Study population not in line with PICO
Porath A, Arbelle JE, Fund N, Cohen A, Mosseri M. Statin Therapy: Diabetes Mellitus Risk and Cardiovascular Benefit in Primary Prevention. The Israel Medical Association journal : IMAJ. 2018;20(8):480-5.	Non-Western country
Ribe AR, Vestergaard CH, Vestergaard M, Fenger-Gron M, Pedersen HS, Lietzen LW, et al. Statins and Risk of Intracerebral Haemorrhage in a Stroke-Free Population: A Nationwide Danish Propensity Score Matched Cohort Study. EClinicalMedicine. 2019;8:78-84.	Study population not in line with PICO
Tagalakis V, Eberg M, Kahn S, Azoulay L. Use of statins and reduced risk of recurrence of VTE in an older population. A population-based cohort study. Thrombosis and haemostasis. 2016;115(6):1220-8.	Study population not in line with PICO
Veronese G, Montomoli J, Schmidt M, Horvath-Puho E, Sorensen HT. Statin Use and Risk of Atrial Fibrillation or Flutter: A Population-based Case-Control Study. American journal of therapeutics. 2015;22(3):186-94.	No data on objectives
Yokomichi H, Nagai A, Hirata M, Tamakoshi A, Kiyohara Y, Kamatani Y, et al. Statin use and all-cause and cancer mortality: BioBank Japan cohort. Journal of epidemiology. 2017;27(3):S84-S91.	Study population not in line with PICO

15.4 Results of the included non-randomised studies on primary prevention in CVD

<table>
<tr><th>Reference</th><th>Mortality</th><th>CV events</th><th>Combined endpoints</th><th>Treatment-associated adverse events</th></tr>
<tr><td>Izzo, 2013[34]</td><td>-</td><td>-</td><td>-</td><td>Diabetes mellitus type 2
Unadjusted risk of incident diabetes at end of follow-up in relation of prescribed statin therapy before diagnosis of diabetes was not significantly different:
- Statins: 10.2%
- No statins: 8.7%
- RR = 1.02; 95% CI NR; p=0.192

In a Cox model, adjusted for gender, duration of hypertension, initial diastolic blood pressure, heart rate, plasma glucose, total & non-HDL cholesterol and triglycerides, statin prescription was confirmed to be not associated with incident diabetes mellitus</td></tr>
<tr><td>Ramos, 2018[33]</td><td>All-cause mortality<table><tr><th></th><th>No. of events</th><th>Incidence rate/1000 py (95%CI)</th><th>HR (95% CI)</th></tr><tr><td colspan="4">75-84 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>1109</td><td>32.6 (30.7-34.5)</td><td rowspan="2">0.98 (0.91-1.05)</td></tr><tr><td>No statins</td><td>7075</td><td>37.0 (36.1-37.8)</td></tr><tr><td colspan="4">≥85 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>471</td><td>116.2 (105.7-126.8)</td><td rowspan="2">1.00 (0.90-1.11)</td></tr><tr><td>No statins</td><td>4077</td><td>120.0 (116.3-123.7)</td></tr><tr><td colspan="4">75-84 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>503</td><td>41.5 (37.9-45.2)</td><td rowspan="2">0.84 (0.75-0.94)</td></tr><tr><td>No statins</td><td>1752</td><td>54.5 (52.0-57.1)</td></tr><tr><td colspan="4">≥85 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>140</td><td>134.6 (112.3-156.9)</td><td rowspan="2">1.05 (0.86-1.28)</td></tr><tr><td>No statins</td><td>696</td><td>137.0 (126.8-147.2)</td></tr></table></td><td>Atherosclerotic CVD<table><tr><th></th><th>No. of events</th><th>Incidence rate/1000 py (95%CI)</th><th>HR (95% CI)</th></tr><tr><td colspan="4">75-84 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>600</td><td>18.8 (17.3-20.3)</td><td rowspan="2">0.94 (0.86-1.04)</td></tr><tr><td>No statins</td><td>3229</td><td>17.8 (17.2-18.4)</td></tr><tr><td colspan="4">≥85 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>115</td><td>30.6 (25.0-36.2)</td><td rowspan="2">1.00 (0.80-1.24)</td></tr><tr><td>No statins</td><td>801</td><td>24.9 (23.2-26.2)</td></tr><tr><td colspan="4">75-84 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>271</td><td>24.0 (21.1-26.8)</td><td rowspan="2">0.76 (0.65-0.89)</td></tr><tr><td>No statins</td><td>865</td><td>29.2 (27.2-31.1)</td></tr><tr><td colspan="4">≥85 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>30</td><td>30.6 (19.6-41.5)</td><td rowspan="2">0.82 (0.53-1.26)</td></tr><tr><td>No statins</td><td>159</td><td>33.5 (28.2-38.7)</td></tr></table></td><td>Fatal and non-fatal stroke<table><tr><th></th><th>No. of events</th><th>Incidence rate/1000 py (95%CI)</th><th>HR (95% CI)</th></tr><tr><td colspan="4">75-84 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>364</td><td>11.1 (9.9-12.2)</td><td rowspan="2">0.94 (0.83-1.07)</td></tr><tr><td>No statins</td><td>2066</td><td>11.2 (10.7-11.6)</td></tr><tr><td colspan="4">≥85 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>83</td><td>21.7 (17.0-26.3)</td><td rowspan="2">1.10 (0.85-1.41)</td></tr><tr><td>No statins</td><td>581</td><td>17.8 (16.3-19.2)</td></tr><tr><td colspan="4">75-84 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>165</td><td>14.2 (12.0-16.4)</td><td rowspan="2">0.81 (0.66-0.99)</td></tr><tr><td>No statins</td><td>525</td><td>17.1 (15.6-18.5)</td></tr><tr><td colspan="4">≥85 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>16</td><td>15.8 (8.1-23.6)</td><td rowspan="2">0.66 (0.37-1.17)</td></tr><tr><td>No statins</td><td>107</td><td>22.1 (17.9-26.3)</td></tr></table></td><td>Cancer<table><tr><th></th><th>No. of events</th><th>Incidence rate/1000 py (95%CI)</th><th>HR (95% CI)</th></tr><tr><td colspan="4">75-84 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>730</td><td>27.1 (25.2-29.1)</td><td rowspan="2">1.02 (0.93-1.11)</td></tr><tr><td>No statins</td><td>4125</td><td>27.3 (26.5-28.2)</td></tr><tr><td colspan="4">≥85 y without type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>87</td><td>28.6 (22.6-34.6)</td><td rowspan="2">0.92 (0.72-1.17)</td></tr><tr><td>No statins</td><td>734</td><td>28.5 (26.4- 30.6)</td></tr><tr><td colspan="4">75-84 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>258</td><td>26.7 (23.4-30.0)</td><td rowspan="2">0.93 (0.79-1.10)</td></tr><tr><td>No statins</td><td>733</td><td>29.3 (27.2- 31.4)</td></tr><tr><td colspan="4">≥85 y with type 2 diabetes mellitus</td></tr><tr><td>Statins</td><td>17</td><td>21.3 (11.2-31.4)</td><td rowspan="2">0.64 (0.37-1.10)</td></tr><tr><td>No statins</td><td>117</td><td>31.0 (25.4-36.7)</td></tr></table></td></tr>
</table>

Coronary heart disease (fatal and nonfatal angina, fatal and non-fatal MI, or cardiac revascularisation)

	No. of events	Incidence rate/1000 py (95%CI)	HR (95% CI)
75-84 y without type 2 diabetes mellitus			
Statins	270	8.2 (7.2-9.1)	0.94 (0.81-1.09)
No statins	1328	7.1 (6.7-7.5)	
≥85 y without type 2 diabetes mellitus			
Statins	38	9.6 (6.5-12.6)	0.84 (0.58-1.24)
No statins	254	7.6 (6.7-8.5)	
75-84 y with type 2 diabetes mellitus			
Statins	125	10.6 (8.7-12.5)	0.75 (0.60-0.94)
No statins	385	12.4 (11.2-13.7)	
≥85 y with type 2 diabetes mellitus			
Statins	14	13.9 (6.6-21.1)	1.15 (0.58-2.28)
No statins	57	11.5 (8.5-14.6)	

Diabetes mellitus type 2

	No. of events	Incidence rate/1000 py (95%CI)	HR (95% CI)
75-84 y without type 2 diabetes mellitus			
Statins	430	15.8 (14.3-17.3)	1.02 (0.90-1.15)
No statins	2133	13.8 (13.2-14.4)	
≥85 y without type 2 diabetes mellitus			
Statins	41	13.1 (9.1-17.1)	0.87 (0.60-1.26)
No statins	336	12.6 (11.3-14.0)	

Haemorrhagic stroke

	No. of events	Incidence rate/1000 py (95%CI)	HR (95% CI)
75-84 y without type 2 diabetes mellitus			
Statins	98	3.4 (2.7-4.0)	0.89 (0.70-1.13)
No statins	639	3.9 (3.6-4.2)	
≥85 y without type 2 diabetes mellitus			
Statins	19	5.8 (3.2- 8.4)	1.13 (0.67-1.92)
No statins	145	5.3 (4.4-6.1)	
75-84 y with type 2 diabetes mellitus			
Statins	49	4.8 (3.4-6.1)	0.96 (0.67-1.38)
No statins	157	5.8 (4.9-6.7)	
≥85 y with type 2 diabetes mellitus			
Statins	6	7.3 (1.4-12.8)	1.96 (0.67-5.75)
No statins	18	4.4 (2.4-6.5)	

