Stakeholderrückmeldungen zum HTA Bericht

“Statins for primary prevention of cardiovascular events and mortality in Switzerland”

Folgende Stakeholderverbände wurden zur Stellungnahme zum HTA Bericht angeschrieben.

ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana
BLV/ EEK eidg. Ernährungskommission
BSV - Bundesamt für Sozialversicherung, Invalidenversicherung
curafutura - Die innovativen Krankenversicherer
DVSP - Dachverband Schweizerischer Patientenstellen
FMH - Verbindung der Schweizer Ärztinnen und Ärzte
FRC - Fédération romande des consommateurs
GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren
H+ - Die Spitäler der Schweiz
Intergenerika - Swiss Generics and Biosimilars
Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz
Konsumentenforum
MTK - Medizinaltarif-Kommission
pharmaSuisse - Schweizerischer Apothekerverband
PUE - Preisüberwachung
SAMW - Schweizerische Akademie der Medizinischen Wissenschaften
santésuisse - Die Schweizer Krankenversicherer
SAPW - Schweizerische Akademie der Pharmazeutischen Wissenschaften
SBK - ASI - Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner
Schweizerische Herzstiftung
SDG-ASD - Schweizerische Diabetesgesellschaft - diabetesschweiz
SDS - Schweiz. Diabetes-Stiftung
SGE - SSN Schweiz. Gesellschaft für Ernährung
SGED-SSED - Schweiz. Gesellschaft für Endokrinologie und Diabetologie
SGK - Schweizerische Gesellschaft für Kardiologie
SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte
SHG-SCS-SSS - Schweizerische Hirnschlaggesellschaft
SHRS - Schweizerische Herzrhythmus Stiftung
SKS - Stiftung für Konsumentenschutz
SPO – Patientenschutz
SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen
Verein Ethik und Medizin Schweiz VEMS, M. Romanens
VIPS - Vereinigung Pharmafirmen in der Schweiz

Folgende sechs Stakeholder haben eine Stellungnahme zum HTA Bericht eingereicht:

Médecins Fribourg - Ärztinnen und Ärzte Freiburg (MFÄF), Verein Ethik und Medizin Schweiz VEMS; Santesuisse santésuisse, curafutura, Interpharma, SGK - Schweizerische Gesellschaft für Kardiologie

Stellungnahmen, welche nicht im vorgegebenen Feedbackformular eingingen, wurden sinngemäss ins Feedbackformularformat übertragen. Die individuellen Kommentare der Stakeholder zum vorliegenden HTA Bericht sowie die Würdigung der Kommentare durch die Sektion HTA des BAG und durch die Auftragnehmer sind nachfolgend aufgeführt.

Formular A: Kommentare und Stellungnahmen der Stakeholder zum vorliegenden HTA Bericht Statine in der Primärprävention

General comment		
Stakeholder	**Stakeholder comment**	**Response**
MFÄF	**Original comment:** Le comité de MFÄF est quelque peu étonné que le mandat de cette étude ait été confié à un institut hollandais, alors qu'il s'agit d'une évaluation purement nationale. Les conclusions de cette étude sont assez décevantes, puisqu'elles concluent à un manque de données sur l'utilisation des statines en prévention primaires en Suisse. Concernant le bénéfice-risque de cette utilisation, les auteurs rejoignent les conclusions de multiples études internationales résumées dans l'outil décisionnel élaboré par la Mayo Clinic sur lequel la majorité des praticiens suisses se fondent pour proposer à leurs patients un traitement anticholestérol. Ces propositions sont évidemment faites après avoir recommandé des changements de l'hygiène de vie qui ne sont, malheureusement, que trop peu suivis. **Translated comment:** The MFÄF committee is somewhat surprised that the mandate for this study was given to a Dutch institute, when it is a purely national assessment. The findings of this study are quite disappointing, as they conclude that there is a lack of data on the use of statins for primary prevention in Switzerland. Regarding the risk-benefit of this use, the authors agree with the conclusions of multiple international studies summarized in the decision-making tool developed by the Mayo Clinic on which the majority of Swiss practitioners rely to offer their patients an anti-cholesterol treatment. These proposals are obviously made after recommending changes in lifestyle that are, unfortunately, too little followed.	We would like to emphasize that the primary aim of this study was to investigate the cost-effectiveness of statins in primary prevention across CVD risk groups and the lack of data mentioned in the report is related to CVD risk group-specific data. In general, it can be concluded that primary prevention with statin therapy is effective, safe and cost-effective compared to no treatment. However, there is uncertainty about these estimates in specific CVD risk groups in the primary prevention population. FOPH addition: an HTA evaluates all best available evidence in term of efficacy/effectiveness and safety. The selection of the best available evidence goes beyond country borders. The choice of HTA agency to conduct our HTAs is based on the credentials of the agency, not its nationality. National and international agencies are invited to bid for the HTA assignment. This is a transparent application procedure, where the best bidder gets rewarded.
VEMS	This report experimentally assesses statin effects. The results are driven by assumptions that dysfavor positive effects (on unstable angina and coronary revascularisation rates) and the conclusions do in part not reflect the results. Authors are not careful enough in discussing the many limitations of the report.	Although we agree that including unstable angina and coronary revascularization would reflect a more complete picture of the complex reality of this decision problem, we do not believe that this specific assumption drives our results as we included the most important positive effects of statins on preventing MI, stroke and CVD deaths. The decision to focus on the most important CVD events was made in deliberation with our clinical expert and the FOPH. We summarized this and other limitations in the discussion section of the HTA report.
VEMS	The report does not address:	We performed a systematic literature search for Swiss specific cost inputs and our considerations for choosing the most appropriate

