Cost-effectiveness analysis of statins in primary care: results from the Arteris cohort study

Romanens Michel[a], Adams Ansgar[b], Bojara Waldemar[c], Balint Sandor[d], Warmuth Walter[e]

[a] Vascular Risk Foundation (Varifo), Olten, Switzerland
[b] BAD Gesundheitsvorsorge und Sicherheitstechnik GmbH, Bonn, Germany
[c] Akademisches Lehrkrankenhaus der Universitätsmedizin der Johannes-Gutenberg-Universität Mainz, GermanyAkademisches Lehrkrankenhaus der Universitätsmedizin der Johannes-Gutenberg-Universität Mainz, Klinik für Innere Medizin Schwerpunkt Kardiologie, Koblenz, Germany
[d] Privatpraxis, Binningen, Switzerland
[e] Gesundheitsforen Leipzig, Germany

Summary

BACKGROUND: The Swiss Federal Office of Public Health performed a health technology assessment regarding statins in primary care. The chosen models may lead to a situation where a clinically indicated statin therapy is estimated not to be cost effective.

METHODS: We performed a cohort study regarding cardiovascular events, comparing SCORE and AGLA risk categories with tertiles of carotid plaque burden and used two models for cost-effectiveness analysis of high-potency statins.

RESULTS: Subjects (n = 2842) were followed up for 5.9 ± 2.9 years with the occurrence of 154 cardiovascular events (extrapolated 10-year risk was 9.2%). Carotid plaque imaging (total plaque area, TPA) significantly improved cardiovascular risk prediction compared with AGLA and SCORE for event-free survival prediction, test accuracy (discrimination) and calibration. Discrimination was significantly improved by about 4% with the inclusion of TPA. Cost-effectiveness analysis using quality-adjusted life years (QALYs) and sensitivity analyses (based on 16 models) ranged between CHF 144,496 and −128,328 per QALY. Cost-effectiveness analysis using direct and indirect costs showed that a treat-them-all strategy in the Swiss population would be cost effective with a return-on-investment per patient in 10 years of between CHF 4442 and 19,059, and the use of carotid imaging was also cost effective (incremental cost-efficiency ratio −2.97 to −7.86).

CONCLUSIONS: Carotid ultrasound significantly improved cardiovascular risk stratification and is cost effective. The Swiss Medical Board QALY model presents several drawbacks, which are shown in our sensitivity analysis, where results vary considerably and are not useful for clinical decision making. A "treat them all" strategy with statins in the Swiss population aged 30–65 years may be cost effective, when indirect costs of avoidable cardiovascular events are included, even at an unacceptably low value of a statistical life year.

Correspondence:
Michel Romanens, MD,
Vascular Risk Foundation,
Spitalstr. 9, CH-4600 Olten,
michel.romanens[at]hin.ch

Introduction

Statins reduce cardiovascular risk by 22% per 1 mmol/l reduction in low-density lipoprotein (LDL) in secondary prevention [1] and by 29% in primary prevention [2]. A shared decision to treat patients with statins is based on evidence and guidelines, such as the European Lipid Guidelines 2019 [3].

According to The Swiss Federal Office of Public Health, the prescription of statins in primary care may not be cost effective and should be evaluated in a health technology assessment, based on the results of a scoping report from Pallas Health Research and Consultancy and from Institute for Medical Technology Assessment, Erasmus University of Rotterdam [4].

Because of a possible restriction of reimbursement for statin therapy in the population at low or intermediate risk, we designed and conducted an individual-level cohort study using outcome data to test the hypothesis that a patient who will experience a cardiovascular event in the future cannot be correctly stratified by means of AGLA (the Swiss "Arbeitsgruppe Lipide und Atherosklerose") and SCORE (Systematic COronary Risk Evaluation) risk