Hepatotoxicity

	No. of events	Incidence rate/1000 py (95%CI)	HR (95% CI)
75-84 y without type 2 diabetes mellitus			
Statins	2	0.4 (−0.2 - 1.0)	1.01 (0.20-

No statins	13	0.5 (0.2-0.7)	4.99)	
≥85 y without type 2 diabetes mellitus				
Statins	0	-	-	
No statins	0	-		
75-84 y with type 2 diabetes mellitus				
Statins	3	0.6 (−0.1 - 1.3)	-	
No statins	1	0.2 (−0.2 - 0.6)		
≥85 y with type 2 diabetes mellitus				
Statins	0	-	-	
No statins	0	-		

Myopathy

	No. of events	**Incidence rate/1000 py (95%CI)**	**HR (95% CI)**
75-84 y without type 2 diabetes mellitus			
Statins	0	-	-
No statins	12	0.5 (0.2-0.7)	
≥85 y without type 2 diabetes mellitus			
Statins	0	-	-
No statins	7	1.1 (0.3-2.0)	
75-84 y with type 2 diabetes mellitus			
Statins	0	-	-
No statins	1	0.2 (−0.2 - 0.6)	
≥85 y with type 2 diabetes mellitus			
Statins	0	-	-
No statins	1	1.0 (−0.98 - 3.0)	

Keys: CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, RR = risk ratio

15.5 Search terms legal search (other HTA domains)

PubMed	Legal issues
CVD	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])
Legal issues	((((legal*[Title/Abstract]) OR law*[Title/Abstract] OR legisl*[Title/Abstract]) OR (Search "Legislation" [Publication Type] OR "Licensure"[Mesh] OR "Liability, Legal"[Mesh] OR "Legal Case" [Publication Type] OR "legislation and jurisprudence" [Subheading] OR "International Law"[Mesh])))
Hits	63 (no publication period limits) 39 (01-01-2009 – 12-02-2020)

EMBASE	Legal issues
CVD	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh]

	OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])
Legal issues	(legal*:ti,ab OR law*:ti,ab OR legisl*:ti,ab OR 'licensing'/exp OR 'legal liability'/exp OR 'legislation and jurisprudence'/exp OR 'international law'/exp)
Hits	231 (no publication period limits) 153 (01-01-2009 – 12-02-2020)

15.6 Search terms social and ethical search (other HTA domains)

PubMed	Social and ethical issues
CVD	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])
Social and ethical issues	("Ethics"[Mesh] OR "Healthcare Disparities"[Mesh] OR health-care-delivery[majr] OR health-care-access[majr] OR (“social value*”[tiab] OR “ethnic value*”[tiab] OR “personal value*”[tiab]) OR (harm[tiab] OR “benefit-harm”[tiab] OR “harm-benefit”[tiab]) OR (rawls[tiab] OR rawlsian[tiab] OR utilitarian*[tiab] OR “patient choice”[tiab] OR “patient decision making”[tiab] OR “conflicting interests”[tiab] OR equity[tiab] OR peril[tiab] OR stigma[tiab] OR stigmatiz*[tiab] OR stigmatis*[tiab]) OR (“societal value*”[tiab] OR “value of society”[tiab] OR fraud[tiab] OR falsified[tiab]))
Hits	1,467 (no publication period limits) 1,091 (01-01-2009 – 20-02-2020)

EMBASE	Social and ethical issues
CVD	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab]

	OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])
Social and ethical issues	(ethics/de OR 'medical ethics'/de OR health-care-disparity/exp OR health-care-delivery/mj or health-care-access/mj OR (social-value* OR ethnic-value* OR personal-value*):ti,ab,kw OR (harm OR benefit-harm OR harm-benefit):ti,ab,kw OR (rawls OR rawlsian OR utilitarian* OR patient-choice OR patient-decision-making OR peril OR conflicting-interests OR equity OR stigma OR stigmatiz* OR stigmatis*):ti,ab,kw OR (societal-value* OR value*-of-society OR fraud OR falsified):ti,ab,kw)
Hits	573 (no publication period limits) 445 (01-01-2009 – 20-02-2020)

15.7 Swiss costing studies search methods and results

To identify the most recent Swiss cost data available to use as input in the cost-effectiveness model, a comprehensive search for resource use and costs data of primary prevention of cardiovascular events using statins or treatment of cardiovascular events in Switzerland was performed. This Appendix provides more information on the methods and the results of this search. The tables below show the search strings that were utilised to conduct the systematic search.

Table 15.7.1. Search string costing studies PubMed

PubMed (MEDLINE)	Costing studies
CVD	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Costing studies	((economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “eco-nomic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”) OR (“healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance) OR ((cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)) OR (economic* OR pharmacoeconomic* OR price* OR pricing) OR ((healthcare OR “health care”) AND (utilization OR utilisation)) OR (cost* AND (treat* OR therap*)) OR ((direct OR indirect) AND cost*) OR (“resource use” OR “resource utilization" OR “resource utilisation”) OR (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”))
Country	Switzerland[tiab] OR Swiss[tiab]
Period	01-01-2009 – 17-02-2020
Hits	387

Table 15.7.2. Search string costing studies Embase

EMBASE.com	Costing studies
CVD	('cardiovascular disease'/exp OR CVD:ti,ab OR CVDs:ti,ab OR stroke*:ti,ab OR coronary*:ti,ab OR heart*:ti,ab OR cardio*:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR angina*:ti,ab OR hypertensi*:ti,ab OR 'hyperlipidemia'/exp OR hyperlip*:ti,ab OR triglycerid*:ti,ab OR hypertriglycerid*:ti,ab OR hyperlipoprotein*:ti,ab OR 'cholesterol'/exp OR hypercholesterol*:ti,ab OR cholesterol*:ti,ab OR HDL:ti,ab OR LDL:ti,ab)
Costing studies	Economics/exp OR Cost/exp OR 'Health Economics'/exp OR Budget/exp OR budget*:ab,ti OR (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed):ab,ti OR (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed):ab,ti OR (cost* adj2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)):ab,ti OR (value adj2 (money OR monetary)):ab,ti
Country	Switzerland:ab,ti OR Swiss:ab,ti
Period	01-01-2009 – 17-02-2020
Hits	708

Results

The selection of studies is illustrated in 15.7.1. The references and decisions of the 37 studies that were included in the full-text screening are reported in Table 15.7.5. Data on costs was extracted from 12 studies (Table 15.7.3). Five studies were not chosen as a source for cost data in the model because they provided no information about any relevant unit cost.[174–178] Three other studies were excluded because the costs were only reported for a certain subgroup of patients that were not representative for the total population.[179–181] The remaining four studies are discussed in more detail below.

Figure 15.7.1. PRISMA flowchart studies on healthcare costs

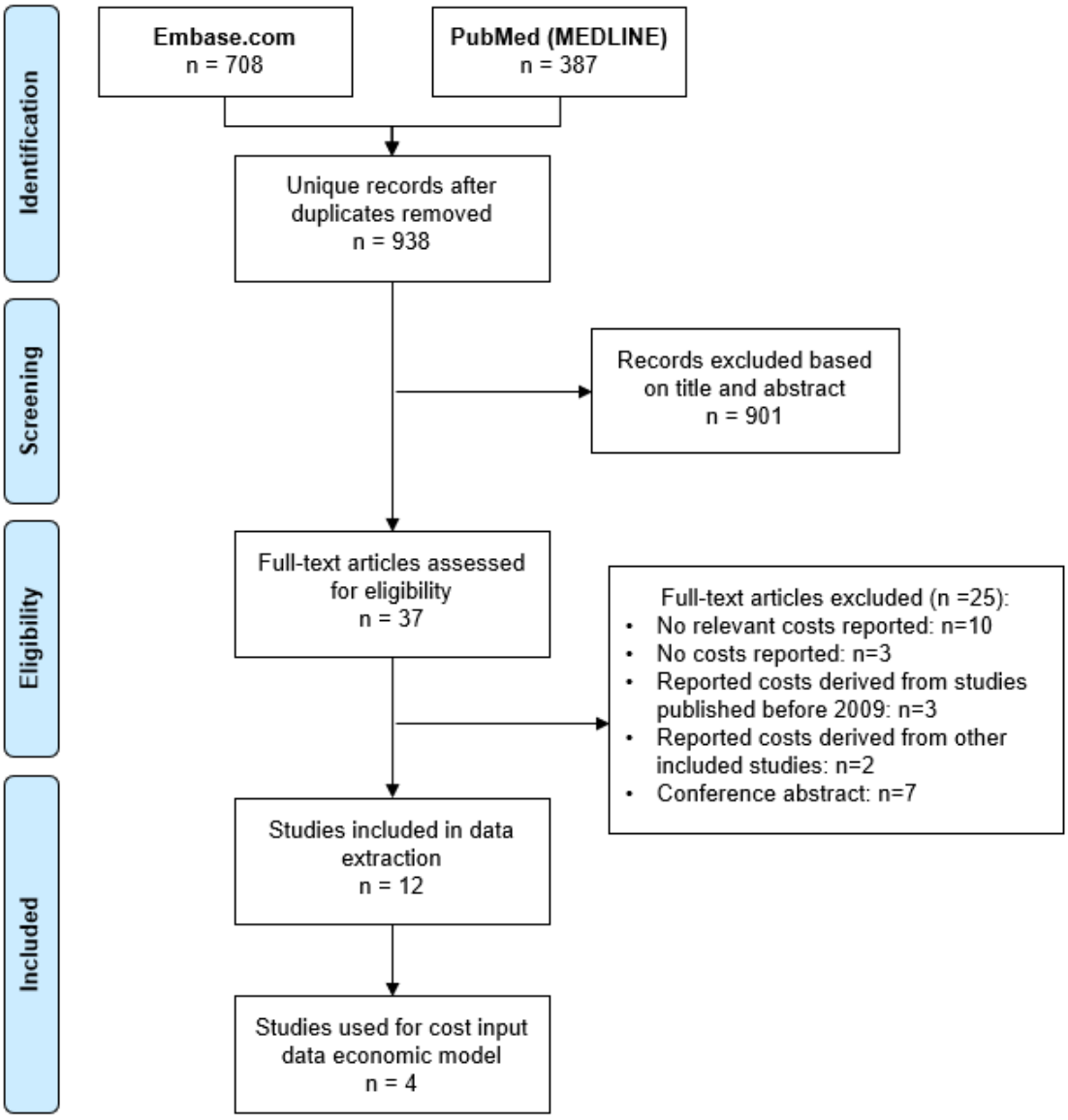


Table 15.7.3. Data extraction costs (in CHF).