	• the treatment costs of cardivascular disease in CH (Schwenkglenks et al), • it does not discuss the value of a statistical life, which is not appropriate for calculations regarding life-time perspectives and • it does not make an attempt to discuss the beneficial effects of statins on avoidable social costs.	source of input data are reported in Appendix 15.7 of the report. To our knowledge, there is no formal estimate for the value of a statistical life in Switzerland. It was not the objective of this study to discuss this value. The FOPH requested us to perform the analyses from a healthcare payer perspective, therefore societal costs (such as productivity losses or informal care costs) were not included in our analysis.
VEMS	The report is too much focused on AGLA risk estimates and does not discuss at all, that single risk factors such as very high LDL or presence of atherosclerotic plaque do shift patients to higher risk categories for which statins are also appropriate. There should be no restriction of statin reimbursement in CH, if clinically indicated.	The decision to focus on the AGLA risks was driven by the fact that AGLA risk is the most often used cardiovascular risk scoring system in Switzerland and was discussed and agreed upon by the FOPH project team. In our limitations section we acknowledged the limitation of only using the AGLA risk for CVD risk classification. We added high LDL and presence of atherosclerotic plaque explicitly in the discussion of this limitation.
santésuisse	**Original comment:** Der Bericht ist gut und verständlich aufgebaut und adressiert das grundsätzliche Thema der primären Prävention kardiovaskulärer Ereignisse mit Statinen. Zur Literatursuche wurden nur PubMed und Embase verwendet. In einem full-HTA dürfte erwartet werden, dass weitere und bekannte Datenbanken durchsucht werden, zumal bereits bei den beiden einbezogenen Quellen Unterschiede aus der Suche resultierten. Ebenfalls nicht verwendet wurden Quellen mit laufenden Studien wie clinicaltrials.gov etc. Damit besteht ein gewisses Risiko, dass laufende und absehbar relevante Studien nicht berücksichtigt wurden. Auch wenn zum Zeitpunkt des vorliegenden HTAs noch keine Resultate vorliegen, könnte zumindest auf diese kommenden Daten und auf die in der entsprechenden Studie adressierten Hypothesen hingewiesen werden. **Translated comment:** The report is well structured and easy to understand and addresses the fundamental topic of primary prevention of cardiovascular events with statins. Only PubMed and Embase were used for the literature search. In a full HTA, it should be expected that additional and known databases will be searched, especially since the search results in differences between the two sources included. Sources with ongoing studies such as clinicaltrials.gov etc. were also not used. This means that there is a certain risk that ongoing and foreseeable relevant studies were not taken into account. Even if no results are available at the time of the present HTA, reference could at least be made to these upcoming data and to the hypotheses addressed in the corresponding study.	The choice was made not to search in other databases because in general there is much overlap between databases. Cochrane reviews are also enclosed in the PubMed (Medline) and Embase.com databases. The choice for the literature databases was discussed and agreed upon by the FOPH project team. For the cost-effectiveness systematic literature search, additional searches were conducted in topic-specific databases. For ongoing studies reporting preliminary results, it is not possible to assess in detail all bias aspects and the overall quality of the study. Therefore, RCTs were included only when full study results are reported.
Curafutura	**Original comment:** Der vorliegende HTA-Bericht scheint aus methodischer Sicht zu Beginn korrekt gemacht. Die Literaturrecherche wird beschrieben, wobei auffällt, dass zwei Metaanalysen (Yebio & Taylor) übernommen wurden und die Fragestellung durch die Autoren nicht selbst bearbeitet wird. Mit einer unkritischen Übernahme des Inhalts von zwei Publikationen ist der HTA-Auftrag aus unserer Sicht nicht erfüllt. Die Wirksamkeit von Statinen bei Patienten mit erhöhtem kardiovaskulärem Risiko ist bereits seit	The original question of the applicant was very broad and encompassed both primary and secondary prevention of cardiovascular events and mortality and referenced the SMB report on statins with primary prevention. Since there is a lot of evidence on the benefits of statins for secondary prevention, the FOPH requested us to focus on primary prevention compared to adaptations of life style or no therapy and where possible make distinctions in to low, moderate, and high CVD risk groups (as stated in the scoping report).