ABBREVIATIONS	
ASCVD	atherosclerotic cardiovascular disease
CABG	coronary artery bypass grafting
CEA	cost-effectiveness analysis
ICER	incremental cost-effectiveness ratio
LDL	low-density lipoprotein
PTCA	percutaneous transluminal coronary angioplasty
ROC	receiver operating curves
TPA	total plaque area (carotid plaque)
PROCAM	Prospective Cardiovascular Münster Study for fatal and nonfatal myocardial infarction
SCORE	SCORE Risk charts and equations, European Society of Cardiology, for fatal cardiovascular events
SMB	Swiss Medical Board
Varifo	Vascular risk foundation, Olten, Switzerland
VSL	value of a statistical life

categories, because a substantial portion of cardiovascular events occur in patients at low and intermediate risk. However, presence of carotid plaque may allow a substantially improved risk stratification. We used the Swiss Medical Board quality-adjusted life year (QALY) model with sensitivity analysis in order to calculate the cost effectiveness of the different models in the whole outcome population to show the hypothetical variability of cost-effectiveness analysis (CEA). We calculated the (from the outcome population) extrapolated preventive effects of a "treat them all with statins" strategy in the Swiss population aged 30–65 years and calculated preventable events and associated direct and indirect costs over a 10-year time horizon, to test the hypothesis that statins are cost effective in primary prevention.

Materials and methods

We performed a cohort study and compared carotid imaging (total carotid plaque area, TPA) with coronary/cardiovascular risk equations as predictors.

For sample size estimation, we calculated n = 252 with 12 cases for receiver operating curves (ROC) analysis, n = 2208 with 138 cases for comparative ROC analysis. Patients with known atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus were excluded. Consecutive patients aged 30–65 years were included in the study. All data were entered into an Excel spreadsheet for data processing and pseudonymisation.

Subject selection
In the Swiss Imaging Centre in Olten, subjects were self-referred to the vascular risk foundation Varifo after public advertisements approved by the local ethics committee. In the German Centre in Koblenz, all subjects were referred within a working medicine setting. Subjects had to be free of cardiovascular symptoms or disease and diabetes mellitus, and be within the age range of 30–65 years. Laboratory values, blood pressure and medical history were measured locally and entered into a spreadsheet (Excel, Microsoft, Richmond, USA).

Patient information
Blood pressure was recorded in the sitting position using a standard sphygmomanometer and blood samples were obtained (usually in the fasting state) from all patients for lipid measurements. Smoking status, family history of premature coronary disease and presence of diabetes mellitus were self-reported. Patients with diabetes mellitus were excluded from the study.

Follow-up information
We contacted patients by telephone, email or post mail and asked them to inform us about occurrence of cardiovascular events (fatal or nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass grafting [CABG], fatal or nonfatal stroke or transient ischaemic attack [TIA], or presence of a significant stenosis assessed with invasive coronary angiography). Whenever possible, and always in unclear situations, we obtained clinical records from treating physicians. When coronary revascularisation was performed in patients with an acute myocardial infarction, the endpoint

was adjudicated to myocardial infarction. The primary endpoint was a composite of acute myocardial infarction, stroke/TIA or CABG. The secondary endpoint was the primary endpoint plus PTCA and coronary artery disease. Results were further compared with a single outcome measure (fatal or nonfatal myocardial infarction only).

Sensitivity analysis
Because 20% of subjects were lost to follow-up, we performed a sensitivity analysis by comparing patients with complete follow-up with the total group of patients potentially available for our cohort study.

Ethical aspects
Subjects self-referred to the Vascular Risk Foundation gave written consent. The study protocol was approved by the local ethics committee of Solothurn, Switzerland. Subsequently, subjects were entered into an anonymised study registry, for which current legislation in Switzerland and Germany does not require formal ethics committee consent.

Carotid imaging
The burden of longitudinal carotid plaque surface was imaged with a high-resolution ultrasound linear transducer probe (7.5–12.0 MHz), which identified plaques with intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed to give the total plaque area (TPA) in mm^2. All TPA measurements were made by AA in Koblenz and by MR in Olten. Arterial age was calculated as previously published [5].

