Observed effects in two large primary prevention groups from Germany and Switzerland

Medical costs per QALY of statins based on Swiss Medical Board assumptions

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Summary

Aims: The Swiss Medical Board (SMB) recommends statins in primary care, if risk for coronary death or noncoronary vascular death (SCORE) is above 7.5% in 10 years, because cost per quality-adjusted life years (cost/QALY) is CHF 210 279 over 5 years. Rationale and effect require further examination.
Methods: The SMB cost-efficiency model is applied to 10 rather than 5 years, and for different risk levels for vascular events. These SMB recommendations were studied in a population of 5144 healthy subjects from Germany and Switzerland, in whom the prevalence of advanced carotid atherosclerosis (total plaque area ≥80 mm^2: TPA80) was assessed.
Results: Cost/QALY was CHF 210 279 in 5 years for SCORE risk of 0.91%. Cost/QALY was CHF 2089 in 10 years for an SCORE risk of 7.5% and was CHF 62 057 for a SCORE risk of 2.5%. At SCORE risk of ≥5% and ≥7.5%, respectively, 86% and 96% of Swiss and 89% and 96% of German subjects aged 40–65 years with TPA80, would be excluded from statin intervention.
Conclusion: Cost/QALY of statins is acceptable at a SCORE below 5%. The SMB recommendation to use statins only above the 7.5% SCORE risk threshold cannot be derived from the SMB model. The atherosclerotic burden in primary care is highly prevalent in patients with a SCORE below 5%. Adjustments to lower contemporary risk thresholds for statins should be discussed.

Key words: preventive medicine; QALY; atherosclerosis; carotid plaque imaging; statins

Introduction

The Swiss Medical Board (SMB) published a report showing costs per quality adjusted life years (cost per quality-adjusted life year [cost/QALY]) to be extremely unfavourable (CHF 210 000/QALY) for statins in primary care in Switzerland when administered for a 5-year period. In its final report, the SMB recommended that statins should be used in primary prevention only if the SCORE risk is at least 7.5% over 10 years [1]. This is in contrast to current Swiss guidelines, which recommend that patients with a risk of 5% in 10 years for fatal cardiovascular disease may be offered statin medication.

In a 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 low density lipoprotein (LDL) cholesterol at the same risk levels improved prediction of who might benefit more from statins (an observation from the U.S. NHANES study [3]). In the Copenhagen General Population Study, a SCORE threshold of 2.4% appeared sufficiently sensitive for the treatment of those with future cardiovascular events [4]. In 3172 subjects hospitalised for a first myocardial infarction in Switzerland, the sensitivity of a SCORE threshold of 5% was only 37%, and only 16% of these 3172 subjects were on statin treatment when the myocardial infarction occurred [5]. Therefore, clinical evidence suggests that the SCORE threshold for starting statin treatment, based on prevention of cardiovascular events, should be lower than 5% in 10 years, but costs/QALY have not been reported for lower decision thresholds in Switzerland and Germany.

We first aimed to determine cost/QALY for various thresholds of SCORE risk, using the SMB assumptions, for treatment periods of 5 and of 10 years. Second, we looked at the risk distribution for SCORE in two large primary care populations with advanced carotid atherosclerosis and tried to define a sufficiently sensitive SCORE threshold.

Methods

Subject selection

The two groups of subjects were examined at a practice-based level. In the Swiss Imaging Centre 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 Centre 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 and blood pressure were measured locally and these results, with the medical history, were entered into a data spreadsheet (Excel, Microsoft, Richmond, USA).

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 nonfatal myocardial infarction within 10 years) [6]. Intraobserver reproducibility (M.R.) was tested for the right carotid artery in 57 patients with a correlation coefficient of r^2 0.964 (left carotid artery: r^2 0.944, both arteries r^2 0.986). For the cutoffs of TPA 0–9 mm^2, 10–49 mm^2, 50–99 mm^2 and greater than 100 mm^2, the kappa value was 0.69 (95% confidence interval [CI] 0.54–0.84). The sensitivity to detect TPA80 was calculated for three SCORE thresholds (2.5, 5.0 and 7.5%).