	Jahrzehnten erwiesen und ein HTA mit der vorliegenden Fragestellung deshalb überflüssig. Ein HTA müsste anstatt dessen untersuchen, inwiefern die Risk-Scores angesichts neuer Untersuchungstechniken wie CTA und FFR verfeinert werden können. Dies würde eine bessere Risikoselektion in der Bevölkerung ermöglichen (Optimierung der NNT). Auf die ursprüngliche Fragestellung des Antrags von curafutura wird nicht eingegangen. Sämtliche kritische Literatur, die zur Fragestellung existiert, wurde ausgeblendet. **Translated comment:** From a methodological point of view, the present HTA report seems to have been made correctly at the beginning. The literature research is described, whereby it is noticeable that two meta-analyzes (Yebio & Taylor) were adopted and the question is not dealt with by the authors themselves. In our opinion, the HTA mandate is not fulfilled with an uncritical takeover of the content of two publications. The efficacy of statins in patients with an increased cardiovascular risk has been proven for decades and an HTA is therefore superfluous with the present question. Instead, an HTA would have to investigate to what extent the risk scores can be refined in light of new investigation techniques such as CTA and FFR. This would enable better risk selection in the population (optimization of the NNT). The original question of curafutura's application is not addressed. All critical literature that exists on the question has been hidden.	However, our results showed that there is a lack of data on CVD risk group specific costs and benefits of statins for primary prevention.
Interpharma	**Original comment:** Wir danken Ihnen für die Gelegenheit zur Stellungnahme zum vorliegenden HTA-Bericht. Mit seinen 23 Mitgliedsfirmen vertritt Interpharma Firmen, deren Produkte fast 80 Prozent des verschreibungspflichtigen Marktes und über 90 Prozent der patentgeschützten Medikamente in der Spezialitätenliste abdecken. Interpharma unterstützt ein HTA-Programm, das dazu beiträgt die Qualität und Effizienz des Gesundheitswesens zu verbessern. Das HTA setzte den primären Fokus der Fragestellung auf die Kosteneffizienz von Statinen. Die Autoren attestieren dieser Arzneimittelklasse eine gute Wirksamkeit bei tragbaren Kosten. Für die Beantwortung der Frage, ob Statine auch bei Patienten mit niedrigem Risiko für eine Herz-Kreislauferkrankung kosteneffizient seien, fehlen gemäss den Autoren die Daten. Auch sind Daten zur Anzahl Patienten in dieser Kategorie, welche Statine einnehmen für die Schweiz nicht verfügbar. Um diese Frage zu beantworten, regen wir an, die entsprechende Grundlagenforschung zu unterstützen. Auf Basis der verfügbaren Daten erscheint uns jedoch nicht möglich, in dieser Frage eine vergütungswirksame Entscheidung zu treffen. Der Zugang zu einem wirksamen Arzneimittel darf für betroffene Patientinnen nicht lediglich nach ökonomischen Gesichtspunkten eingeschränkt werden und würde insbesondere die WZW Kriterien unterlaufen. Wir möchten daher betonen, dass wir eine Einschränkung des Zuganges ausschliesslich aus Kostengründen als heikel und kontraproduktiv erachten	We would like to emphasize that the conclusions in our report are not solely based on costs, but rather on the balance between efficacy, effectiveness, and safety on the one hand and costs on the other hand. This means that for health interventions with substantial health benefits, high costs can be acceptable.

	Translated comment: We thank you for the opportunity to comment on this HTA report. With its 23 member companies, Interpharma represents companies whose products cover almost 80 percent of the prescription market and over 90 percent of the patented drugs in the specialties list. Interpharma supports an HTA program that helps improve the quality and efficiency of the healthcare system. The HTA set the primary focus of the question on the cost-effectiveness of statins. The authors confirm that this class of drugs is highly effective at affordable costs. According to the authors, there is no data to answer the question of whether statins are also cost-effective in patients with a low risk of cardiovascular disease. Data on the number of patients in this category who take statins are also not available for Switzerland. To answer this question, we encourage you to support the relevant basic research. On the basis of the available data, however, it does not appear to us to be able to make a remuneration-relevant decision on this issue. Access to an effective drug for affected patients must not be restricted only from an economic point of view and would in particular undermine the WZW criteria. We would therefore like to emphasize that we consider restricting access solely for cost reasons as sensitive and counterproductive	
SGK	The HTA Bericht was done carefully. However some important data are missing and should be taken in account (NEJM 2016; 374:2021-2031, EHJ 2019 40, 3516–3525, Curr Ather Rep 2019 21: 28, Circulation. 2020;142:827–837, all PDF as attachment). Too little is known about potential benefits of lipid lowering earlier in life versus the costs of delaying lipid lowering to later in life. The data by Pencina et al showed that CV risk increases considerably if young people with high cholesterol are not treated. It was also shown that the stop of statin treatment in people older than 75 y. also increases risk.	The NEJM 2016; 374:2021-2031 publication of Yusuf et al. was found with our update search for original RCTs. However, the study was excluded, because it was already included in one of the systematic reviews included in our systematic review. The EHJ 2019 40, 3516–3525 publication of Giral et al. is published after the closing date of our systematic literature search and therefore not assessed in full text. This study discusses the effect of discontinuation of statins in people older than 75 years but did not compare statins with the comparator in our PICO and therefore did not fulfil our inclusion criteria and would have been excluded. However, the increased CVD risk for people without statin therapy observed in Giral et al. is included in our model at all ages. The Circulation. 2020;142:827–837 publication of Pencina et al. is published after the closing date of our systematic literature search and therefore not assessed in full text. This study did not report on observed data and therefore did not fulfil our inclusion criteria and would have been excluded. However, the findings in Pencina et al. are comparable to our finding that starting statin therapy in younger adults is associated with a higher number of CVD events prevented.
SGK	As also highlighted by the authors "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 especially in case of primary	-

	prevention." also argue against any restriction in reimbursement of statins in primary prevention.	