Computation of cardiovascular risk and risk for myocardial infarction only
Cardiovascular risk was computed using the published risk formulae in an Excel spread sheet for SCORE and Framingham, and PROCAM risk for myocardial infarction only. We used the European Society of Cardiology risk equation for low risk populations (SCORE [3]) and the German PROCAM risk [6] multiplied by a correction factor of 0.7, as proposed by AGLA [7]. Further, we calculated risk based on Framingham cardiovascular disease risk using lipids and body mass index [8]. For net reclassification improvement calculations we calculated sensitivity and specificity of TPA tertiles and arterial age classes, and derived post-test risk calculations for PROCAM and SCORE using the Bayes theorem, as described elsewhere [9].

Effect estimates of LDL lowering
For each of the four TPA groups (no plaque, TPA tertiles), average LDL levels are presented with the expected risk reduction achievable with statins (atorvastatin 80 mg or rosuvastatin 20 mg per day at a daily cost of less than CHF 1.00), for which an average ≥50% LDL reduction is clinically feasible [10]). Absolute risk reduction is a standard statistical entity, which describes an event rate with and without a medical intervention, expressed in percent of the affected population. Absolute risk reduction is therefore reduced by an effective medical therapy that provides a certain amount of relative risk reduction (e.g., 20%). Therefore, if risk is reduced by 20% from 10% to 8%, then the absolute risk reduction is 2%. Number needed to treat is 100/(absolute risk reduction). From that, absolute risk re-

duction, either with a relative risk reduction of 22% or 29%, was calculated and the number needed to treat derived for each individual. Computation of risks associated with TPA tertiles and comparison with no plaque as the comparator is a standard procedure to stratify risk [11, 12].

Effect model of the Swiss Medical Board
The Swiss Medical Board (SMB) model [13] for calculating cost/QALY (incremental cost-effectiveness ratio, ICER) 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 with CHF 8000 in subsequent years. Loss of QALYs 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. Loss of QALYs at 2.5 years was therefore $2 \times 2.5 \times 1 = 5.0$ QALYs for fatal events and $9 \times 2.5 \times 0.2 = 4.5$ QALYs for nonfatal events, and thus $5.0 + 4.5 = 9.5$ QALY in 1000 persons or 0.0095 QALYs 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, $4 \times 5 \times 1 = 20$ QALYs for fatal and $18 \times 5 \times 0.2 = 18$ QALYs for nonfatal events, or a total of 38 QALY losses, can be prevented in 1000 persons, which is 0.038 QALYs per person. Therefore, the effect model is 4 times higher in 10 years than in 5 years (multiplicative QALYs [14]). The SMB based its assumptions regarding statin effects on the Cholesterol Treatment Trialists' study published in 2012 [2, 15].

Calculation of direct and indirect medical costs:
Direct and indirect costs of fatal and nonfatal myocardial infarction and stroke were calculated as follows. Based on the final Swiss report on non-communicable disease costs 2014 [16] for the year 2011 (www.docfind.ch/CVD-Costs2011.xlsx):

– Acute myocardial infarction cost estimates CHF 4,798,000,000 (direct costs: CHF 2,760,000,000)
– Stroke cost estimates CHF 3,168,000,000 (direct costs: CHF 2,089,000,000)
– Swiss death registers recorded 7703 deaths due to ischaemic heart disease in the year 2011.

Assuming that for every death there are three nonfatal myocardial infarctions (based on Framingham data), we estimated the number of fatal and nonfatal myocardial infarctions to be 38,515 (Switzerland, 2011). Assuming a ratio of myocardial infarction and stroke of 3.5:1, which is comparable to the ratio derived from Framingham risk charts (4.5 in males and 2.6 in females, average 3.5), then 11,805 strokes are estimated to have occurred in 2011. The sum of first myocardial infarctions and strokes is therefore 50,320. For subsequent events we estimated an additional a rate of 34% for myocardial infarction and of 24% for stroke over a period of 5 years [17]. Direct and indirect costs for myocardial infarction are divided by 37,578 patients with events, resulting in CHF 147,995 per myocardial infarction or CHF 345,125 per stroke. Accounting for the case-mix estimate, the average costs per patient are CHF 251,622. In view of the fact that avoidable cost was calcu-

lated over a time period of 10 years, these costs per patient may even underestimate true costs, since we did not include an additional cardiovascular event that may have occurred in years 6 to 10. In order to achieve a conservative estimation of costs, we used avoidable direct and indirect medical costs of CHF 200,000 per event (coronary revascularisation included) over 10 years. Our cost estimate is comparable to the key inputs in the economic model of Fonarow et al. [18] and is a conservative estimate of direct and indirect costs associated with cardiovascular diseases in Switzerland. We calculated ICER in a standard manner using (costs with statin − costs without statins) and effects (with statin − without statin) by dividing costs/effects.

