

To:

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Dear colleagues

As noted in the SMB report on Statins, you are called-in experts. A few weeks ago, I was able to publish arguments against the report in the Swiss Medical Journal¹ and an oral presentation at the annual meeting of the Swiss Society of Internal Medicine, Basel, 2015². The answers to my arguments were given by the SMB and by Prof. Christoph A. Meier³. Apparently, these authors did not sufficiently understand my points, and none of these authors is a member of AGLA, the Swiss authority for the definition of lipid guidelines.

I would like to share some considerations with you in order to receive your opinion, because the SMB report on statins contains 3 important falsifications which are in part due to a statistical utilitarian bias.

Appropriateness and effectiveness are two key points in medical daily decision making, when we apply a medical intervention. The SMB touches upon both by issuing a guideline that says not to use statins in primary care when ESC risk is below 7.5% in 10 years⁴. The calculations of the SMB are based upon the CTT report 2012, where effectiveness was found to be 11 avoided major cardiovascular events in 1000 persons in 5 years per 1.0 mmol/L LDL reduction. Second, the SMB used a self-developed model on costs per QALY.

The following considerations touch upon the effectiveness; herein I do not give considerations about the QALY concept of the SMB, which is per se problematic.

If we accept the costs per QALY assumptions of the SMB, I can now present the number associated with the effectiveness. First, it has to be said that the above-mentioned CTT finding is an aggregation of well-established effects of statins in people with a risk for major coronary events that falls below 10% in five years⁵. These subjects under investigations were in fact all below the high risk threshold of 20% in ten years for fatal and nonfatal myocardial infarction. The SMB calculates that for an ESC risk (for fatal heart attacks only) of 5% in 10 years or, by inference of 2.5% in 5 years, an about four times higher risk for nonfatal myocardial infarction can be expected, which ends up with a risk of 10% in 5 years. The SMB assumes that in subjects with ESC threshold of 5% in 10 years, costs per QALY would be about 210'000 Swiss Francs. Further, they calculate that at an ESC threshold of 7.5%, cost per QALY would still be very high, eventually 160'000 Swiss Francs.

The SMB assume that 11 myocardial infarctions are preventable for a group of 1000 subjects in 5 years for an ESC risk threshold of 5% in 10 years. Using a relative risk reduction for fatal myocardial

¹ <http://www.saez.ch/docs/saez/2015/22/de/SAEZ-03514.pdf>

² <http://www.docfind.ch/QALY.pdf>

³ <http://www.saez.ch/docs/saez/2015/22/de/SAEZ-03678.pdf>

⁴ We are not talking here about familial hypercholesterolemia

⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22607822>

infarction of 22% and for nonfatal myocardial infarction of 22%⁶, therefore, 50 major coronary events (MCE) should occur in order to be able to avoid 11 MCE in 1000 subjects in 5 years. This corresponds however not to a 10 year 5% ESC risk for which costs per QALY of 210'000 SFr were calculated by the SMB, but to an ESC risk of 0.91% in 5 years⁷. In fact, for an ESC risk of 2.5% in 5 years, costs per QALY are 53'110 SFr in 5 years, and for an ESC risk of 5% in 10 years, costs per QALY are 17'081 SFr (Figure 1), when using the correct relative risk reductions, costs per QALY would be -5'339 SFr⁸. What is the reason for this obvious falsification?

In the CTT metaanalysis, see webfigure 8 of their appendix, the cardiac death rate in the control group was 1:1000 and 7.5:1000 in the two lowest risk categories, therefore 4.25:1000 or 0.4%; for the intervention groups, cardiac death rate in 5 years was 2.8:1000 or 0.3%. At 10 years, the ESC death rate would be 0.8% in the control group and 0.6% in the intervention group.

In the CTT analysis, webfigure 5 of the appendix, the cardiac death and nonfatal myocardial infarction rate in the control group was 9.5:1000 and 39.5:1000 in the two low risk categories, therefore 24.5:1000 or 2.5%; for the intervention groups, this rate at 5 years was 15:1000 or 1.5%. Therefore, for 1.0 mmol/L LDL reduction in 5 years, risk was reduced by about 10:1000, which is about the effect that the SMB used for their calculations (absolute risk reduction 11:1000).