Author – publication year	Type of study	Patient population	Source costs	N	Mean age	Male %	Cost estimates								
							Prevention	Non-fatal stroke			Fatal stroke	Non-fatal MI			Fatal MI
								Treatment	Year 1	Year 2+		Treatment	Year 1	Year 2+	
Ademi 2017[175]	CEA	Chronic heart failure with reduced ejection fraction	DRG	NA	64	NA		13,536				9,276			
Akerborg 2012[1]	CEA	Atrial fibrillation	DRG and disabled and elderly long-term care	NA	72	NA		10,437	18,076	8,333					
Ambavane. 2017[174]	CEA	Acute MI visiting emergency department	DRG and other publicly available costs	NA	NR	NA						14,497			
Fladt 2019[178]	Cohort study	Non-disabling acute ischaemic stroke	Stroke Center of university hospital	442	Median: 72	67		11,238							

Gasche 2013[89]	CEA	Acute coronary syndrome	Cost survey from the Winterthur Institute of Health Economics	NA	62	72			19,693	11,885			16,807	1,722	
Ito 2011[182]	Cost analysis	Statins for CVD prevention	Assumptions and local hospital costs	NA	Range: 35-75	NA	971					18,354	25,278	1,933	
Muehlemann 2019[176]	Cost analysis	Stroke with or without dysphagia	Hospital discharge databases	6,037	<65: 29% 65-85: 53% >85: 19%	55		6,120							
Nilsson 2013[181]	CEA	Atrial fibrillation	DRG	NA	72	53		10,437	18,076	8,333					
Pletscher 2013[90]	CEA	Atrial fibrillation	Swiss Medical Statistics of Hospitals (MedStat), list of laboratory analyses, the TARMED medical tarif, and the list	NA	71/69	63/65		24,802	37,796	17,326	9,799		26,184		7,207

			of medical specialties, and published studies.												
Snozzi 2014[179]	Cost of illness study	Stroke	Hospital Statistics and Statistics of Sociomedical Institutions 2003	509	70	55		46,286	65,445						
Wein 2017[177]	CEA	Acute coronary syndrome	DRG	1,997	62	77						10,818			
Wieser 2012[183]	Cost of illness study	Patients with acute coronary syndrome	Swiss Federal Office of Statistics, Swiss health insurer association, and a German expert survey adapted to the Swiss standard by expert interviews	19,046	68	67							29,668		

CEA = cost-effectiveness analysis.

The stated health state costs were converted to CHF when necessary using exchange rates from the OECD website and adjusted for inflation to 2019 prices using inflation rates from the Swiss Federal Statistical Office accessed from the OECD website.

Cardiovascular risk scoring system used and cardiovascular risk and risk group were not reported in any of the studies.

Prevention costs

The costs of prevention of CVD using statins in Ito et al. (2011) were composed of daily costs of drug treatment, medical visits, and biological measurements (either total cholesterol only or an 'optimal' set of tests including total and high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and creatinine).[182] However, these costs were not used in the model because more recent unit costs for the primary prevention elements were available from SASIS AG Tariffpool[88] and TARMED[24].

CVD event costs: MI and stroke

Gasche et al. (2013) reported costs for the first year after non-fatal MI, costs in subsequent years after non-fatal MI, costs for the first year after non-fatal stroke, and costs in subsequent years after non-fatal stroke in patients with acute coronary syndrome in Switzerland.[89] These costs are derived from a previous study from the Winterthur Institute of Health Economics who used different sources to estimate the costs of stroke and MI (e.g. literature analysis, interviews with stakeholders from health care providers and health insurers, and patient databases). Their cost estimates included all follow-up costs of an event in the first year and in each subsequent year, respectively.[89] The follow-up costs included inpatient and outpatient costs for acute care and rehabilitation. The cost estimates reported in Gasche et al. were directly applicable to the MI, post-MI, stroke, and post-stroke health states in our model. Ito et al. also reported costs on MI treatment for the first and subsequent years after MI.[89] However, these estimates were not used in the base-case because it was preferred to derive the costs of MI and stroke from the same source for consistency reasons. Both Pletscher et al.[90] and Wieser et al.[183] also reported costs on MI treatment in the first year but did not report follow-up costs in subsequent years. Therefore Gasche et al. was preferred as the source for MI costs in the base-case analyses.

Pletscher et al. also reported costs on strokes and MI[90], but these were not selected for input in the economic model for the following reasons. Costs for stroke were separately reported for patients who were independent, moderately dependent, and totally dependent after stroke without reporting the distribution of patients over these categories. Therefore, it was not possible to calculate a weighted average for treatment of stroke for all patients. The follow-up costs after stroke reported by Pletscher et al. represent the average resources an 80-year old person uses over its average remaining lifetime and was

[24] https://www.tarmed-browser.ch/de

therefore not representative for younger persons. Finally, the follow-up costs in subsequent years after MI were not reported in Pletscher et al.

Ito et al. also reported costs on MI treatment[182], however, these costs were derived from costing studies published before 2009 and are therefore not preferred over the other, more recent, cost estimates identified in the literature search.

Adverse event costs

None of the included studies in the healthcare costs search reported costs of any of the four adverse events included (i.e. myopathy, rhabdomyolysis, renal dysfunction, and hepatic dysfunction).

However, seven of the cost-effectiveness studies that were previously identified in the systematic literature search in the scoping phase of this project included costs of adverse events. Five of the seven studies that report adverse events costs were performed in the US, however considering the large differences in healthcare system between the US and Switzerland, these costs were not considered representative for Switzerland.[98,103,105–107] In Conly et al.[111] the costs of rhabdomyolysis in Canada ($78,740) was based on a study with only two case studies. De Vries et al.[92] assumed that treatment of myopathy included two general practitioner (GP) visits (€59.50). In our model, the same assumption was applied using Swiss unit costs for GP visits in our cost-effectiveness analysis. De Vries et al. base the costs of treatment of rhabdomyolysis (€11,126) on a US cost study.[93] Since we could not find any non-US estimates for the treatment of rhabdomyolysis, this source was used for rhabdomyolysis costs. No cost estimates for renal and hepatic dysfunction were identified in the cost-effectiveness studies.

Costs of (CVD) death

Pletscher et al. reported the healthcare costs of several fatal CVD events, including stroke (CHF 9,799) and MI (CHF 7,207). [90] A weighted average of these healthcare costs based on the proportion of MI and stroke observed in placebo arms of trials on statins was used as a proxy for healthcare costs of all CVD deaths (CHF 8,511).

The included studies did not report recent estimates of costs of all-cause mortality. Brändle et al.,[91] that was excluded because the cost estimates reported were derived from studies published before 2009, was the only study that reported costs of all-cause mortality and assumed the same healthcare costs for CVD deaths (CHF 4,191). These costs were derived from a study based on a cost-effectiveness model for diabetes management.[184]

Eight of the cost-effectiveness studies that were identified in the systematic literature search in the scoping phase included costs of fatal events or death. Three studies only reported costs of fatal MI or

stroke.[105,106,116] Three of the five studies that report costs of (CVD) death are performed in the US and considering the large differences in healthcare system with Switzerland, these costs were not considered representative for Switzerland.[35-37] In the other two studies, the costs of death was based on expert opinion reported in a study published in 1995 and was therefore also not considered a reliable source.[92,104]

Therefore, the costs of Brändle et al.[91] were considered the most relevant cost estimate for input in our economic model.

Table 15.7.4. Costs used in the base-case or scenario analyses of the economic model (in CHF).

	Base-case	Scenario analyses
Primary/secondary prevention with statins	971[182]	
Non-fatal MI 1st year	16,923[89]	25,278[182] 26,249[90] 29,038[183]
Non-fatal stroke 1st year	19,828[89]	
Non-fatal MI subsequent years	1,734[89]	1,933[182]
Non-fatal stroke subsequent years	11,967[89]	
Myopathy	2 GP visits (at 127.06 per visit; data from FOPH)	
Rhabdomyolysis	9,236[93]	
Hepatic dysfunction	No cost estimates identified yet	
Renal dysfunction	No cost estimates identified yet	
CVD death	8,511[90]	
Other death	4,191[91]	

Note: The stated health state costs were converted to CHF when necessary using exchange rates from the OECD website and adjusted for inflation to 2019 prices using inflation rates from the Swiss Federal Statistical Office accessed from the OECD website.