Comments on efficacy, effectiveness, and safety		
Stakeholder	**Stakeholder comment**	**Response**
MFÄF	**Original comment:** Concernant le bénéfice-risque de cette utilisation, les auteurs rejoignent les conclusions de multiples études internationales résumées dans l'outil décisionnel élaboré par la Mayo Clinic sur lequel la majorité des praticiens suisses se fondent pour proposer à leurs patients un traitement anticholestérol. Ces propositions sont évidemment faites après avoir recommandé des changements de l'hygiène de vie qui ne sont, malheureusement, que trop peu suivis. **Translated comment:** Regarding the risk-benefit of this use, the authors agree with the conclusions of multiple international studies summarized in the decision-making tool developed by the Mayo Clinic on which the majority of Swiss practitioners rely to offer their patients an anti-cholesterol treatment. These proposals are obviously made after recommending changes in lifestyle that are, unfortunately, too little followed.	Adaption of lifestyle was one of the comparators included in our study. However, there was no evidence of the efficacy, effectiveness and safety of statin therapy compared to lifestyle adaptations.
VEMS	Efficacy should be discussed in observed LDL levels in the population and achievable LDL reductions and corresponding relative risk reductions (RRR) in the sensitivity analysis.	The efficacy results change in total blood cholesterol concentration and change in LDL-C blood cholesterol concentration are presented in the HTA report. Statin use resulted in a significant reduction of both cholesterol concentrations.
VEMS	Effectiveness should be discussed in such a manner that patients and health care authorities understand, that uncompliant behaviour creates a huge financial burden on the health care system.	Adherence was one of the parameters in the health economic analyses and we showed that this is indeed an important parameter for the cost-effectiveness of statins.
VEMS	It should also be discussed that the results pertain to treatment costs only and that for certain reasons, that have to be named in detail, social costs are exluded from the report. There should be at least an attempt to quantify such costs.	The FOPH requested us to perform the analyses from a healthcare payers perspective, therefore societal costs (such as productivity losses or informal care costs) were not included in our analysis.
VEMS	Thirs, VSLY should be calculated, it is not accetable to value a Swiss life lost with CHF 8 511.	The cost price of CHF 8511 does not represent the value of a statistical life but rather the healthcare costs associated with dying. We have clarified this in the report.
VEMS	Safety issues should be addressed more appropriately as being in almost all cases transient and reversible and that negative reporting on statin safety has caused many deaths and ASCVD events.	The research question on safety focused on the difference between intervention and comparator in the occurrence of adverse events. In the scenario analysis including adverse events it was assumed that the adverse events would only have an impact on costs and utility during one cycle (i.e. one year) and therefore the transiency and reversibility of the adverse events is taken into account in the economic analyses.

		The impact of media coverage reported in the published literature was summarized in chapter 9.2.4.
VEMS	Exclusion of unstable angina and coronary revascularisation is not appropriate.	Although we agree that including unstable angina and coronary revascularization would reflect a more complete picture of the complex reality of this decision problem, we do not believe that this specific assumption drives our results as we included the most important positive effects of statins on preventing MI, stroke and CVD deaths. The decision to focus on the most important CVD events was made in deliberation with a clinical expert and the FOPH as described in paragraph 8.1.4. We have stated this limitation in the discussion section of the HTA report.
santésuisse	**Original comment:** Die Beurteilung basierend auf zwei Systematic Reviews (SRs) kann als Grundlage dienen. Umso wichtiger wäre die zusätzliche Recherche für RCTs in einer umfassenden Zahl an Datenbanken. SRs selber u.a. selektionieren nach vorgegebenen Kriterien und berücksichtigen unter Umständen nur wenige Datenbanken. Die Begründung für den Ausschluss des SMB-Berichts aus dem Jahr 2013 ist unzureichend, da dieser u.a. als Grundlage für die Themeneingabe diente. Der Ausschluss weiterer Studien ist unklar (ältere Personen, Vergleiche Statine etc.) Alle hier adressierten Aspekte wurden mit einer Literaturrecherche abgedeckt. Sicherheit sollte aber u.a. kurz- und längerfristige Aspekte, unterschiedliche Dosierungen oder Differenzen zwischen Wirkstoffen adressieren - andere / zusätzliche Studien wären zu berücksichtigen. Das Aufzeigen möglicher Unterschiede zwischen einzelnen Substanzen fehlt gänzlich - auf Grund der zahlreichen Studien ist dies nicht nachvollziehbar - eine Begründung fehlt. **Translated comment:** The assessment based on two Systematic Reviews (SRs) can serve as a basis. The additional research for RCTs in a large number of databases would be all the more important. SRs themselves, etc. select according to specified criteria and may only consider a few databases. The justification for the exclusion of the 2013 SMB report is inadequate as it, among other things, served as the basis for entering the topic. The exclusion of further studies is unclear (older people, comparisons with statins, etc.) All aspects addressed here were covered by a literature search. But security should include Addressing short- and long-term aspects, different dosages or differences between active ingredients - other / additional studies would have to be considered. The demonstration of possible differences between individual substances is completely missing - due to the numerous studies this is not understandable - there is no justification.	Since a large amount of studies has been published on statin therapy for the primary prevention of CVD events and mortality in adults without established CVD and good quality meta-analyses are conducted, it was decided not to conduct a complete systematic review from scratch. We agree that building on existing systematic reviews introduces limitations, which is highlighted in the discussion section of the HTA report. An update search for RCTs based on the closing search dates of the included systematic reviews was conducted, however no additional RCTs were found for our research objectives. This project built on and aimed to close the gap to the HTA published in 2013 in the report 'Statine zur Primärprävention kardiovaskulärer Erkrankungen' by the Swiss Medical Board. The exclusion of systematic reviews on older people is explained with a footnote below the flowchart. Studies with drug comparators (e.g. statins versus statins or comparison of different doses of statins) were out of scope for this HTA. The research question specifically stipulates that the current HTA considered statins as a class (as opposed to individual statins).
Curafutura	**Original comment:** Die Ergebnisse zeigen, dass eine Statintherapie vor allem bei Patienten mit erhöhtem Risiko	Our main outcome measure of interest is the RR. This is a general and well-known measure to express the outcome in the intervention