Computation of risk

Cardiovascular risk was computed with the published risk formulas in an excel spreadsheet (Excel, Microsoft, Richmond, USA), with use of SCORE for low risk populations [7].

Effect model of the SMB

The SMB model for calculating cost/QALY is as follows. For one fatal cardiovascular event (myocardial infarction, stroke, coronary revascularisation), 4.5 nonfatal events occur. The cost is CHF 8500 per fatal event and CHF 25 000 per nonfatal event in the first year and CHF 8000 in subsequent years. Loss of QALY is 1.0 for fatal and 0.2 for nonfatal events. The annual preventive medical cost per individual, including statin costs, is CHF 470, all cardiovascular events occur uniformly after 50% of the total observation time of five years. Loss of QALY at 2.5 years was therefore 2 × 2.5 ×1 = 5.0 QALY for fatal events and 9 × 2.5 × 0.2 = 4.5 QALY for nonfatal events, and thus 5.0 + 4.5 = 9.5 QALY in 1000 persons or 0.0095 QALY per person. When this effect model is applied to a 10-year period, then 4 fatal events and 18 nonfatal events can be prevented; therefore, 4 × 5 × 1 = 20 QALY for fatal and 18 × 5 × 0.2 = 18 QALY for nonfatal events, or a total of 38 QALY losses, can be prevented in 1000 persons, which is 0.038 QALY per person. Therefore, the effect model is 4 times higher in 10 years when compared with 5 years. The SMB based its assumptions on the Cholesterol Treatment Trialists' (CTT) study published in 2012 and on the effect of statins on LDL, which is assumed to be a reduction of 1.0 mmol/l to obtain the above mentioned preventive effects [8]. The SMB QALY calculator can be accessed online for further details and for calculation of examples [9].

Effects of statins in primary care

The aggregated relative risk reduction per 1 mmol/l LDL reduction used by the SMB is 22% [8, 10]. This 22% relative risk reduction was chosen by the SMB despite the fact, that in low risk subjects, relative risk reduction was shown to be 30% for major vascular events (CTT Appendix 2012, web figure 5, statins versus placebo only, 22 trials) [10]. In order to calculate cost/QALY, we used relative risk reductions of 22% and of 30%.

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. The self-referred subjects of the Vascular Risk Foundation privided informed written consent. The study (Cordicare II) was approved by the joint ethics committee of the cantons of Solothurn and Aargau.

Statistics

Sensitivity (see table 4) and number needed to treat (NNT, see table 2) were calculated with established formulas. The SMB calculations are outlined in the SMB effect model described above.

Results

Study population description

On average, the Swiss group (n = 2203) included older subjects than the German group (n = 2942, 57 ± 9 vs 46 ± 10 years) and more women (49 vs 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 vs 15%). Lipid pro-

files were comparable. Average coronary risk was low (table 1).

Table 1: Baseline characteristics, prevalence of risk and average total plaque area for Switzerland and Germany.

Baseline Characteristics	Switzerland	Germany
Number of subjects (n)	2203	2942
Female (n, %)	1083 49%	989 34%
Age, years (mean ± 1 SD)	57 ± 9	46 ± 10
Family history of 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
SCORE 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	–

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low density lipoprotein; SD = standard deviation; TPA = total plaque area

Cost/QALY calculations

For a 5-year statin treatment period, cost/QALY as calculated by the SMB is CHF 210 279 (table 2). These costs are applicable to 1000 statin-treated persons with a risk of 5% for cardiovascular events, corresponding to a SCORE risk of 0.91% according to the SMB assumption that for every two fatal events, nine nonfatal events occur (1:4.5 ratio). In these 1000 persons, 11 cardiovascular events would be prevented, based on a relative risk reduction of 22%. With a relative risk reduction of 30%, 15 cardiovascular events could have been prevented at reduced cost/QALY of CHF 144 380.