First falsification

When the SMB says that the effect of statins in their model pertain to an ESC risk threshold of 5% in 10 years, for which costs/QALY are 210'000 SFr, where instead this effect pertains to an ESC risk of 0.4%, which is about ten times lower, then the SMB commits a first falsification of medical evidence. The correct wording is: "In a group of subjects who all had an ESC risk lower than 5% in 10 years and a ESC event rate for fatal myocardial infarction of 0.9% (in the SMB Model) and 0.4% (in the CTT study), the statin effect was observed to reduce major cardiovascular events by 11:1000 at costs of 210'000 SFr per QALY". Therefore, the falsification is to say: costs per QALY are 210'000 SFr in all people below ESC risk of 5% in 10 years where in fact this is true for 0.9% (or in reality: in 0.4%) risk in 5 years to experience a fatal myocardial infarction. The same is true for the 160'000 costs/QALY at the 7.5% ESC risk threshold.

⁶ A relative risk reduction of 22% is an established aggregated value per 1.0 mmol/L LDL reduction when dealing with major vascular events. The details of the calculations are available at: <http://www.docfind.ch/QALYVarifo.xlsx>

⁷ However, based on CTT 2012 Appendix Webfigure 5, relative risk reduction is 20% for fatal myocardial infarction and is 42% for nonfatal myocardial infarction in subjects with a 5-year risk below 10% in 5 years for MCE per 1.0 mmol/L LDL reduction. If we enter these numbers in the QALY model of the SMB, costs per QALY become 129'431 SFr.

⁸ Using instead a 20% relative risk reduction for fatal myocardial infarction and a 42% relative risk reduction for nonfatal myocardial infarction, costs per QALY at 10 years for an ESC risk of 5% would be -5'339 SFr.

Second falsification

In the corrected version of the SMB statin report in Mai 2014, a small footnote that appears only in the abstracts (German, French, and Italian) says, that due to an inconsistency in the formula detected by an expert in the field, statins are not indicated at an ESC risk below 7.5% instead of 10%. However, there is no formula presented in the report that creates a connection between the costs per QALY calculation and this cutoff for statins at an ESC risk of 7.5%

The second falsification is committed by the fact, that the SMB pretends, that they used a formula that finds that statins are not cost-efficient at an ESC threshold below 7.5%, where in fact there is no such formula.

Therefore, the SMB calculations are correct, if each of these 1000 subjects has the same baseline aggregated coronary risk of ESC 0.91%⁹, which according to the SMB assumptions, corresponds to a MCE risk of 5% in 5 years. There is no formula that calculates, how an MCE risk of 5% at five years should led to a recommendation to avoid statins in risks below ESC 7.5% in 10 years.

As the SMB states, with higher risk, the NNT goes down, as do the costs per QALY. They calculate that at a risk threshold of ESC 7.5% in 10 years 2.5 fatal and 11.25 nonfatal myocardial infarctions will be prevented. Using these numbers with a total of 13.75 prevented MCE in 5 years (that is 27.5 in 10 years or 2.75%), they find costs per QALY to be 160'000 Sfr. However, for these costs per QALY, the ESC risk is 2.3% and not 7.5%. Further, cost per QALY of 160'000 pertain to an ESC risk of 1.14% in 5 years; in 10 years, we expect 5 instead of 2.5 avoidable deaths, which corresponds to an ESC risk of 2.28% in 10 years and the avoidance of these events costs about 70'000 Sfr per QALY and not 160'000. At a risk threshold of ESC 7.5%, costs per QALY are 2'089 Sfr, because at this risk 75 fatal myocardial infarctions are expected to occur, and according to the SMB assumptions, another nonfatal number of myocardial infarction will occur (N=338), therefore at this risk of 7.5% in 10 years, 413 myocardial infarctions will occur, and of these 22% can be prevented, that is 91 prevented myocardial infarctions in 10 years (and not 27.5).