	bezüglich der Morbidität wirksam ist. Bei den Resultaten fehlt neben dem RR die Angabe der NNT, obwohl dieser Wert in vielen der RCT angegeben ist. Dieser Wert sollte zur besseren Interpretation der Resultate dargestellt werden. In Tabelle 7.10 ist ersichtlich, dass die Qualität der Evidenz häufig nur moderat war. Eine kritische Auseinandersetzung mit dem Risk-of bias fehlt in der Synthese der Resultate. Zur effectiveness wurde im HTA Report zu wenig Literatur gefunden, um aus den Resultaten Schlüsse ziehen zu können. Es wäre hier wichtig, weitere Literatur zu suchen und einzuschliessen, damit eine Aussage zur Wirksamkeit unter real-world Bedingungen gemacht werden kann. **Translated comment:** The results show that statin therapy is particularly effective in patients with an increased risk of morbidity. In the results, the NNT is missing in addition to the RR, although this value is given in many of the RCTs. This value should be shown for better interpretation of the results. Table 7.10 shows that the quality of the evidence was often only moderate. The synthesis of the results does not include a critical examination of the risk of bias. Too little literature on effectiveness was found in the HTA report to be able to draw conclusions from the results. It would be important here to search for and include further literature so that a statement can be made on the effectiveness under real-world conditions.	relative to the comparator groups (i.e. the effect of the intervention). Only two effectiveness studies could be included in this HTA which were in line with our research objective and PICO. Most data in real-world settings compare two types or two different doses of statins, this comparison was out of scope for the HTA (see research question). The details of the risk of bias and quality of the RCTs underlying Table 7.10 is reported in Table 7.6.
AGLA/SGK	The report confirms that statins are generally effective and safe in the primary and secondary prevention of cardiovascular events and mortality and this across different age, gender and cardiovascular risk. The sentence "There was no evidence of the efficacy, effectiveness and safety of statin therapy compared to lifestyle adaptations." is not correct first because lifestyle changes led to a very small reduction of LDL-cholesterol and second because every study comparing statin vs. placebo was on top of lifestyle changes. As such in secondary and primary prevention therapy with statin was shown to be superior to lifestyle.	Yebyo et al. did not report whether the intervention and placebo groups in the RCTs were also offered lifestyle interventions. In the systematic review of Taylor et al. 5 of the 18 RCTs also included lifestyle interventions such as advice, counselling or information on health-behaviour modification (e.g. diet, smoking cessation, or exercise). However, no further results were reported on the effect of these interventions. The two included non-randomised studies did not report any data on lifestyle adaptations.

Comments on cost-effectiveness		
Stakeholder	**Stakeholder comment**	**Response**
MFÄF	**Original comment:** Sur l'aspect économique, on peut relever que le prix des statines en Hollande est dix fois inférieur au prix suisses, ce qui serait peut-être une piste pour réaliser des économies substantielles à la charge des caisses maladies et des patients. **Translated comment:** From the economic point of view, it can be noted that the price of statins in Holland is ten times lower than the Swiss price, which would perhaps be an avenue for achieving substantial savings at	The price of statins is lower in the Netherlands compared to Switzerland. In our economic analysis, the average price of statins in Switzerland was included. Even with this relatively high price, statin therapy was associated with cost-savings or acceptable incremental cost-effectiveness ratios in most subgroups. A reduction of the price of statins in Switzerland would indeed further increase savings and lower the incremental cost-effectiveness ratios.

	the expense of health insurance funds and patients.	
VEMS	The impact of statin treatment at the population level is not appropriately calculated and discussed. There are no numbers on avoided deaths and events using statins and the cost savings associated regarding direct and indirect costs. This is a key message of HTA, we miss completely (https://www.docfind.ch/VarifoGutachten2019.pdf).	We deliberately did not provide a lot of detail in the results of the population-level costs, because of the limitations associated with this analysis that are mentioned in the report.
VEMS	Further, multiplicative effects of statins on QALY over time are not discussed. It should be stated that the longer statins can exert a protective effect, the higher is the numbers of avoided events in a multiplicative manner (not linear).	We are not sure what exactly the stakeholder means with a linear vs. multiplicative effect, but we assume the multiplicative effect relates to the fact that preventing the first CVD event also prevents the increased risk of having a second CVD event. Secondary events are not included in the model explicitly because we focused on modelling primary prevention of CVD events but the consequences of the first 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.
VEMS	VSLY should be included in the report with at least 150 000 to 200 000 CHF per year lost. In doing so, statin cost effectiveness and efficiency further importantly increases.	It is uncommon to use the VSLY (Value of a statistical life year) as an input parameter in an economic analysis. The outcomes of an economic analysis can be compared with a cost-per-QALY threshold. However, in Switzerland there is no formal cost per QALY threshold. Therefore, we provided colour coding of the ICERs for several arbitrary cost-per-QALY thresholds ranging from 50,000 CHF/QALY to150,000 CHF/QALY.
VEMS	Disutilites are taken as fixed values, they are not. This variable may vary over time and sensitivity analysis should address this more appropriately in the calculations and in the report, as well as in the discussion and the conclusion.	The disutility of MI was only assumed to occur during the first year after the occurrence of MI, based on findings from Reed et al. who showed that the utility of patients after MI recovered to (at least) the utility of the general population after one year. The disutility of stroke was assumed to remain 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. These assumptions were tested in sensitivity analyses where the duration of the disutility was varied between 1 year and lifetime.
santésuisse	**Original comment:** Die gesundheitsökonomische Analyse adressiert die relevanten Fragen. Die Resultate der Kosten-Nutzen-Analyse können nachvollzogen werden und sind plausibel. Die Sensibilitätsanalyse gibt eine guten Überblick über die relevanten Einflussfaktoren auf die Kosteneffektivität. Den grössten Einfluss auf die Kosteneffektivität haben die Therapietreue und das Risiko eines Schlaganfalles. Diese Erkenntnisse sollten in die Regulierungsmassnahmen einfliessen. **Translated comment:** The health economic analysis addresses the relevant questions. The results of the cost-benefit analysis can be understood and are plausible. The sensitivity analysis gives a good overview of the relevant factors influencing cost effectiveness. Adherence to therapy and the risk of stroke have the greatest influence on cost-effectiveness. These findings should flow into the regulatory	-

