Urgent Feedback reply to Q Dr Romanens:

Stakeholder Feedback	Response
I would like to point out already now that a **fundamental mistake** has been made. With the AGLA calculator, the absolute risk in, to suffer a fatal **coronary** event or a non-fatal myocardial infarction within 10 years can be calculated. This corresponds to the mortal or non-fatal **CHD** (coronary heart disease) risk. However, the report erroneously states, with reference to the AGLA website (reference no. 79), that the AGLA calculator would calculate non-fatal (CHD) and fatal **CVD** (cardiovascular disease) (see Table 3.1 and Box 1 in the report). This is incorrect. Fatal strokes are not included in the AGLA calculator. Thus, the HTA report is based on a wrong premise, which of course falsifies all further calculations.	We would like to thank the reviewer for looking at the HTA report in detail and bringing this issue to our attention. Indeed, the model did not include all CVD deaths due to a misinterpretation of the AGLA risk scoring system on our end. We adjusted our calculations to correctly include coronary heart disease deaths using the AGLA and add to this the risk of deaths due to other heart diseases, cerebrovascular diseases (i.e. including stroke), and other diseases of the circulatory system. The details of this calculation are provided in the enclosed updated version of the report. As a result of this correction, the number of MIs, strokes, and CVD deaths increased. Consequently, the benefits of using statins increased and the ICERs decreased. Despite the reduction in the ICERs, the general main conclusions in our report did not change due to this correction. This means that we agree with you that statins are cost-effective for most subgroups and disinvestment may only be considered in patients with a low AGLA risk score, especially those with an AGLA risk of 1% or lower at a high age.
A further problem is the fact that PTCA and CABG must also be considered in the CVD, as statins also prevent such interventions.	We are aware that statins can also prevent the need for revascularization procedures such as PTCA and CABG. We discussed the events to include in our model with our clinical expert who advised us to focus on the major events of MI, stroke and CVD (and the most important adverse events of statins). Other events, such as revascularization and unstable angina have been discussed as well. Together with our clinical expert and the FOPH we decided not to include these events explicitly. In the case of revascularization, the model includes PTCA and CABG costs if the simulated patient experiences MI. If an MI event is prevented due to statins, savings occur in the model for the prevented treatment costs of MI, which can include the costs of revascularization procedure.

	Because we agree that this is an important subject that deserves attention our report, we add a limitation to the discussion section in our report to emphasize that the health economic model is a simplification of the complex reality of cardiovascular disease and that the exclusion of other CVD events (such as revascularization intervention) may result in an underestimation of the benefits of statins.
I therefore think it would be useful if you could pass on my fundamental objection to the report authors for examination and, if the error is accepted, the report would be completely rewritten. This is because the error has considerable consequences for the thus underestimated cost-effectiveness of statins in the low-risk range. CHD (AGLA) x 2 = CVD can be used as a rule of thumb	As described above, we corrected this mistake and adapted the results accordingly. Instead of the rule of thumb mentioned by the reviewer, we used data from Eurostat for Switzerland in 2017 on the proportion of coronary heart disease deaths of all cardiovascular disease deaths (more details are provided in the updated report). This data supports the rule of thumb described in this comment. For example, an AGLA risk of 10% is now equal to a total CVD risk of 22.0% instead of 15.7%).
Second e-mail: According to Box 1 calculation, AGLA is 10% = risk 15.7% if you calculate wrong, and is 21.2% if you calculate right (if fatal stroke and fatal AMI 1:1), plus CABG and PTCA with relative 36% (https://cardiologyres.org/index.php/Cardiologyres/article/view/1067), then we are at 28.9%. That means, if you define ASCVD as stroke / AMI then AGLAx2=CVD, if you define ASCVD as stroke / AMI / clinical CAD then AGLAx3 = CVD. A low AGLA risk is not a low CVD risk (https://www.zora.uzh.ch/id/eprint/165634/1/1-s2.0-S2211335518302754-main.pdf) compared to SCORE. The cost effects of statins are stroke, / AMI / clinical CAD. For these events there is no longer any doubt about the cost-effectiveness of statins in primary care.	If we understand correctly, this comment explains what the impact of (1) correcting our mistake in the interpretation of the AGLA and (2) including clinical CAD (i.e. revascularization using CABG and PTCA) would be on the AGLA risk. (1) We did correct our mistake of the interpretation of the AGLA risk and indeed the total risk in the example now increases from 15.7% (in the old version of the report) to 22.0% (in the correct version of the report). (2) As described above, we made a deliberate choice together with our clinical expert and FOPH not to include revascularization before the occurrence of MI in our model. But we agree that this may underestimate the cost-effectiveness of statins and therefore we added this to the limitation section of our study.