Table 15.7.5. References and decisions of studies included in full-text screening of healthcare costs systematic literature search

Reference	Decision
Ademi Z, Hancock E, Trueman D, Pfeil A, Haroun R, Deschaseaux C, et al. Cost-effectiveness of sacubitril/valsartan (formerly LCZ696) in chronic heart failure patients with reduced ejection fraction-an analysis for Switzerland. Value Health. 2016;19(7):A655.	Conference abstract
Ademi Z, Pfeil AM, Hancock E, Trueman D, Haroun RH, Deschaseaux C, et al. Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss medical weekly. 2017;147:w14533.	Included in data extraction, but only reported hospitalization costs and no follow-up costs after stroke.
Agnelli, G., Gitt A.K., Bauersachs R., Fronk E.-M., Laeis P., Mismetti P., Monreal M. et al. The management of acute venous thromboembolism in clinical practice - study rationale and protocol of the European PREFER in VTE Registry. Thromb J. 2015;13(1).	No costs reported
Åkerborg Ö, Nilsson J, Bascle S, Lindgren P, Reynolds M. Cost-effectiveness of dronedarone in atrial fibrillation: results for Canada, Italy, Sweden, and Switzerland2012 2012-Aug. 1788-802 p.	Included in data extraction, but post-stroke healthcare costs only based on patients who receive disabled or elderly long-term care.
Ambavane A, Lindahl B, Giannitsis E, Roiz J, Mendivil J, Frankenstein L, et al. Economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department. PloS one. 2017;12(11):e0187662.	Included in data extraction, but only reported hospitalization costs and no follow-up costs after MI.
Blum MR, Øien H, Carmichael HL, Heidenreich P, Owens DK, Goldhaber-Fiebert JD. Cost-Effectiveness of Transitional Care Services After Hospitalization With Heart Failure. Annals of internal medicine. 2020.	No relevant costs reported
Boltyenkov AT, Navarro F, Hren R. Health economics analysis of	Conference abstract

point-of-care HbA1c monitoring in Belgian, German, and Swiss patients with diabetes mellitus type 2. Diabetes. 2018;67:A334.	
Brändle M, Erny-Albrecht KM, Goodall G, Spinas GA, Streit P, Valentine WJ. Exenatide versus insulin glargine: a cost-effectiveness evaluation in patients with Type 2 diabetes in Switzerland. Int J Clin Pharmacol Ther. 2009;47(8):501-15.	No full text available
Brändle M, Goodall G, Erny-Albrecht KM, Erdmann E, Valentine WJ. Cost-effectiveness of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease in a Swiss setting. Swiss medical weekly. 2009;139(11):173-84.	Reported costs derived from studies published before 2009.
Brüngger B, Blozik E. Hospital readmission risk prediction based on claims data available at admission: a pilot study in Switzerland. BMJ open. 2019;9(6):e028409.	No costs reported
Desmaele S, Putman K, De Wit L, Dejaeger E, Gantenbein AR, Schupp W, et al. A comparative study of medication use after stroke in four countries2016 2016-Sep. 96-104 p.	No costs reported
Eichler K, Krass A, Fendl A, Thüring N, Brügger U. Integrated care for patients with heart failure in Switzerland: A cost analysis. Vernetzte betreuung bei patienten mit herzinsuffizienz in der Schweiz: Eine kostenstudie. 2009;98(15):809-15.	No full text available
Fladt J, Hofmann L, Coslovsky M, Imhof A, Seiffge DJ, Polymeris A, et al. Fast-track versus long-term hospitalizations for patients with non-disabling acute ischaemic stroke2019 2019-01. 51-e4 p.	Included in data extraction, but only reported hospitalization costs and no follow-up costs after stroke.
Gasche D, Ulle T, Meier B, Greiner R-A. Cost-effectiveness of ticagrelor and generic clopidogrel in patients with acute coronary syndrome in Switzerland2013 2013. w13851 p.	Used as source for costs for MI, stroke, post-MI, and post-stroke in the economic model.
Gerlier L, Sidelnikov E, Kutikova L, Lamotte M, Annemans L. Rationale and design of a multi-center survey to evaluate productivity losses and indirect costs after cardiovascular events in Europe. Value Health. 2016;19(7):A396-A7.	Conference abstract

Huber CA, Diem P, Schwenkglenks M, Rapold R, Reich O. Estimating the prevalence of comorbid conditions and their effect on health care costs in patients with diabetes mellitus in Switzerland. Diabetes, metabolic syndrome and obesity : targets and therapy. 2014;7:455-65.	No relevant costs reported
Ito MK, Nanchen D, Rodondi N, Paccaud F, Waeber G, Vollenweider P, et al. Statins for cardiovascular prevention according to different strategies: a cost analysis. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2011;11(1):33-44.	Reported prevention costs but not used in the model because more recent data was available.
Moschetti K, Petersen SE, Pilz G, Kwong RY, Wasserfallen J-B, Lombardi M, et al. Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the european cardiovascular magnetic resonance registry2016 2016-Jan-11. 3 p.	No relevant costs reported
Muehlemann N, Jouaneton B, de Léotoing L, Chalé J-J, Fern, es J, et al. Hospital costs impact of post ischemic stroke dysphagia: Database analyses of hospital discharges in France and Switzerland. PloS one. 2019;14(1):e0210313.	Included in data extraction, but only reported hospitalization costs and no follow-up costs after stroke.
Navarro F, Hren R, Boltyenkov A. Budget impact analysis (BIA) of point-of-care of hba1c monitoring in Belgian, German and Swiss patients with diabetes mellitus type II. Value Health. 2018;21:S164.	Conference abstract
Navarro F, Hren R, Boltyenkov A. The importance of health economics modeling in assessing costs of point-of-care HbA1c monitoring of patients with diabetes mellitus type II in high-income countries. Clin Chim Acta. 2019;493:S292.	Conference abstract
Nicholson G, Paoli CJ, Ra SR. Systematic litertaure review of direct health care costs for cardiovascular events among European patients with dyslipidemia or high cardiovascular risk. Value Health. 2015;18(7):A387.	Conference abstract

Nilsson J, Åkerborg O, Bégo-Le Bagousse G, Rosenquist M, Lindgren P. Cost-effectiveness analysis of dronedarone versus other anti-arrhythmic drugs for the treatment of atrial fibrillation - Results for Canada, Italy, Sweden and Switzerland. Eur J Health Econ. 2013;14(3):481-93.	Included in data extraction, but post-stroke healthcare costs only based on patients who receive disabled or elderly long-term care.
Panczak R, Luta X, Maessen M, Stuck AE, Berlin C, Schmidlin K, et al. Regional variation of cost of care in the last 12 months of life in Switzerland: Small-area analysis using insurance claims data. Med Care. 2017;55(2):155-63.	No relevant costs reported
Pavlovic N, Sticherlinga C, Kühne M. Atrial fibrillation - European and Swiss perspectives: Reflections on epidemiology, costs and treatment options: An article from the series "atrial fibrillation - update 2014". Kardiovaskulare Med. 2014;17(6):167-70.	No relevant costs reported
Pletscher M, Plessow R, Eichler K, Wieser S. Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in Switzerland2013 2013. w13732 p.	Used as source for costs for fatal MI and fatal stroke in the economic model.
Romanens M, Ackermann F, Szucs T, Sudano I, Adams A. Medical costs per QALY of statins using the Swiss Medical Board (SMB) assumptions: Observed effects in two large primary prevention cohorts from Germany and Switzerland. Praxis. 2015;104:38-9.	Reported costs derived from other included studies (i.e. Pletscher et al. 2013)
Romanens M, Adams A, Warmuth W. Value-based PCSK9-inhibitor prices derived from fixed QALY-based and individual LDL based models. Kardiovaskulare Med. 2019;22(3).	No relevant costs reported
Romanens M, Sudano I, Szucs T, Adams A. Medical costs per QALY of statins based on Swiss Medical Board assumptions. Kardiovaskulare Med. 2017;20(4):96-100.	Reported costs derived from other included studies (i.e. Pletscher et al. 2013)
Ruch R, Stoessel L, Stein P, Ganter MT, Button DA. Outcome, quality of life and direct costs after out-of-hospital cardiac arrest in an urban region of Switzerland. Scandinavian journal of trauma, resuscitation and emergency medicine. 2019;27(1):106.	No relevant costs reported

Schäfer HH, Scheunert U. Costs of current antihypertensive therapy in Switzerland: an economic evaluation of 3,489 patients in primary care. Swiss medical weekly. 2013;143:w13854.	No relevant costs reported
Snozzi P, Blank PR, Szucs TD. Stroke in Switzerland: social determinants of treatment access and cost of illness2014 2014-May. 926-32 p.	Included in data extraction, but costs after stroke only reported for patients with initial inpatient treatment, while 14% received outpatient treatment. In addition, no follow-up costs in subsequent years reported.
Szucs T.D., Waeber B., Tomonaga Y. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: An analysis of the HYVET study from a Swiss perspective. J Hum Hypertens. 2010;24(2):117-23.	Reported costs derived from studies published before 2009.
Wein B, Coslovsky M, Jabbari R, Galatius S, Pfisterer M, Kaiser C. Prasugrel vs. clopidogrel in contemporary Western European patients with acute coronary syndromes receiving drug-eluting stents: Comparative cost-effectiveness analysis from the BASKET-PROVE cohorts2017 2017-Dec-01. 20-7 p.	Included in data extraction, but only reported hospitalization costs and no follow-up costs after MI.
Wieser S, Riguzzi M, Pletscher M, Huber CA, Telser H, Schwenkglenks M. How much does the treatment of each major disease cost? A decomposition of Swiss National Health Accounts. Eur J Health Econ. 2018;19(8):1149-61.	No relevant costs reported
Wieser S, Rüthemann I, De Boni S, Eichler K, Pletscher M, Radovanovic D, et al. Cost of acute coronary syndrome in Switzerland in 2008. Swiss medical weekly. 2012;142:w13655.	Only reported costs for first year after MI.
Witassek F, Conen D, Osswald S, Moschovitis G, Meyre P, Brüngger B, et al. Inpatient costs of atrial fibrillation and related comorbidities. Kardiovaskulare Med. 2018;21(5):123.	No full text available

