Medical Costs per QALY of Statins Using Swiss Medical Board (SMB) assumptions: Observed Effects in Two Large Primary Prevention Groups from Germany and Switzerland

A Vascular Risk Foundation Analysis

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Data Source
Database encompasses over 5'000 primary care subjects with data on file about all independent cardiovascular risk factors and total plaque area from both carotid arteries. The cohort is continuously updated. For more details refer to: https://sites.google.com/site/arteriscohorts/

Additional Material
www.docfind.ch/QALYVarifo2016.xlsx
www.docfind.ch/NTTSwitchTableHelp.xlsx
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Content

Abstract

Aims

The Swiss Medical Board (SMB) recommends use of statins in primary care, if risk for coronary death (ESC calculator) is above 7.5%, because cost per quality adjusted life years (cost/QALY) was calculated to be 210,000 CHF in 5 years. The effect of this recommendation on coronary risk management requires further examination.

Methods and Results

With the SMB model we calculate cost/QALY for five and ten years at different ESC risk levels. A real-life check was performed in 5,154 healthy subjects from Germany and Switzerland. Cost/QALY was 210,000 CHF in 5 years for an ESC risk <1%, 2,000 CHF in 10 years for an ESC risk of 7.5% and 32,000 CHF for an ESC risk of 3.75%. Using the SMB guideline, the probability for statin treatments was reduced to almost zero in 5,145 subjects with a coronary risk equivalent defined by carotid ultrasound (TPA80, CH and DE prevalence 22% and 15% respectively).

Conclusion

Cost/QALY is dependent on the probability for coronary events with better cost-efficiency in higher risk subjects. High cost/QALY (>210,000 CHF) is only correct for an ESC risk <1%; the ensuing SMB recommendation to use statins only above the 7.5% ESC risk threshold cannot be derived from the SMB model. In a CH/DE real-life evaluation we found the SMB ESC 7.5% threshold not to be a preventive option in subjects with a coronary risk equivalent defined by TPA80. We found that adherence to the SMB recommendation is likely to increase cardiovascular disease and associated costs in Switzerland.

Introduction

The Swiss Medical Board (SMB) published a report showing costs per quality adjusted life years (cost/QALY) to be extremely unfavorable (CHF 210,000/QALY) for statins in primary care in Switzerland. These costs/QALY pertain to an ESC risk (risk of death from ischemic heart disease) of 0.9% in 5 years. In the final report it was recommended however, that statins should be used in primary prevention only, if ESC risk is at least 7.5% in 10 years[1]. This recommendation is in sharp contrast to current guidelines, since it would allow to treat a risk for myocardial infarction in the Swiss population of about 40% in 10 years, if we replace ESC risk with Framingham risk.

Others made attempts to improve the prediction about who might benefit most from preventive statins. In a recent Framingham Offspring Study improved coronary risk stratification by the use of lower thresholds of coronary risk in younger subjects showed increased sensitivity at somewhat maintained specificity[2]. Further, higher levels of LDL cholesterol at same risk levels improves the prediction, who might benefit more from statins, an observation from the U.S. NHANES study published recently[3]. The US blood cholesterol guidelines published in 2013 created debates about very high numbers of patients qualifying for statin treatments [4]: over 80% of patients aged 60 years or older would require statins [5].

We aim to test various coronary risk thresholds in two healthy populations from Switzerland (CH) and Germany (DE) to detect coronary risk equivalents defined by the total carotid plaque burden and to determine cost/QALY for various risk factor based thresholds of ESC risk using the SMB assumptions in a study with a cross-sectional design.

Methods

Subject selection

The two groups of subjects were examined at a practice-based level. In the Swiss Imaging Center in Olten, subjects were referred by their general practitioner (GP) or self-referred (56% and 44% respectively) to the Vascular Risk Foundation (Olten, Switzerland). In the German Imaging Center in Koblenz, all subjects were referred within a working medicine setting. Subjects had to be free of cardiovascular symptoms or diseases: Diabetic subjects and those with previous cardiovascular disease were excluded from this analysis because they have a high coronary risk by definition. Laboratory values, blood pressure were measured locally and along with medical history entered into a data spreadsheet (Excel, Microsoft, Richmond, USA). In this study we used a case-control design for the performance of coronary risk equations to detect a coronary risk equivalent at the practice-based level.