For a 10-year statin treatment period, and with treated baseline risks of SCORE 2.5, 5.0 and 7.5%, cost/QALY decreased to CHF 62 057, CHF 17 081 and CHF 2089, respectively, when a relative risk reduction of 22% was used in the calculation, and decreased to CHF 38 070, CHF 5088 and CHF –5906, respectively, when the evidence-based purely relative risk reduction of 30% was used. Therefore, cost/QALY is acceptable at a SCORE risk of 2.5%, and three times lower than the recommendation of the SMB (table 2).

Performance of various SCORE thresholds to detect TPA80

The proportion of subjects with TPA80 increased with increasing levels of SCORE (table 3). The proportion of subjects with TPA80 was substantial in all age categories (11%, 25%, 45% in Switzerland and 13%, 41% in Germany). Of note, in the age group 40–65 years, most TPA80 were found in those with a SCORE risk below 2.5%. The rate of those with TPA80 (true positives) and those missed (false negatives) differed by SCORE thresholds of 2.5%, 5.0% and 7.5% in the age group 40–65 years: sensitivity was 28%, 9% and 2% in Switzerland and 28%, 5% and 1% in Germany (table 4).

Discussion

First, we found good cost efficiency of CHF 38 000/QALY with statin treatment of those at a SCORE risk above 2.5%, if treated for a 10-year period and with a relative risk reduction of 30%. The relative risk reduction of 30% instead of 22% is based on the evidence of 22 trials in primary care comparing statins with placebo [8, 10]. The cost-efficient SCORE risk of 2.5% is three times lower than the SCORE threshold of 7.5% recommended by the SMB and corresponds to a cardiovascular risk of 14% when nonfatal events are added. This acceptable level of cost efficiency was of a similar order (CHF 62 057/QALY) when we used the relative risk reduction of 22% proposed by the SMB (table 2).

Because the number of QALYs increased by a factor four when patients are treated for 10 instead of 5 years, the cost efficiency is exponentially influenced by the duration of treatment. Risk calculations are typically based on a 10-year period and, therefore, it is clinically more convincing to derive cost efficiency from 10 instead of 5 treatment periods in chronic noncommunicable diseases.

Second, in our cross-sectional observation of otherwise healthy subjects with advanced carotid atherosclerosis from Switzerland and Germany, we showed that the statin treatment recommendation of the SMB would leave virtually all these patients untreated, because at the age of 40–65 years, the decision level of SCORE 7.5% to initiate statin therapy would treat only 5 of 302 subjects with advanced atherosclerosis in Switzerland (sensitivity 2%) and 6 of 443 subjects with advanced atherosclerosis in Germany (sensitivity 1%, table 4). We found that in subjects aged 40–65 years and with advanced carotid atherosclerosis, TPA80 was detected with a sensitivity of only 28% when a SCORE threshold of 2.5% was used (Germany: 28%). The sensitivity decreased to <10% for SCORE thresholds of 5.0% and 7.5% (table 4). By consequence, reservation of

Table 2: Cost per quality adjusted life year (QALY) for 5 and 10 years and for different levels of coronary risk [8], with relative risk reductions of 30% and 22%.

	Relative risk reduction 30%				Relative risk reduction 22%			
SMB cost/QALY model	**5 years**	**10 years**			**5 years**	**10 years**		
Fatal event	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Nonfatal event	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Cost of fatal event	8500	8500	8500	8500	8500	8500	8500	8500
Cost of nonfatal event (1st year)	25000	25000	25000	25000	25000	25000	25000	25000
Cost of nonfatal event (after 1st year)	8000	8000	8000	8000	8000	8000	8000	8000
Statin and monitoring cost (per year)	470	470	470	470	470	470	470	470
Effect [(improvement of life) * (quality)]	13.0	71.3	142.5	213.8	9.5	52.3	104.5	156.8
Total cost (per 1000 individuals)	477750	1987500	3975000	5962500	350350	1457500	2915000	4372500
Total cost (per individual)	478	1988	3975	5963	350	1458	2915	4373
Statin and monitoring cost (observation years)	2350	4700	4700	4700	2350	4700	4700	4700
Avoided health care costs	1872	2713	725	–1263	2000	3243	1785	328
Cost:efficiency ratio (cost per QALY)	144380	38070	5088	–5906	210279	62057	17081	2089
Fatal risk in % in years	0.91	2.50	5.00	7.50	0.91	2.50	5.00	7.50
Number of individuals	1000	1000	1000	1000	1000	1000	1000	1000
Expected fatal events	9	25	50	75	9	25	50	75
Expected nonfatal events	41	113	225	338	41	113	225	338
Total number of events (fatal + nonfatal)	50	138	275	413	50	138	275	413
Avoidable fatal events	2.7	8	15	23	2.0	5.5	11.0	16.5
Avoidable nonfatal events	12.3	33.8	67.5	101.3	9.0	24.8	49.5	74.3
Total number of avoidable events	15.0	41.3	82.5	123.8	11.0	30.3	60.5	90.8
Absolute risk	5.0	14	28	41	5.0	14	28	41
Avoidable risk	1.5	4	8	12	1.1	3	6	9
Number needed to treat	67	24	12	8	91	33	17	11