15.8 Swiss health-related quality of life studies search methods and results

To identify the most recent Swiss utility data available to use as input in the cost-effectiveness model, a comprehensive search for baseline utilities for patients without cardiovascular events, disutilties associated with CVD events, disutilties for long-term post-CVD events, disutilities associated with adverse events, and disutility of statin use (i.e. 'taking a pill every day') in Swiss patients was performed. The search terms are provided in Table 15.8.1 and 15.8.2. A search filter for utilities was added to the clinical search strings regarding cardiovascular disease. In line with the systematic literature search for costs and resource use, the search strings regarding statins were not added in this search because studies reporting utilities after cardiovascular events in patients who are not using statins could also be relevant. The search filter for utilities were based on the search string that was developed by CADTH to identify studies on the health utilities and/or quality of life of patients in Medline and Embase.[25] Once again, we omitted search terms that were already included in the preliminary search for cost-effectiveness analyses to avoid overlapping studies.

Table. 15.8.1.Search terms HRQoL PubMed

PubMed (MEDLINE)	HRQoL studies
CVD	"cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab]
HRQoL/Utilities	"Quality of Life"[Mesh] OR "Value of Life"[tiab] OR "Quality of Life"[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR eq5d[tiab] OR "eq 5d"[tiab]
Country	Switzerland[tiab] OR Swiss[tiab]
Period	01-01-2009 – 17-02-2020
Hits	97

[25] https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco

Table 15.8.2. Search terms HRQoL Embase

EMBASE.com	HRQoL studies
CVD	('cardiovascular disease'/exp OR CVD:ti,ab OR CVDs:ti,ab OR stroke*:ti,ab OR coronary*:ti,ab OR heart*:ti,ab OR cardio*:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR angina*:ti,ab OR hypertensi*:ti,ab OR 'hyperlipidemia'/exp OR hyperlip*:ti,ab OR triglycerid*:ti,ab OR hypertriglycerid*:ti,ab OR hyperlipoprotein*:ti,ab OR 'cholesterol'/exp OR hypercholesterol*:ti,ab OR cholesterol*:ti,ab OR HDL:ti,ab OR LDL:ti,ab)
HRQoL/Utilities	'quality of life'/exp OR 'Value of Life':ab,ti OR 'Quality of Life':ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR eq5d/exp OR eq5d:ab,ti OR 'eq 5d':ab,ti
Country	Switzerland:ab,ti OR Swiss:ab,ti
Period	01-01-2009 – 17-02-2020
Hits	446

Results

The selection of studies is illustrated in Figure . The references and decisions of the 13 studies that were included in the full-text screening are reported in Table 15.8.6. None of the included for full text screening report any information on utilities for the relevant health states as defined by our model structure. However, one study[89] mentioned that the utilities used in their economic model were based on the PLATO study and referred to the study by Nikolic et al. 2013.[95] Nikolic et al. use the exact same health states as our model. This study also reported utility values for the general population and utility decrements for all the health states. The utilities and utility decrements from Nikolic et al. are displayed in Table 15.8.3.[95]

Figure 15.8.1. PRISMA flowchart costs on health-related quality of life

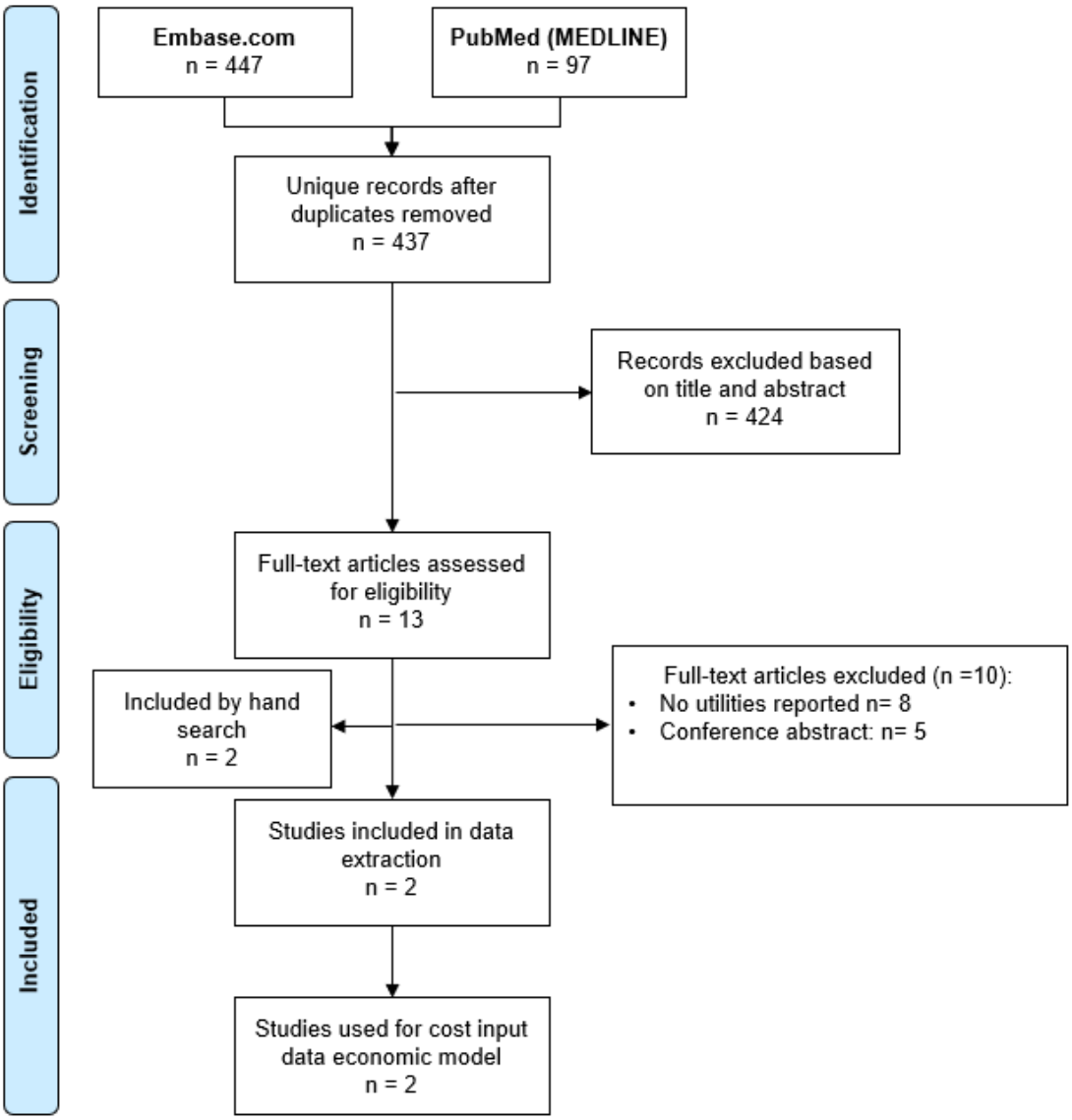


Table 15.8.3. Utility values based on PLATO study (Nikolic et al. 2013)[95]

	Utility value or decrement
General population	0.81
Stroke	-0.063
MI	-0.138
Post Stroke	-0.063
Post MI	-0.138

In a pragmatic literature search, one study was found that reported age and sex specific data on general population utility values for Switzerland.[94] Perneger et al. conducted a mail survey in French-speaking Switzerland which included the EQ-5D instrument and descriptive variables. A response rate of 52.1% was achieved, totaling 1,956 Swiss adults.

Table 15.8.4. Swiss General population utilities (EQ-5D)[94] 15.8.4 shows the results of the study.

Table 15.8.4. Swiss General population utilities (EQ-5D)[94]

	Women	**Men**
18-29	0.86	0.90
30-39	0.86	0.87
40-49	0.84	0.85
50-59	0.81	0.83
60-69	0.80	0.83
70-79	0.76	0.80
80 and over	0.74	0.76

No data on utility decrements for the adverse events included in the model were found in the systematic literature search.