Carotid Imaging

Presence and amount of longitudinal carotid plaque surface was imaged with a high-resolution ultrasound linear transducer using a 7.5–12.0 MHz probe, which identified all plaques defined by intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed up to compute the value for the total plaque area (TPA) in mm^2. All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. A TPA≥80 mm^2 (TPA80) defined a coronary risk equivalent (risk > 20% for fatal and non-fatal myocardial infarction in 10 years)[6].

Computation of Risk

Cardiovascular risk was computed using the published risk formulas in an excel spreadsheet (Excel, Microsoft, Richmond, USA). The PROCAM risk was calculated manually online, since the algorithm is not published. For Switzerland, PROCAM risk was multiplied by a factor of 0.7 (according to the Swiss AGLA guidelines 2014).

Effect Model of the SMB

The model of the SMB to calculate cost/QALY is as follows: for one fatal myocardial infarction (MI), 4.5 non-fatal MI shall occur; cost per fatal MI is CHF 8,500, per non-fatal MI is CHF 25,000 in the first year and CHF 8,000 in subsequent years loss of QALY is 1.0 for fatal and 0.2 for non-fatal MI; annual preventive medical cost per individual including statin costs CHF 470, all MI events occur uniformly after 50% of the total observation time. The SMB used an effect model of statins where two fatal MI and nine non-fatal MI in 1,000 persons in 5 years are prevented. Loss of QALY at 2.5 years was therefore 2x2.5x1QALY = 5.0 QALY for fatal MI and 9x2.5x0.2QALY = 4.5 QALY, therefore 5.0+4.5 QALY = 9.5 QALY in 1,000 persons or 0.0095 QALY per person. When this effect model is applied to a 10 year period, then 4 fatal MI and 18 non-fatal MI can be prevented, therefore 4x5x1QALY = 20 QALY for fatal and 18x5x0.2QALY = 18 QALY for non-fatal MI or a total of 38 QALY losses can be prevented in 1,000 persons, which is 0.038 QALY per person. Therefore, the effect model is 4 times higher in 10 years when compared to 5 years. The SMB based its assumptions on the CTT study published in 2012 and on the effect of statins on LDL, which is assumed to be 1.0 mmol/l to obtain the herein mentioned preventive effects [7]. The SMB QALY calculator can be accessed online for further details and for calculation of examples [8].

Effects of statins in primary care

The aggregated relative risk reduction per 1 mmol/l LDL reduction is 22% [7, 9]; in order to calculate the number needed to treat to obtain the effect of the SMB, we used this relative risk reduction in our treatment and cost/QALY equations. This 22% relative risk reduction was chosen despite the fact, that in low risk subjects, relative risk reduction was shown to be 31% for major vascular events and 39% for major cardiac events (CTT Appendix 2012, web figure 5) [10].

Ethical considerations

For practice-based subjects referred by GPs or within the working setting, informed consent for imaging of carotid arteries and measuring coronary risk factors was the reason for encounter; further preventive therapies were left to the decision of the referring GP. In those self-referred subjects of the Vascular Risk Foundation, there is informed written consent and the study (Cordicare II) was approved by the joint ethical

committee of the cantons of Solothurn and Aargau.

Statistics

Sensitivity, specificity and predictive values and number needed to treat (NNT) were calculated using established formulas. Generation and comparison of ROC curves was performed using the Delong-Delong method [11]. The P-value for statistical significance was defined as $p < 0.05$. Computation was performed using MedCalc (MedCalc Version 13.3.3.0., Ostend, Belgium).

Results

On average, the Swiss group included older subjects than the German group (57±9 versus 46±10 years) and more women (49% versus 34%). The assessment of 10-year risk for both groups showed, that most subjects were in the low risk category. The prevalence of TPA80 was higher in Switzerland (22% versus 15%). Lipid profiles were comparable. Average coronary risk was low (Table 1).