	measures.	
Curafutura	**Original comment:** Das von den Autoren entwickelte de novo Modell zeigt, dass vor allem Patienten mit erhöhtem Risiko von einer Statintherapie unter den von den Autoren verwendeten Annahmen profitieren (cost-effectiveness). Es wurden einige Sensitivitätsanalysen gemacht, welche zeigen, dass beispielsweise eine reduzierte Therapieadhärenz oder Statinpreise einen grossen Einfluss auf den ICER haben und damit die cost-effectiveness in Frage gestellt werden muss. Es stellt sich aber grundsätzlich die Frage, ob die gemachten Annahmen mit der Realität übereinstimmen. In einem übergeordneten Sinne müsste ein gesundheitsökonomisches Modell auch sämtliche anderen Faktoren bezüglich des kardiovaskulären Risikos einbeziehen und mögliche Interventionsansätze bezüglich des Kosten-Nutzens vergleichen. **Translated comment:** The de novo model developed by the authors shows that above all patients with an increased risk benefit from statin therapy under the assumptions used by the authors (cost-effectiveness). Some sensitivity analyzes were carried out which show that, for example, reduced therapy adherence or statin prices have a major influence on the ICER and therefore cost-effectiveness must be called into question. However, the fundamental question that arises is whether the assumptions made correspond to reality. In a broader sense, a health economic model would also have to include all other factors relating to cardiovascular risk and compare possible intervention approaches with regard to cost-benefit.	It was beyond the scope of this project to provide an overview of all the factors relating to cardiovascular risk, therefore we had to rely on the currently most often used cardiovascular risk score system in Switzerland, the AGLA risk score. In addition, it was beyond the scope of the project to evaluate other interventions than mentioned in our PICO (i.e. statins licensed in Switzerland compared to placebo, or no treatment, and/or adaption for lifestyle (i.e. reduction in smoking or smoking cessation, diet adaptation, or increasing physical activity).
AGLA/SGK	The health economy data confirm that the use of statin for prevention of atherothrombotic events is mostly cost-effective. The data by Pencina et al (Circulation. 2020;142:827–837) should also be taken in consideration. The lack of health economy data for Switzerland is a major limitation.	The Circulation. 2020;142:827–837 publication of Pencina et al. is published after the closing date of our systematic literature search and therefore not assessed in full text. This study did not report on observed data and therefore did not fulfil our inclusion criteria and would have been excluded. However, the findings in Pencina et al. are comparable to our finding that starting statin therapy in younger adults is associated with a higher number of CVD events prevented.

Comments on ethical, social and legal domains

Stakeholder	Stakeholder comment	Response
MFÄF	No comments.	-
VEMS	This section has to be rewritten completely. It is driven by a perception, where established medicines are falsely claimed to have exaggerated positive effects while side effects are hidden from health care authorities, who themselves do not appropriately address the safety of statins all over Europe (Jeffersen et al). This single center Cochrane Statement from Norway get's an unjustified attention from the Authors and points to the fact, that they favor the deliberate	This section is a summary of the published evidence on legal domains. The section clearly states that we summarize the findings of the study of Jefferson et al. If we would have identified studies that proved the contrary, those studies would also be mentioned, but this was not the case.