Table 15.8.5. Data extraction health-related quality of life studies

Author – publi-cation year	**Type of study**	**Patient population**	**N**	**Age range**	**Male %**
Nikolic 2013[95]	CEA	Acute coronary syndrome	18,624	eligible for follow-up: 62 (54-71) not eligible for follow-up: 62 (54-70)	eligible for follow-up: 71.1 not eligible for follow-up: 72.3
Perneger 2010[94]	HRQoL study	General population French-speaking Switzerland	1,952	20-80+	56.5

CEA = cost-effectiveness analysis. HRQoL = Health-related quality of life

Table 15.8.6. References and decisions of studies included in full-text screening of health-related quality of life systematic literature search

Reference	Decision
Ademi Z, Hancock E, Trueman D, Pfeil A, Haroun R, Deschaseaux C, Schwenkglenks M. Cost-Effectiveness of Sacubitril/Valsartan (Formerly LCZ696) in Chronic Heart Failure Patients with Reduced Ejection Fraction-An Analysis for Switzerland. Value in Health. 2016 Nov 1;19(7):A655.	Exclude: Conference abstract
Blank, 2010. Cost-effectiveness of ferric carboxymaltose in patients with chronic heart failure: An analysis from the FAIR-HF trial.	Exclude: Conference abstract
Blum MR, Øien H, Carmichael HL, Heidenreich P, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of transitional care services after hospitalization with heart failure. Annals of internal medicine. 2020 Jan 28;28.	Exclude: No utilities reported for relevant health states
Brandle, 2009. Exenatide versus insulin glargine: A cost-effectiveness evaluation in patients with Type 2 diabetes in Switzerland.	Exclude: No utilities reported for relevant health states
Brandle, 2009. Cost-effectiveness of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease in a Swiss setting.	Exclude: No utilities reported for relevant health states
Gasche D, Ulle T, Meier B, Greiner RA. Cost-effectiveness of ticagrelor and generic clopidogrel in patients with acute coronary syndrome in Switzerland. Swiss medical weekly. 2013;143:w13851.	Exclude: No utilities reported for relevant health states. However, referred to PLATO study for utilities.
Gencer, 2015. Determinants of the health-related quality of life of patients surviving acute coronary syndromes: Data from the Swiss ELIPS study.	Exclude: Conference abstract

Gencer B, Rodondi N, Auer R, Nanchen D, Räber L, Klingenberg R, Pletscher M, Jüni P, Windecker S, Matter CM, Lüscher TF. Health utility indexes in patients with acute coronary syndromes. Open heart. 2016 May 1;3(1):e000419.	Exclude: No utilities reported for relevant health states
Huber A, Oldridge N, Benzer W, Saner H, Höfer S. Validation of the German HeartQoL: a short health-related quality of life questionnaire for cardiac patients. Quality of Life Research. 2019 Dec 12:1-3.	Exclude: No utilities reported for relevant health states. However, did report outcomes of HRQoL questionnaires.
Leventhal, 2011. Swiss Interdisciplinary Management programme for Heart Failure (SWIM-HF): A randomised controlled trial study of an outpatient inter-professional management programme for heart failure patients in Switzerland.	Exclude: No utilities reported for relevant health states
Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M, PLATO Health Economic Substudy Group. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. European heart journal. 2013 Jan 14;34(3):220-8.	Included
Oldridge, 2011. Health-related quality of life using the HeartQoL, a new questionnaire for patients with angina, myocardial infarction or ischemic heart failure.	Exclude: Conference abstract
Romanens M, Sudano I, Szucs T, Adams A. Medical costs per QALY of statins based on Swiss Medical Board assumptions. Cardiovascular Medicine. 2017 Apr 12;20(04):96-100.	Exclude: No utilities reported for relevant health states
Yinko, 2013. Health-related quality of life in patients with premature acute coronary syndrome: Does biological sex really matter?	Exclude: Conference abstract

15.9 Additional cost-effectiveness results

Table 15.9.1. Cost-effectiveness results statins vs. no statins in 96 subgroups

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	Age	Sex												
1%	40	Male	No statins	0.18	0.18	40.97	19.26	46,079						
1%	40	Male	Statins	0.14	0.16	41.62	19.43	52,906	4.01	1.52	0.21	0.17	6,828	39,514
5%	40	Male	No statins	0.32	0.33	30.12	15.91	102,927						
5%	40	Male	Statins	0.27	0.33	31.48	16.35	104,928	4.77	-0.34	0.54	0.44	2,001	4,518
10%	40	Male	No statins	0.34	0.35	24.06	13.65	132,860						
10%	40	Male	Statins	0.30	0.36	25.53	14.20	133,460	4.40	-1.19	0.68	0.55	600	1,088
15%	40	Male	No statins	0.35	0.36	20.59	12.19	150,153						
15%	40	Male	Statins	0.31	0.37	22.08	12.79	150,090	4.29	-1.45	0.74	0.60	-63	-105
20%	40	Male	No statins	0.35	0.36	18.24	11.11	162,157						
20%	40	Male	Statins	0.31	0.38	19.71	11.74	161,683	4.24	-1.57	0.78	0.63	-474	-748
25%	40	Male	No statins	0.35	0.36	16.52	10.27	171,062						
25%	40	Male	Statins	0.31	0.38	17.98	10.92	170,308	4.22	-1.64	0.81	0.65	-754	-1,154

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
1%	45	Male	No statins	0.12	0.12	38.12	18.35	39,063						
1%	45	Male	Statins	0.09	0.11	38.55	18.47	46,436	2.99	1.31	0.15	0.12	7,373	59,300
5%	45	Male	No statins	0.29	0.30	30.06	15.72	88,336						
5%	45	Male	Statins	0.24	0.29	31.18	16.09	90,517	5.03	0.61	0.46	0.38	2,181	5,798
10%	45	Male	No statins	0.33	0.34	24.49	13.65	118,996						
10%	45	Male	Statins	0.28	0.34	25.83	14.15	119,459	4.68	-0.60	0.62	0.50	464	925
15%	45	Male	No statins	0.34	0.35	21.00	12.21	137,598						
15%	45	Male	Statins	0.30	0.36	22.39	12.77	137,335	4.46	-1.10	0.70	0.56	-262	-466
20%	45	Male	No statins	0.35	0.36	18.60	11.14	150,357						
20%	45	Male	Statins	0.30	0.37	20.00	11.74	149,678	4.36	-1.33	0.75	0.60	-679	-1,134
25%	45	Male	No statins	0.35	0.36	16.79	10.28	160,051						
25%	45	Male	Statins	0.31	0.37	18.18	10.91	159,091	4.31	-1.46	0.78	0.62	-960	-1,542
1%	50	Male	No statins	0.08	0.08	34.62	17.18	34,474						
1%	50	Male	Statins	0.06	0.07	34.89	17.27	42,134	2.07	0.97	0.10	0.09	7,660	88,152

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
5%	50	Male	No statins	0.24	0.25	28.79	15.14	75,643						
5%	50	Male	Statins	0.19	0.24	29.67	15.45	78,203	4.86	1.27	0.38	0.31	2,561	8,291
10%	50	Male	No statins	0.31	0.31	24.07	13.34	105,491						
10%	50	Male	Statins	0.26	0.31	25.22	13.78	105,886	4.95	0.18	0.55	0.44	394	890
15%	50	Male	No statins	0.33	0.34	20.87	12.01	124,460						
15%	50	Male	Statins	0.28	0.34	22.12	12.52	123,991	4.71	-0.54	0.64	0.51	-469	-913
20%	50	Male	No statins	0.34	0.35	18.54	10.98	137,874						
20%	50	Male	Statins	0.29	0.36	19.82	11.53	136,958	4.54	-0.94	0.70	0.55	-917	-1,652
25%	50	Male	No statins	0.34	0.35	16.76	10.15	148,019						
25%	50	Male	Statins	0.30	0.36	18.05	10.73	146,824	4.45	-1.17	0.73	0.58	-1,195	-2,055
1%	55	Male	No statins	0.06	0.06	30.63	15.76	32,852						
1%	55	Male	Statins	0.04	0.05	30.81	15.82	40,333	1.50	0.73	0.08	0.07	7,481	114,080
5%	55	Male	No statins	0.19	0.20	26.59	14.23	65,256						
5%	55	Male	Statins	0.15	0.18	27.25	14.48	68,267	4.31	1.51	0.30	0.25	3,011	12,185

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
10%	55	Male	No statins	0.27	0.28	22.87	12.73	92,474						
10%	55	Male	Statins	0.22	0.27	23.82	13.11	92,974	5.02	0.90	0.47	0.38	500	1,318
15%	55	Male	No statins	0.31	0.31	20.15	11.57	110,887						
15%	55	Male	Statins	0.26	0.31	21.23	12.03	110,298	4.95	0.17	0.57	0.45	-590	-1,297
20%	55	Male	No statins	0.32	0.33	18.04	10.63	124,477						
20%	55	Male	Statins	0.27	0.33	19.18	11.13	123,340	4.78	-0.36	0.63	0.50	-1,138	-2,268
25%	55	Male	No statins	0.33	0.34	16.36	9.85	134,984						
25%	55	Male	Statins	0.29	0.35	17.53	10.38	133,540	4.64	-0.73	0.67	0.53	-1,444	-2,714
1%	60	Male	No statins	0.04	0.04	26.59	14.20	31,534						
1%	60	Male	Statins	0.03	0.03	26.71	14.25	38,726	1.03	0.51	0.06	0.05	7,191	157,037
5%	60	Male	No statins	0.15	0.15	23.86	13.08	56,326						
5%	60	Male	Statins	0.11	0.14	24.32	13.27	59,795	3.55	1.45	0.23	0.19	3,469	18,288
10%	60	Male	No statins	0.23	0.24	21.06	11.88	79,804						
10%	60	Male	Statins	0.18	0.22	21.80	12.19	80,642	4.74	1.36	0.39	0.31	838	2,694