By simply applying the calculations of the SMB to various ESC risk threshold, we immediately see, that the SMB operates with falsified numbers: they allocate costs per QALY to the wrong risk threshold with falsifying factors between 3 and 5.

From a utilitarian view of this problem, I understand that statins have to be rationed, in order to save resources for a (better?) allocation in the population. As Prof. Stefan Felder stated at an open public meeting on May 5th, 2015 (about the value of the life of a human being), there exists a legal request to ration health care expenditures in Switzerland. The SMB has apparently detected statins as a field for possible rationing in primary care, but they did not declare this as such.

In this section, I make a short fact check in 5144 healthy subjects from Germany and Switzerland. They have an average age of 51±11 years and their 10 years ESC risk is 1.0%±1.3%. The following question is: how many of these subjects have an ESC risk ≥7.5%? There are 30 subjects or 0.6%. At 5% ESC risk, we find 2% with this risk, at 4% ESC 3.9% and at 3% ESC risk 7.4%. Therefore, there is no risk of a statin plethora in primary prevention of myocardial infarction (Figure 1). Further, costs/QALY at the ESC risk level of 7.5% are 2'000 and not 160'000 Sfr.

⁹ If again we use the correct relative risk reduction, costs per QALY of 210'000 would be obtained at an ESC risk of 0.63% in 5 years.

Now let me look at a cabinet of a Physician. On Monday, a patient comes in. The GP measures blood pressure and so on and finds an ESC risk of 0.91% in five years. He considers a low dose statin in this patient and thinks that the patients LDL will probably be reduced by 1.0 mmol/l. He uses his calculator that includes the SMB assumptions and finds an NNT of 91 for costs per QALY of 210'279 Swiss Francs. He then recalls the established guidelines and says, well, for that risk I would never treat a patient with statins anyhow. Just for fun, he then calculates for this patient costs per QALY if he would treat this patient for 10 years instead of 5 years and he finds a NNT of 45 and cost per QALY of 95'666 Swiss Francs, and he shakes his head again and says no way should I treat this patient with a statin. But why is the effectiveness so low in this patient? Based upon the CTT study, the risk of fatal myocardial infarction is reduced by 2 in 5 years per 1.0 mmol/l reduction, if this patient has a baseline risk of 0.91 fatal myocardial infarctions in 5 years. So, despite an acceptable relative risk reduction of 22%, the absolute risk reduction is 1.1% and therefore very low.

The next day, another patient comes in. The GP performs again the ESC risk calculations and finds a risk of 7%. He recalls the SMB guideline and thinks, well, again no indication for statins, in view of the very high costs per QALY in subjects with a risk below 7.5%. Nevertheless, he has a brief look at his calculator. So he sees that his patient has a risk for fatal myocardial infarction of 70/1000 in 10 years or 35/1000 in 5 years of which 15 and 7.5 can be avoided respectively. For 10 years he finds a NNT of 12 and for 5 years an NNT of 24. Interestingly, costs per QALY are 4'231 Swiss Francs for 10 years statin treatment and are 27'409 Swiss Francs in 5 years. Anyway, he dismisses this patient without a statin treatment, because the SMB says not to treat subjects below an ESC risk of 7.5% in 10 years. However, some doubts arise about this recommendation. He goes through his electronic record of patients and tries to find out, how many of his patients reach an ESC risk of 7.5% in 10 years. After going through more than 1'000 records of patients below the age of 65, he finds 3 cases. Now, this GP has a heretical thought: why measure cholesterol at all, if it would not be lowered anyway?

This GP has now a conflict. The SMB recommends not treating subjects with an ESC risk below 7.5% in 10 years, because costs per QALY are 160'000 Swiss Francs in this group. But when he looks at individual patients, costs are dramatically less in most cases that seek his attention for primary prevention of heart attacks. Why do patients not adhere to their expected average risk, why are they reluctant to fulfill the assumptions of the SMB?