	spreading of such fake informations.	
VEMS	Disutilites are not discussed appropriately and largely depend on prior assumptions of the interrogated persons, with many influences that are completely unstable and can have variation effects from 0 to 100. This instability of QALY assumptions should be named by Authors, because it is here were in fact a large amount of information exists.	The disutilties of MI and stroke were based on previously published literature and were varied in scenario and sensitivity analyses. In contrast to what the stakeholder suggests, our one-way sensitivity analysis showed that the relative difference of a disutility 20% lower and higher than the base-case estimate was limited (3.34% for stroke and 0.32% for MI). The scenario analyses on the duration of disutilities of MI and stroke also showed that the impact of these assumptions on the cost-effectiveness results were limited: lifetime disutility after MI instead of one-year lowered the ICER with 7% and a 1-year disutility after stroke instead of lifetime increased the ICER with 8%.
santésuisse	**Original comment:** Die in diesem Kapitel aufgeführten Resultate zeigen einige interessante Aspekte auf. **Translated comment:** The results presented in this chapter reveal some interesting aspects.	-
Curafutura	**Original comment:** Im Rahmen einer langandauernden medikamentösen Prävention wäre eine vertiefte Auseinandersetzung mit den unerwünschten Wirkungen und Folgen wünschenswert. Hier fehlt im HTA-Report die kritische Auseinandersetzung mit dieser Thematik. **Translated comment:** In the context of long-term drug prevention, an in-depth examination of the side effects of statins and consequences would be desirable. The HTA report lacks a critical discussion of this topic.	In Chapter 7.2.6 we present our findings concerning the safety of Statins. In the summary statement we state: 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. It is not possible to draw a conclusion on the adverse event myalgia, because the results of the two SRs are inconsistent.
AGLA/SGK	Any limitation of statin prescription will represent a very important ethical issue if some groups of persons/patients are excluded because of economical issues. This would affect mostly vulnerable persons/patients. The conclusion that there is limited evidence for starting statin treatment in older people with low CVD risk should not be translated into the request to stop statin treatment at a certain age, because stop of statin treatment was found to increase the risk of cardiovascular events. Moreover, we face a big difference between biological and chronological age, a factor that clinicians should take in consideration for personalised medicine.	We acknowledge the ethical issues on discontinuation of statin therapy. It is however beyond the scope of an assessment report to connect it with an appraisal judgement.

Comments on organisational domain		
Stakeholder	**Stakeholder comment**	**Response**
MFÄF	No comments.	-

VEMS	The impact of negative reports about statins in public media has not been addressed at all. Many obeservational studies found an increase of cardiovascular deaths and events after negative reports in the press about statins.	The impact of media coverage reported in the published literature was summarized in chapter 9.2.4.
VEMS	Also, Authors should make comments on the negative impact in public media of the SMB report 2013 on statins, which is a on point narrative calculation which has been completely falsified by the Authors in the present statin HTA report.	As requested by the FOPH, the findings on organisational issues were only based on published scientific literature as identified by our literature search. The negative impact in public media of the SMB was not discussed in the published literature.
santésuisse	**Original comment:** Es werden hier verschiedene und interessante, organisatorische Faktoren aufgezeigt, die den Einsatz und die Einnahme von Statinen beeinflussen. Unklar bleibt, ob verschiedene Faktoren in verschiedenen Ländern unterschiedlich ausgeprägt zu beobachten sind. Damit bleibt auch offen, welche Faktoren in der Schweiz relevant sind. **Translated comment:** Various and interesting organizational factors are shown here that influence the use and intake of statins. It remains unclear whether different factors can be observed differently in different countries. This also leaves open which factors are relevant in Switzerland.	-
Curafutura	**Original comment:** Es stellt sich die Frage warum das BAG den gestellten Antrag nicht sorgfältiger bearbeitet hat. Es besteht nun der Eindruck, dass die gleichen Antworten wie auf das parlamentarische Postulat von NR Fridez (im Antrag zitiert) geliefert wird. Für den Antragsteller stellt sich die Frage nach dem Sinn und der Zielsetzung von HTAs. Wenn sie lediglich dazu dienen, das Bestehende zu bestätigen und nicht vertieft zu hinterfragen, dann ist das HTA-Programm des Bundes eine nutzlose Verschwendung von Steuergeldern und kein Beitrag zur Optimierung der verwendeten Ressourcen im Gesundheitswesen. **Translated comment:** The question arises why the BAG did not process the application more carefully. There is now the impression that the same answers are provided as to the parliamentary postulate of NR Fridez (quoted in the motion). For the applicant, the question arises as to the meaning and purpose of HTAs. If they only serve to confirm the status quo and not to question it in depth, then the federal HTA program is a useless waste of taxpayers' money and no contribution to optimizing the resources used in the health care system.	A HTA report evaluates the available evidence that answers an original research question. When an application question contains subjective elements, covers more than one research question or addresses appraisal issues, the HTA team may have to reformulate the research question. The applicant was given the opportunity to comment the potentially reformulated research question during the scoping report consultation round. Once the PICO is definitive (after the scoping report review), it can no longer be changed.
AGLA/SGK	As the author conclude "As there are 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" The comment on statin in obesity doesn't fit well to this part and the evidence shown is weak and not helpful for the purpose of the document.	We agree with the stakeholder’s comment on the paragraph on statins in obesity patients and removed it from the report.