According to the SMB, for 2 fatal 9 non-fatal MI can be prevented. Therefore the statin effect of 22% relative risk reduction per 1 mmol/l LDL risk reduction needs 9 fatal and 41 non-fatal MI, therefore a total of 50 MI, to obtain treatment effects [9]. This corresponds to a risk of 5% in five or 10% in 10 years. Since ESC count only fatal MI, the ESC risk of this population has to be 0.9% in 5 years or 1.8% in 10 years in order to obtain the expected effect with cost/QALY of CHF 210,279 (NNT 91). The SMB recommends however, not to use statins in people with a 10 year ESC risk of <7.5% instead of 1.8%. At an ESC risk of 7.5%, cost/QALY would be CHF 2,089 (NNT 11). For a threshold of NNT 22, statins (ESC threshold of 3.75% in 10 years) cost/QALY are CHF 32,073 (Table 2).

In the age groups 40-55, 56-65 and 66-75 years the threshold of ESC 7.5% was rarely reached. In the age group 40-55 years and at an ESC risk of 3.75% or less, the prevalence of TPA80 was 10.5% in 902 subjects in Switzerland and was 12.8% in 1729 subjects in Germany. At the SMB threshold of ESC 7.5%, no subject would meet the threshold for statins in the age group 40-55; in the age group 56-65, 0.3% would eventually be treated with a statin in Switzerland (in Germany 0.0% for ESC). In the age group 66 to 75 (only available for Switzerland), a possible indication for statins would be present in 1.3%. When defining treatment thresholds for statins for ESC (≥ 5.0%) and AGLA (≥10%), less than 4% of those having TPA80 would be treated in Switzerland in all age groups for ESC, less than 10% for PROCAM (Germany) and less than 4% for AGLA (Switzerland, Table 3).

In the group of subjects with TPA80 (N=935), 20 (2.1%) subjects had an ESC risk ≥7.5%. For thresholds that may define an indication for statin treatments (AGLA and PROCAM ≥ 10%, ESC ≥5%), the sensitivities were low and specificities were high for TPA80. In the younger age group (40-55) AGLA had a sensitivity of 19%, PROCAM 40%, CH-ESC 1%, and DE-ESC 0%. The highest sensitivity was observed for PROCAM in those aged between 56 to 65 years: 50% sensitivity, 75% specificity.

The diagnostic performance using receiver operating curves (ROC analysis) to detect TPA80 was not uniform among risk calculators. DE-ESC performed best wit 0.84 (95%CI: 0.83-0.86), second was DE-PROCAM with 0.83 (95%CI: 0.82-0.84, p=0.1097 versus DE-ESC), third was CH-ESC with 0.77 (95%CI: 0.76-0.79) and worst was CH-AGLA with 0.74 (95%CI: 0.76-0.79, p=0.0011 versus CH-ESC).

Discussion

First, by using the SMB calculator, we showed the expected dependence of cost/QALY from (a) coronary event probabilities and (b) durations of the statin use. Second, in a cross-sectional observation of health subjects with various amounts of advanced carotid atherosclerosis from Switzerland and Germany, we showed that the statin treatment recommendation of the SMB would leave virtually all patients with a coronary risk equivalent, defined by advanced carotid plaque formation, untreated.

Following the SMB assumptions but applying the calculations to different pre-intervention risks and two different durations of intervention, we used a *relative* risk reduction with statins of 22%[7], [10] and treatment effects of 10 instead of 5 years. We found cost/QALY decreases from CHF 210,279 in a low risk category (ESC 0.91% in

5 years, NNT 91) to CHF 2,089 in a high risk category (ESC 7.5% in 10 years, NNT 11, Table 2). Although there is no accepted threshold for cost-efficiency with respect to NNT, we calculated that at the NNT level of 25, cost/QALY would be CHF 40'251, which corresponds to a 10 year risk for myocardial infarction of 18%.

Contemporary US guidelines recommend to use statins (irrespective of the LDL level) based on the pooled risk equation (PCE) risk for major vascular events of greater than 7.5% and to consider statins starting from a PCE risk of 5.0% [12]. These numbers would correspond to an ESC risk of 1.7% and 1.1%. The British Health Care System (NICE) recommends a similar threshold[13]. Therefore, the SMB assumptions are not in line with these recommendations and raise the suspicion that the SMB is not sufficiently validated for correct cost/QALY calculations. Further, it does not incorporate indirect costs of an event, which further reduces its applicability.