Table 3: Coronary risk categories for SCORE by age groups, by the distribution of subjects with total plaque area ≥80 mm² (TPA80) and by country (Switzerland, n = 2124, or Germany, n = 2280).

CH-SCORE %	40–55 (n)	TPA80 (n)	TPA80 (%)	56–65 (n)	TPA80 (n)	TPA80 (%)	65–75 (n)	TPA80 (n)	TPA80 (%)
0.00–0.99	706	55	8	288	27	9	12	3	25
1.00–2.49	171	31	18	377	108	29	129	42	33
2.50–4.99	26	10	38	141	62	44	181	89	49
5.00–7.49	2	1	50	20	8	40	41	25	61
7.50+	0	0	0	7	5	71	23	16	70
Total	**905**	**97**	**11**	**833**	**210**	**25**	**386**	**175**	**45**

DE-SCORE %	40–55 (n)	TPA80 (n)	TPA80 (%)	56–65 (n)	TPA80 (n)	TPA80 (%)
0.00–0.99	1397	99	7	137	31	23
1.00–2.49	292	91	31	266	104	39
2.50–4.99	37	28	76	123	73	59
5.00–7.49	3	3	100	18	14	78
7.50+	1	1	0	6	5	0
Total	**1730**	**222**	**13**	**550**	**227**	**41**

Table 4: Sensitivity of various SCORE thresholds to detect TPA80 in those aged 40–65 years, for Switzerland and Germany separately.

SCORE threshold CH	**2.50%**	**5.00%**	**7.50%**
True positives (n)	86	14	5
False negatives (n)	221	146	302
Sensitivity (%)	28%	9%	2%
SCORE threshold DE	**2.50%**	**5.00%**	**7.50%**
True positives (n)	124	23	6
False negatives (n)	325	426	443
Sensitivity (%)	28%	5%	1%

Statins to those with SCORE above 7.5% would lead to a rationing of a cost-effective intervention with Statins. Therefore, we expect the SMB recommendation to have disadvantage effects at the population level, where preventive therapy should start early in life [11–14].

Our results fit well into contemporary US guidelines, which 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% [15]. These numbers would correspond to an SCORE risk of 1.7% and 1.1%. The British Health Care System (NICE) recommends a similar threshold [16]. 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 study the effect of the SMB threshold (SCORE 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 [17]. TPA80 is 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].

Conclusion

By applying the SMB recommendation of SCORE 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.

With regard to the cost-efficiency analysis, the results of greater than CHF 210 000 reported by the SMB can only be applied to a SCORE risk of less than 1% in 5 years, with substantial increases in cost efficiency from a SCORE risk of 2.5% in 10 years (CHF 38 070/QALY). The SMB recommendation is not derived from the cost model proposed and is very likely to pose a significant safety problem in subjects with low and intermediate cardiovascular risk, in whom 67% of first myocardial infarctions occur in Switzerland. Future guidelines should consider SCORE thresholds lower than 5% (e.g., 1.1–2.5%) for the initiation of statins in primary care for those aged 40–65 years.

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References
The full list of references is included in the online version of the article at www.cardiovascmed.ch.