Comments on discussion and conclusion		
Stakeholder	**Stakeholder comment**	**Response**
MFÄF	No comments.	-
VEMS	Few information on efficacy limitations in a real-world setting is not appropriately discussed. Studies like WOSCOPS longterm have cleary shwon the effects of statins on long-term safety and efficiency after the randomized study period.	The long-term WOSCOPS (=West of Scotland Coronary Prevention Study) data is taken into account in the included SRs of Yebyo et al. and Taylor et al. Only two effectiveness studies could be included in this HTA which were in line with our research objective and PICO. Most data in real-world settings compare two types or two different doses of statins, this comparison was out of scope for the HTA.
VEMS	Cost-efficiency is not appropriately discussed and the impact of the error on stroke probabilities in AGLA is not mentioned. Authors should positively state, that based on their initial calculations, statins are cost-effective at the 100 000 / QALY level in almost all risk levels (except AGLA 1%) and that after correction of the error from STROKE 15.7% to 18%, statins are even more cost-effective.	We would like to thank the stakeholder again for pointing out the calculation error in the previous version of the report. However, there is no additional value for the public to publish an an error made in an intermediate report of the HTA development process.
VEMS	Further it should be discussed that with the inclusion of unstable angina and coronary revascularization prevention cost-effectiveness further increases in statin adherent patients.	This limitation was already acknowledged in the discussion of the report and also states that, as a consequence of excluding these CVD events the benefits of statin therapy may be higher than reported in this report.
VEMS	Further, Authors should state a threshold for men and women, up from which statins are costeffective at <100 000 / QALY, probably at AGLA 3% risk (...no room for more)...	The objective of this study was to inform the FOPH on the cost-effectiveness of statins in primary prevention in different CVD risk groups. Defining a specific cut-off point is out of the scope of this study.
santésuisse	**Original comment:** In der Diskussion und den Schlussfolgerungen werden in kurzer Form die wichtigsten Erkenntnisse des vorliegenden HTAs zusammengefasst. Dies entspricht den in den verschiedenen Kapiteln erfolgten Ausführungen. Dabei werden jedoch deutlich die zahlreichen Grenzen wie auch die fehlenden Evidenzen einerseits der berücksichtigen Literatur und anderseits des hier erfolgten HTAs aufgezeigt. Wie bereits in früheren Literaturen bekannt, bleibt der effektive Nutzen in der Anwendung von Statinen im klinischen Alltag / real world in der primären Prävention in den verschiedenen Risikogruppen unklar. Dennoch sollte eine verstärkte Regulierung des Statineinsatzes auf u.a. Patienten mit bestimmtem CVD-Risiko kombiniert mit Fragen der Compliance etc. zumindest geprüft werden, auch wenn der effektive Nutzen und die damit verbundenen Kosteneinsparungen nicht vorgängig bezifferbar sind. **Translated comment:** In the discussion and the conclusions, the most important findings of the present HTA are summarized in a short form. This corresponds to the statements made in the various chapters.	-

	However, the numerous limits as well as the lack of evidence on the one hand in the literature considered and on the other hand in the HTA carried out here are clearly shown. As already known in earlier literature, the effective use of statins in everyday clinical practice / real world in primary prevention in the various risk groups remains unclear. Nevertheless, increased regulation of statin use should include: Patients with a certain CVD risk combined with questions of compliance etc. are at least checked, even if the actual benefit and the associated cost savings cannot be quantified in advance.	
Curafutura	**Original comment:** Im Bericht wird zusammengefasst, dass die Evidenz aufgrund fehlender Studien nur schwer übertragbar ist auf die breite Bevölkerung (real world setting) und die cost-effectiveness von einzelnen Parametern abhängt und damit nicht abschliessend geklärt ist. Diese Unsicherheiten sollten in der Diskussion klarer zum Ausdruck kommen. Des Weiteren fehlt in der Diskussion eine Auseinandersetzung mit der vorhandenen kritischen Literatur. Kritische Literatur bezüglich dem unkritischem Einsatz von Statinen in der Primärprävention ist vorhanden (siehe ursprünglicher Antrag und (https://www.media.uzh.ch/de/medienmitteilungen/2018/Statin.html) und sollte hier miteinbezogen und die Resultate des HTAs in deren Relation gestellt werden. Die Schlussfolgerungen fassen in der vorliegenden Form nur die Kostenfolgen und die Resultate der cost-effectivness Analyse zusammen. Auch dort sollte zum Ausdruck kommen, dass die Evidenz bezüglich Efficiency fehlt. **Translated comment:** The report summarizes that, due to the lack of studies, the evidence is difficult to transfer to the general population (real world setting) and that the cost-effectiveness depends on individual parameters and is therefore not conclusively clarified. These uncertainties should be more clearly expressed in the discussion. Furthermore, the discussion does not deal with the existing critical literature. Critical literature on the uncritical use of statins in primary prevention is available (see original application and (https://www.media.uzh.ch/de/medienmitteilungen/2018/Statin.html) and should be included here and the results of the HTA in their relation. In the present form, the conclusions only summarize the cost consequences and the results of the cost-effectiveness analysis. There, too, it should be expressed that there is a lack of evidence regarding efficiency.	The discussion was modified accordingly, addressing efficacy, effectiveness and safety is a more equal manner. The limitations of our studies and evidence gaps that were identified are discussed in the discussion. The literature on the uncritical use of statins due to adverse events is discussed in Chapter 7.2.6. In most studies, treatment with statins did not result in an increased risk of adverse events and there are limitations with regard to the definitions of these outcomes in the RCTs. The meta-analysis underlying the study of Yebyo et al. the stakeholder is referring to did not consider differences in follow-up duration between the trials. Therefore, we performed a random-effects meta-analysis using inverse variance weighting based on the number of follow-up patient-years. The results of our analysis presented in Table 8.10 showed that it is very uncertain if statin use is associated with an increase in the adverse events myopathy, rhabdomyolysis, hepatic dysfunction and renal dysfunction (i.e. the 95% confidence intervals of the incidence rate ratios all include 1). A summary of the evidence on efficacy, effectiveness, and safety was added to the discussion.
AGLA/SGK	The discussion is balanced but some conclusions are not evidence-based and not applicable to the Swiss situation due to lack of specific data.	The limitations of our studies and evidence gaps that were identified are discussed extensively in the discussion. We are not aware of any conclusions that were not evidence-based