In order to further study the effect of the SMB threshold (ESC risk 7.5% or more for an appropriate statin intervention in primary care), we used atherosclerosis imaging. Similar to coronary calcifications, the total carotid plaque burden contains important prognostic information and ability for reclassification [14]. We found that virtually all subjects with a high risk finding of carotid atherosclerosis (TPA80) would not qualify for a statin in all age groups (40-55, 56-65, 66-75, Table 3).

TPA80 is indeed a high risk finding for incident myocardial infarction: 6,257 subjects with 894 incident cases of myocardial infarction were observed over a median follow-up time of 15.4 years, TPA of 40±22 mm^2 derived from the right carotid artery was associated with an unadjusted coronary risk of 23.9% (95%CI: 21.2–27.1) in 10 years. The hazard ratio per 1-SD increase in TPA (2.43 mm^2) was 1.23 (95%CI: 1.15–1.32) using age as time scale and adjustments for sex, body mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and hypertension [6]. Therefore, we expect the SMB recommendation to have disadvantage effects at the population level, where preventive therapy should start early in life [15–18].

Conclusion

By applying the SMB recommendation of ESC 7.5% for an eventual statin eligibility and using a very conservative calculation for treatment effects of statins, such medication would virtually be eliminated from primary care. More traditional thresholds for statin eligibility (AGLA or PROCAM≥10%) showed sensitivities to detect TPA80 below 50% and for ESC≥5% 1% and 0% in Switzerland and Germany, respectively. Such findings may have implications for future guidelines to halt the epidemic of Atherothrombosis at the population level.

With regard to cost efficiency analysis, the results of greater than CHF 210,000 reported by the SMB can only be applied to an ESC risk of less than 1% with dramatic increases in cost efficiency up from an ESC risk of 3.5% and more, even if very conservative treatment effects of statins are computed. We found that the SMB guideline is not appropriate to decide about an eventual statin treatment in Switzerland and in Germany. Further, the SMB Guideline may pose a significant safety problem in subjects with low and intermediate coronary risk, especially those with advanced atherosclerosis.

Future costs per effect calculations should include direct and indirect costs of any cardiovascular event preventable by statins, baseline risk for such events, baseline LDL prior to statin intervention and the expected total cost of the preventive intervention. With these variables at hand, QALY can be eliminated from the calculator and cost-efficiency is likely to be calculated in a more realistic manner.

Tables

Table 1: Baseline Characteristics, prevalence of risk and average TPA for Switzerland and Germany

Baseline Characteristics	**CH**		**DE**	
Number of subjects (N)	2,203		2,942	
Female, N, %	1,083	49%	989	34%
Mean age (N ± 1 SD)	57 ± 9		46 ± 10	
Family history for CAD (N, %)	386	18%	660	22%
Current smoker (N, %)	458	21%	770	26%
Blood pressure systolic, mm Hg mean ± 1 SD	129 ± 16		123 ± 16	
TPA mm^2 mean ± 1 SD	52 ± 50		36 ± 50	
Individuals with TPA≥80 mm^2 (N, %)	484	22%	452	15%
Total cholesterol, mmol/l, mean ± 1 SD	5.9 ± 1.2		5.9 ± 1.2	
HDL cholesterol, mmol/l, mean ± 1 SD	1.5 ± 0.5		1.4 ± 0.4	
LDL cholesterol, mmol/l, mean ± 1 SD	3.7 ± 1.0		3.8 ± 0.9	
Triglycerides, mmol/l, mean ± 1 SD	1.5 ± 0.9		1.7 ± 1.2	
ESC average risk in 10 years (%± 1 SD)	1.5 ± 1.7		0.6 ± 0.3	
PROCAM average risk in 10 years (%± 1 SD)	6.2 ± 7.4		4.3 ± 3.5	
AGLA average risk in 10 years (%± 1 SD)	4.3 ± 5.2		-	

Table 2: cost/QALY calculations using the SMB assumptions for 5 and 10 years and different levels of coronary risk [8].