The SMB issues guidelines based upon a unique ESC risk of 0.9% at the individual level for myocardial infarction for a group of 1000 patients. Although the calculations are correct for this aggregated average risk lowering capacity of statins in subjects with an MCE risk **lower than** 5% in 5 years, they are never correct at the individual level, unless an individual has exactly the coronary risk upon which the SMB bases his assumptions¹⁰.

¹⁰ As stated earlier, using the correct relative risk reduction that can be achieved with statins, the SMB calculations disfavor the beneficial statin effects by 16% relative risk reduction.

Third falsification

By pretending, that relative risk calculations are not relevant in the presented context, the SMB creates a falsification of well-known and widely established calculations in the literature about medical prevention.

In the reply, the SMB says, “relative risk reduction is not relevant”¹¹. They wish to apply a uniform absolute risk to a population with different pretest-probabilities at the individual level, which is a technical error. At the individual level, pre-intervention risk probabilities determine the efficiency of a medical intervention. With higher risk probabilities, as you know well, the effect of medical intervention is higher. So, if we have a patient with an ESC risk of 5% in 10 years, we can reduce this risk by 1.1% (absolute fatal myocardial infarction risk reduction 1.1%, NNT 91). By using the SMB assumptions with 4 nonfatal myocardial infarctions per fatal myocardial infarction we get an ARR of 5.5% (NNT 18). If we use a lower risk probability, e.g. 9 fatal myocardial infarction in 10 years in 1000 patients, we get an ARR of 0.2%, a NNT of 505 and at the level of MCE an ARR of 1.0 % with a NNT of 101. By saying, relative risk reduction is not relevant, the SMB eliminates the mathematical possibility to create estimates about medical benefits at the individual level.

Statistical Utilitarian Bias

Obviously, now a “**Statistical Utilitarian Bias**” becomes apparent: ***“The utilitarian bias occurs when medical effectiveness, eventually on behalf of falsification, is mathematically biased to lower risk reductions than published; or when medical effectiveness with a constant relative risk reduction is measured for shorter observation times; or when evidence based medical effectiveness is reduced to an aggregated (average) pre-intervention risk without integrating pre-intervention effectiveness into individual risk and effectiveness calculations”***. The utilitarian bias contains therefore several elements, and one may occur without the other; and this is only a selection of the utilitarian bias, which has much more impact when we consider other mechanisms such as the Simpsons Paradox, aggregation bias and correlation biases.

The SMB report about statins is a utilitarian report. Because this report is based on a utilitarian economical view of patients, where they should all fall into the same aggregated average and very low risk coronary pretest stratum. In reality, this is of course completely wrong and clearly contradicts the Cochrane Report about use of statins in the primary prevention of cardiovascular diseases¹²: ***“Of 1000 people treated with a statin for five years, 18 would avoid a major CVD event which compares well with other treatments used for preventing cardiovascular disease. Taking statins did not increase the risk of serious adverse effects such as cancer. Statins are likely to be cost-effective in primary prevention.”***

¹¹ <http://www.saez.ch/docs/saez/2015/22/de/SAEZ-03678.pdf>

¹² Statins for the primary prevention of cardiovascular disease (Review) 2. The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

In summary, the SMB report is irresponsible and contains 3 important falsifications. The issued guideline will, if followed as such by GP's, increase the numbers of avoidable deaths and myocardial infarctions in Switzerland. Therefore, the report has to be withdrawn or the falsifications have to be eliminated.

The report does not deal with the GP's and his patient's medical reality and is obviously a falsification with the only goal to almost completely ration statins in primary prevention. Further, the SMB recommendation is a clear violation of the legal claim about the Excellency of the Swiss Medical Health Care system, still a constitutional right.

In conclusion, Dear Colleagues, I ask you: can you lend your support to the SMB Statin report as it was issued in 2014, and if yes, I am greedy to hear your arguments, if not: what are your next steps to eliminate this report? Of course, I would also accept a new report with the correct numbers.

Best regards

Michel Romanens, MD

Figure 1: SMB falsification, where costs/QALY are said to be 210'000 at an ESC level of 5% (correct costs: 17'000 SFr) and 160'000 at an ESC Level of 7.5% (correct costs: 2'000 SFr).