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
15%	60	Male	No statins	0.27	0.28	18.88	10.91	96,874						
15%	60	Male	Statins	0.22	0.27	19.77	11.30	96,363	5.01	0.85	0.49	0.39	-511	-1,317
20%	60	Male	No statins	0.30	0.31	17.08	10.08	110,198						
20%	60	Male	Statins	0.25	0.30	18.05	10.52	108,954	4.98	0.32	0.56	0.44	-1,244	-2,832
25%	60	Male	No statins	0.31	0.32	15.61	9.38	120,623						
25%	60	Male	Statins	0.27	0.32	16.62	9.85	118,978	4.87	-0.11	0.60	0.47	-1,645	-3,472
1%	65	Male	No statins	0.03	0.03	22.59	12.53	30,941						
1%	65	Male	Statins	0.02	0.02	22.66	12.57	37,614	0.72	0.37	0.04	0.03	6,672	204,759
5%	65	Male	No statins	0.11	0.11	20.78	11.72	49,267						
5%	65	Male	Statins	0.08	0.10	21.10	11.87	53,014	2.80	1.24	0.18	0.14	3,747	26,356
10%	65	Male	No statins	0.19	0.19	18.84	10.83	67,854						
10%	65	Male	Statins	0.14	0.17	19.37	11.08	69,185	4.17	1.51	0.30	0.24	1,331	5,466
15%	65	Male	No statins	0.23	0.24	17.17	10.05	82,887						
15%	65	Male	Statins	0.19	0.23	17.85	10.37	82,703	4.78	1.32	0.40	0.32	-184	-580

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
20%	65	Male	No statins	0.27	0.27	15.76	9.37	94,943						
20%	65	Male	Statins	0.22	0.26	16.54	9.74	93,838	5.00	0.97	0.47	0.37	-1,106	-2,999
25%	65	Male	No statins	0.29	0.29	14.54	8.77	104,977						
25%	65	Male	Statins	0.24	0.29	15.38	9.18	103,306	5.02	0.57	0.52	0.41	-1,671	-4,115
1%	70	Male	No statins	0.02	0.02	18.72	10.79	30,230						
1%	70	Male	Statins	0.01	0.02	18.77	10.81	36,260	0.49	0.25	0.03	0.02	6,030	274,366
5%	70	Male	No statins	0.08	0.08	17.58	10.23	43,044						
5%	70	Male	Statins	0.06	0.07	17.79	10.33	46,920	2.09	0.98	0.13	0.10	3,876	38,398
10%	70	Male	No statins	0.14	0.15	16.28	9.60	56,971						
10%	70	Male	Statins	0.11	0.13	16.66	9.78	58,817	3.43	1.42	0.23	0.18	1,845	10,214
15%	70	Male	No statins	0.19	0.19	15.13	9.02	68,928						
15%	70	Male	Statins	0.15	0.18	15.62	9.26	69,309	4.23	1.51	0.31	0.24	381	1,565
20%	70	Male	No statins	0.22	0.23	14.09	8.50	79,179						
20%	70	Male	Statins	0.18	0.22	14.68	8.79	78,524	4.69	1.39	0.37	0.29	-655	-2,243

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
25%	70	Male	No statins	0.25	0.26	13.15	8.01	88,212						
25%	70	Male	Statins	0.20	0.25	13.80	8.34	86,822	4.93	1.15	0.42	0.33	-1,390	-4,208
1%	75	Male	No statins	0.01	0.01	15.02	8.98	29,192						
1%	75	Male	Statins	0.01	0.01	15.04	8.99	34,458	0.32	0.17	0.02	0.01	5,266	381,012
5%	75	Male	No statins	0.05	0.06	14.36	8.63	37,240						
5%	75	Male	Statins	0.04	0.05	14.49	8.70	41,086	1.46	0.71	0.08	0.07	3,846	59,023
10%	75	Male	No statins	0.10	0.10	13.58	8.22	46,530						
10%	75	Male	Statins	0.08	0.09	13.81	8.34	48,883	2.57	1.16	0.15	0.12	2,352	19,420
15%	75	Male	No statins	0.14	0.14	12.85	7.84	55,040						
15%	75	Male	Statins	0.11	0.13	13.17	8.00	56,171	3.40	1.41	0.22	0.17	1,131	6,692
20%	75	Male	No statins	0.17	0.18	12.16	7.47	62,845						
20%	75	Male	Statins	0.13	0.16	12.56	7.68	62,987	4.00	1.50	0.27	0.21	142	677
25%	75	Male	No statins	0.20	0.21	11.51	7.12	70,014						
25%	75	Male	Statins	0.16	0.19	11.97	7.36	69,365	4.42	1.47	0.31	0.24	-649	-2,658

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
1%	40	Female	No statins	0.30	0.31	36.40	17.62	72,904						
1%	40	Female	Statins	0.26	0.31	37.65	17.94	77,475	4.90	0.17	0.41	0.32	4,571	14,133
5%	40	Female	No statins	0.35	0.36	24.02	13.50	129,591						
5%	40	Female	Statins	0.31	0.37	25.49	14.02	131,041	4.22	-1.48	0.67	0.53	1,450	2,757
10%	40	Female	No statins	0.35	0.36	19.41	11.52	153,151						
10%	40	Female	Statins	0.31	0.38	20.91	12.12	153,433	4.17	-1.65	0.76	0.60	282	471
15%	40	Female	No statins	0.35	0.36	18.40	10.95	161,085						
15%	40	Female	Statins	0.31	0.38	19.98	11.60	160,614	4.19	-1.65	0.83	0.65	-471	-722
20%	40	Female	No statins	0.36	0.37	16.93	10.24	168,892						
20%	40	Female	Statins	0.31	0.38	18.50	10.92	168,073	4.18	-1.70	0.85	0.67	-819	-1,214
25%	40	Female	No statins	0.36	0.37	15.61	9.59	175,813						
25%	40	Female	Statins	0.31	0.38	17.17	10.28	174,726	4.18	-1.73	0.88	0.69	-1,087	-1,573
1%	45	Female	No statins	0.24	0.24	36.70	17.46	56,702						
1%	45	Female	Statins	0.19	0.23	37.61	17.71	61,892	4.81	1.32	0.31	0.25	5,190	21,095

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
5%	45	Female	No statins	0.34	0.35	25.39	13.82	113,309						
5%	45	Female	Statins	0.29	0.36	26.78	14.30	114,761	4.43	-1.03	0.62	0.48	1,452	3,023
10%	45	Female	No statins	0.35	0.36	20.30	11.75	139,536						
10%	45	Female	Statins	0.31	0.37	21.74	12.32	139,752	4.25	-1.45	0.73	0.56	216	383
15%	45	Female	No statins	0.35	0.36	17.62	10.52	154,028						
15%	45	Female	Statins	0.31	0.38	19.07	11.13	153,602	4.21	-1.58	0.78	0.61	-427	-702
20%	45	Female	No statins	0.35	0.36	15.81	9.64	163,986						
20%	45	Female	Statins	0.31	0.38	17.26	10.28	163,146	4.20	-1.64	0.82	0.64	-840	-1,320
25%	45	Female	No statins	0.35	0.36	17.09	10.13	160,697						
25%	45	Female	Statins	0.31	0.38	18.67	10.80	159,356	4.27	-1.55	0.87	0.68	-1,341	-1,985
1%	50	Female	No statins	0.16	0.17	35.12	16.84	44,286						
1%	50	Female	Statins	0.13	0.15	35.71	17.01	50,349	3.80	1.50	0.22	0.17	6,064	35,175
5%	50	Female	No statins	0.31	0.32	26.00	13.81	97,288						
5%	50	Female	Statins	0.27	0.32	27.25	14.24	98,625	4.84	-0.10	0.55	0.43	1,337	3,114

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
10%	50	Female	No statins	0.34	0.35	20.90	11.82	124,987						
10%	50	Female	Statins	0.29	0.36	22.25	12.35	125,044	4.44	-1.05	0.68	0.52	57	108
15%	50	Female	No statins	0.35	0.36	18.05	10.58	140,701						
15%	50	Female	Statins	0.30	0.37	19.42	11.15	140,124	4.32	-1.34	0.74	0.57	-576	-1,009
20%	50	Female	No statins	0.35	0.36	16.11	9.66	151,568						
20%	50	Female	Statins	0.31	0.37	17.49	10.27	150,572	4.27	-1.47	0.78	0.60	-995	-1,653
25%	50	Female	No statins	0.35	0.36	14.67	8.95	159,776						
25%	50	Female	Statins	0.31	0.38	16.05	9.57	158,480	4.25	-1.55	0.81	0.62	-1,296	-2,075
1%	55	Female	No statins	0.10	0.10	32.40	15.88	35,096						
1%	55	Female	Statins	0.07	0.09	32.74	15.99	41,941	2.51	1.15	0.14	0.11	6,845	61,885
5%	55	Female	No statins	0.27	0.28	25.79	13.54	80,569						
5%	55	Female	Statins	0.22	0.27	26.80	13.90	82,125	5.02	0.98	0.46	0.36	1,557	4,348
10%	55	Female	No statins	0.32	0.33	21.10	11.72	109,189						
10%	55	Female	Statins	0.27	0.33	22.33	12.20	109,013	4.80	-0.25	0.62	0.48	-176	-370