Duration of treatment effect (years)	**5**	**5**	**5**	**10**	**10**	**10**
Assumptions of SMB						
Fatal heart attack	1.0	1.0	1.0	1.0	1.0	1.0
Non-fatal heart attack (factor)	4.5	4.5	4.5	4.5	4.5	4.5
Cost of fatal heart attack	8,500	8,500	8,500	8,500	8,500	8,500
Cost of non-fatal heart attack (1st year)	25,000	25,000	25,000	25,000	25,000	25,000
Cost of non-fatal heart attack (after first 1st year)	8,000	8,000	8,000	8,000	8,000	8,000
statin and monitoring cost (per year)	470	470	470	470	470	470
Effect [(improvement of life) x (quality)]	9.5	26.1	39.2	78.4	104.5	156.8
Total cost (per 1000 individuals)	350,350	962,500	1,443,750	2,186,250	2,915,000	4,372,500
Total cost (per individual)	350	963	1,444	2,186	2,915	4,373
statin and monitoring cost (observation years)	2,350	2,350	2,350	4,700	4,700	4,700
Avoided healthcare costs	2,000	1,388	906	2,514	1,785	328
cost/QALY	210,279	53,110	23,126	32,073	17,081	2,089
Fatal AMI Risk in % in years	**0.91**	**2.50**	**3.75**	**3.75**	**5.00**	**7.50**
Number of individuals	1000	1000	1000	1000	1000	1000
Expected fatal heart attacks	9	25	38	38	50	75
Expected non-fatal heart attacks	41	113	169	169	225	338
Total amount of events (fatal & non-fatal)	**50**	**138**	**206**	**206**	**275**	**413**
Avoidable fatal heart attacks	2	6	8	8	11	17
Avoidable non-fatal heart attacks	9	25	37	37	50	74
Total amount of avoidable events (deadly & non-deadly)	11	30	45	45	61	91
Absolute risk	5	14	21	21	28	41
Avoidable risk	1	3	5	5	6	9
Number needed to treat (NNT)	**91**	**33**	**22**	**22**	**17**	**11**

Table 3: Coronary risk categories (ESC, AGLA, PROCAM) by age groups and percent of subjects with TPA80

CH	Age Groups	40-55	TPA80	56-65	TPA80	65-75	TPA80
ESC Risk	0.00-0.99	711	8.0%	298	9.1%	12	25.0%
	0.00-2.49	878	9.8%	665	20.3%	143	32.2%
	0.00-3.74	902	10.5%	763	23.2%	261	39.1%
	0.00-4.99	903	10.6%	807	24.5%	322	41.6%
	0.00-7.49	905	10.7%	827	24.9%	364	44.0%
	0.00-10.00	905	10.7%	833	25.2%	382	45.3%
AGLA Risk	0.0-3.9	693	7.2%	504	16.1%	129	33.3%
	0.0-9.9	845	9.3%	738	21.8%	301	41.5%
	0.0-15.0	885	10.4%	794	23.8%	352	42.3%
	0.0-20.0	898	10.6%	814	24.7%	368	43.5%
	0.0-30.0	905	10.7%	828	25.1%	382	45.3%
	0.0-40.0	905	10.7%	833	25.2%	386	45.3%

DE	Age Groups	40-55	TPA80	56-65	TPA80
ESC Risk	0.00-0.99	1509	8.9%	162	27.8%
	0.00-2.49	1718	12.4%	456	37.5%
	0.00-3.74	1729	12.8%	521	39.3%
	0.00-4.99	1729	12.8%	537	40.4%
	0.00-7.49	1729	12.8%	544	41.0%
	0.00-10.00	1730	12.8%	546	41.0%
PROCAM Risk	0.0-3.9	1171	5.6%	162	26.5%
	0.0-9.9	1542	8.6%	356	31.7%
	0.0-15.0	1648	10.8%	447	36.2%
	0.0-20.0	1691	11.5%	487	37.8%
	0.0-30.0	1717	12.5%	535	40.4%

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