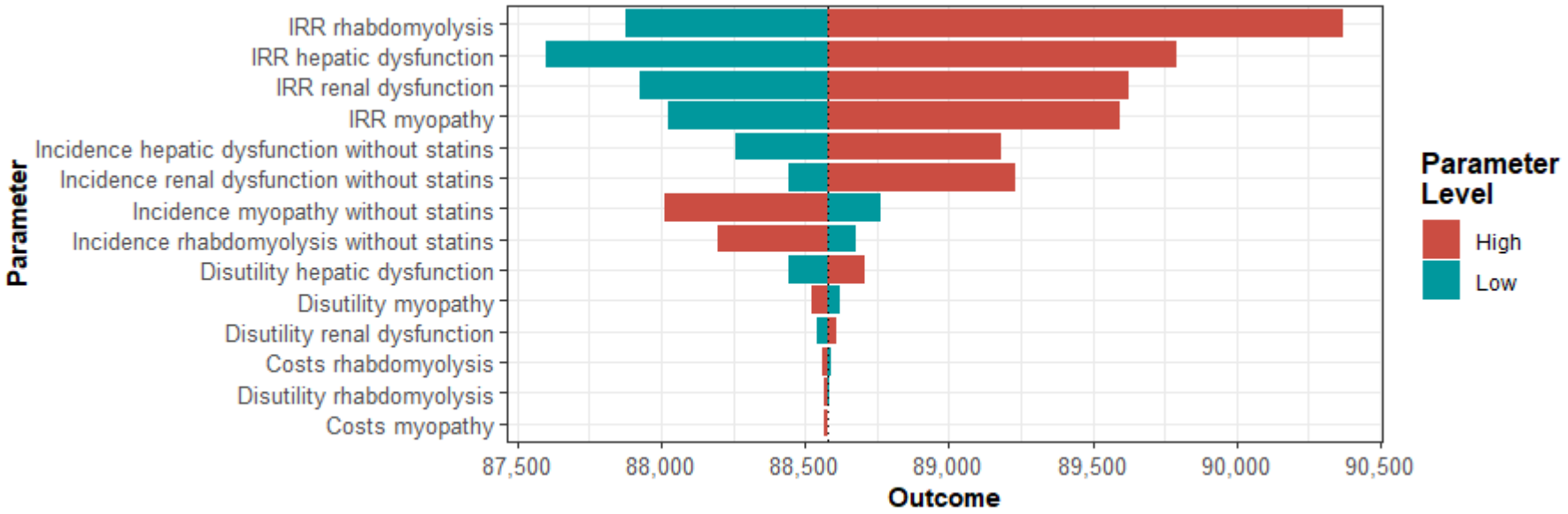
Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
15%	55	Female	No statins	0.33	0.34	18.18	10.47	126,344						
15%	55	Female	Statins	0.29	0.35	19.45	11.00	125,502	4.55	-0.86	0.70	0.53	-842	-1,584
20%	55	Female	No statins	0.34	0.35	16.19	9.56	137,965						
20%	55	Female	Statins	0.30	0.36	17.48	10.12	136,739	4.42	-1.15	0.74	0.56	-1,226	-2,176
25%	55	Female	No statins	0.35	0.36	14.69	8.84	146,751						
25%	55	Female	Statins	0.30	0.37	15.99	9.43	145,249	4.36	-1.31	0.77	0.59	-1,502	-2,563
1%	60	Female	No statins	0.06	0.07	28.73	14.55	30,879						
1%	60	Female	Statins	0.05	0.06	28.95	14.63	37,831	1.69	0.82	0.10	0.08	6,953	91,027
5%	60	Female	No statins	0.21	0.21	24.44	12.90	65,317						
5%	60	Female	Statins	0.16	0.20	25.17	13.18	67,531	4.53	1.50	0.36	0.28	2,214	7,992
10%	60	Female	No statins	0.28	0.29	20.68	11.38	92,297						
10%	60	Female	Statins	0.23	0.28	21.70	11.79	92,134	5.06	0.75	0.53	0.41	-164	-400
15%	60	Female	No statins	0.31	0.32	18.02	10.24	110,021						
15%	60	Female	Statins	0.26	0.32	19.15	10.72	108,907	4.91	-0.02	0.63	0.48	-1,114	-2,322

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
20%	60	Female	No statins	0.33	0.34	16.08	9.36	122,364						
20%	60	Female	Statins	0.28	0.34	17.26	9.88	120,812	4.72	-0.53	0.69	0.52	-1,552	-2,993
25%	60	Female	No statins	0.34	0.34	14.55	8.64	131,907						
25%	60	Female	Statins	0.29	0.35	15.74	9.19	130,099	4.58	-0.86	0.72	0.54	-1,809	-3,327
1%	65	Female	No statins	0.04	0.04	24.89	13.07	27,697						
1%	65	Female	Statins	0.03	0.03	25.01	13.12	34,534	1.05	0.53	0.06	0.05	6,837	139,794
5%	65	Female	No statins	0.15	0.15	22.23	11.95	52,179						
5%	65	Female	Statins	0.11	0.14	22.71	12.15	55,232	3.57	1.47	0.26	0.20	3,053	15,349
10%	65	Female	No statins	0.23	0.24	19.54	10.79	74,913						
10%	65	Female	Statins	0.18	0.22	20.30	11.12	75,303	4.78	1.41	0.42	0.32	389	1,200
15%	65	Female	No statins	0.27	0.28	17.38	9.83	91,804						
15%	65	Female	Statins	0.22	0.27	18.30	10.24	90,791	5.08	0.91	0.53	0.41	-1,013	-2,500
20%	65	Female	No statins	0.30	0.31	15.66	9.04	104,504						
20%	65	Female	Statins	0.25	0.30	16.67	9.50	102,765	5.05	0.38	0.60	0.46	-1,739	-3,811

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
25%	65	Female	No statins	0.32	0.32	14.23	8.36	114,588						
25%	65	Female	Statins	0.27	0.33	15.29	8.85	112,460	4.92	-0.08	0.65	0.49	-2,128	-4,345
1%	70	Female	No statins	0.02	0.02	20.92	11.41	25,674						
1%	70	Female	Statins	0.02	0.02	20.98	11.44	32,097	0.63	0.32	0.04	0.03	6,423	217,042
5%	70	Female	No statins	0.10	0.10	19.37	10.70	41,650						
5%	70	Female	Statins	0.07	0.09	19.66	10.83	45,394	2.52	1.16	0.17	0.13	3,745	28,403
10%	70	Female	No statins	0.17	0.17	17.64	9.90	58,602						
10%	70	Female	Statins	0.13	0.16	18.15	10.13	59,938	3.94	1.53	0.30	0.23	1,336	5,726
15%	70	Female	No statins	0.22	0.22	16.12	9.18	72,607						
15%	70	Female	Statins	0.17	0.21	16.79	9.49	72,326	4.68	1.48	0.41	0.31	-281	-907
20%	70	Female	No statins	0.25	0.26	14.79	8.54	84,264						
20%	70	Female	Statins	0.20	0.25	15.57	8.91	82,917	5.01	1.21	0.49	0.37	-1,347	-3,668
25%	70	Female	No statins	0.28	0.29	13.62	7.97	94,045						
25%	70	Female	Statins	0.23	0.28	14.47	8.38	92,012	5.11	0.86	0.55	0.41	-2,033	-4,963

Subgroup definition			Therapy	MI	Stroke	LYs	QALYs	Costs	∆MI	∆Stroke	∆LYs	∆QALYs	∆ Costs	∆ICER
AGLA risk	**Age**	**Sex**												
1%	75	Female	No statins	0.01	0.01	16.97	9.62	24,175						
1%	75	Female	Statins	0.01	0.01	17.01	9.64	29,936	0.36	0.19	0.02	0.02	5,761	344,412
5%	75	Female	No statins	0.06	0.06	16.15	9.22	33,484						
5%	75	Female	Statins	0.04	0.05	16.32	9.29	37,582	1.62	0.79	0.10	0.08	4,099	51,832
10%	75	Female	No statins	0.11	0.11	15.18	8.73	44,163						
10%	75	Female	Statins	0.08	0.10	15.48	8.88	46,527	2.82	1.26	0.19	0.15	2,364	16,038
15%	75	Female	No statins	0.15	0.16	14.27	8.27	53,876						
15%	75	Female	Statins	0.12	0.14	14.69	8.48	54,836	3.69	1.49	0.27	0.21	960	4,660
20%	75	Female	No statins	0.19	0.19	13.41	7.84	62,718						
20%	75	Female	Statins	0.15	0.18	13.92	8.09	62,555	4.30	1.55	0.34	0.26	-162	-634
25%	75	Female	No statins	0.22	0.22	12.60	7.42	70,773						
25%	75	Female	Statins	0.17	0.21	13.19	7.72	69,727	4.70	1.47	0.40	0.30	-1,047	-3,512

Figure 15.9.1. Tornado diagram of one-way sensitivity analyses of adverse events parameters



Outcome is incremental cost-effectiveness ratio (ICER). Abbreviations: IRR: incidence rate ratio.

Table 15.9.2. Outcomes one-way sensitivity analyses of adverse events parameters

Parameter	Parameter value low	ICER value low	Parameter value high	ICER value high	Absolute difference	Relative difference (%)
IRR rhabdomyolysis	0.35	87,876	2.26	90,368	2,491	2.83
IRR hepatic dysfunction	0.93	87,603	1.39	89,791	2,188	2.50
IRR renal dysfunction	0.69	87,926	1.75	89,625	1,698	1.93
IRR myopathy	0.45	88,022	1.48	89,595	1,572	1.79
Incidence hepatic dysfunction without statins	0.00	88,257	0.01	89,185	927	1.05
Incidence renal dysfunction without statins	0.00	88,442	0.01	89,231	789	0.89
Incidence myopathy without statins	0.00	88,761	0.01	88,012	749	0.84
Incidence rhabdomyolysis without statins	0.00	88,676	0.00	88,195	481	0.54
Disutility hepatic dysfunction	0.05	88,441	0.07	88,709	268	0.30
Disutility myopathy	0.02	88,624	0.03	88,526	98	0.11
Disutility renal dysfunction	0.05	88,542	0.07	88,608	67	0.08
Costs rhabdomyolysis	7388.80	88,592	11083.20	88,558	35	0.04
Disutility rhabdomyolysis	0.05	88,585	0.07	88,565	20	0.02
Costs myopathy	203.30	88,581	304.94	88,569	12	0.01