On-treatment calculation
Because side effects of statins occur rarely and are mild in nature and reversible [15, 19–22], we did not include these additional treatment costs. Further, statin scepticism may reduce the number of patients on treatment [23]. We tried to avoid subjective effects on our cost-effectiveness analysis. Therefore, our analysis calculates on-treatment results.

Decision trees
The decision to treat a patient with a statin can be based on many attributes, such as shared decision making based on patient preferences when there is a borderline indication for statin treatments [3]. For the purpose of this study, we used cost-effectiveness thresholds and cost thresholds for decision making. If cost-effectiveness analysis yields a cost effectiveness below the threshold of CHF 150,000 per QALY, then the threshold for willingness to pay is reached and the decision is in favour of a statin treatment. This approach was chosen for the SMB model. Similarly, when a strategy yields a return on investment, for example treat the whole population or treat the population within the third TPA percentile only, then the decision is in favour of a statin treatment. This approach was used for the model that includes indirect cost estimates of a cardiovascular event.

Statistics
We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons [24]. Groups were compared using a t-test for continuous variables and chi-square for categorical variables. Net reclassification improvements were calculated as described elsewhere [25]. Survival was analysed with Kaplan-Meier survival analysis and Cox proportional-hazards regression after adjustment for cardiovascular risk factors in model 1 (sex, age, smoke, body mass index, total cholesterol, high-density lipoprotein [HDL], LDL, triglycerides, systolic blood pressure, use of hypertensive and lipid lowering drugs) and after adjustment for risk charts (model 2) for both the primary and secondary outcomes. Further we assessed model performance using model fit (chi-square), discrimination (ROC analysis) and calibration (Hosmer and Lemeshow test). Patients were split on the basis of TPA into those without atherosclerosis (reference group) and tertiles of TPA. Sensitivity and specificity of TPA tertiles was analysed and used for post-test calculations with PROCAM and SCORE as the prior probabilities using the Bayes theorem.

The formulae for the calculation of post-test probabilities were:

PTP pos: (PV × SE) / [PV × SE + (1 − PV) × (1 − SP)]

PTP neg: [PV × (1 − SE)] / [PV × (1 − SE) + SP × (1 − PV)]

Where PTP denotes post-test probability, PV denotes prevalence, SE denotes sensitivity, SP denotes specificity, pos denotes positive (test positivity) and neg denotes negative (test negativity). A TPA below the first tertile was considered as a negative test. The level of statistical significance was set at p <0.05.

Results

The Arteris cohort is comprised of subjects from the cardiological practice Kardiolab in Olten, Switzerland (n = 1255), the vascular risk foundation Varifo in Olten, Switzerland (n = 1050) and the prevention centre in Koblenz, Germany (n = 3326). Therefore, the Arteris group includes 5631 subjects, from which the following were excluded for this study: 1255 Kardiolab subjects (no follow-up data, many patients had medical interventions that can alter the predictors used in this study). Of 1050 subjects, Cordicare subjects were excluded for age below 30 or over 65 years (n = 237) or diabetes (n = 30) or death of unknown reason (n = 5); in the Koblenz cohort, excluded subjects were 124 subjects with diabetes and 528 due to age. The remaining 3452 subjects were eligible for study entry and follow up could be obtained for 2842 (82.3) subjects, who were predominantly visited in Koblenz, Germany (80%) and the German cohort contributed to the total of ASCVD events in 123 out of 154 cases (80%). Events were confirmed by medical records in 75% and by telephone interview in 25%.

In the Varifo cohort, 16 deaths occurred, of which 5 were of unknown origin and were excluded from the study. The remaining 11 deaths were attributed to myocardial infarction (n = 9) and to stroke (n = 2). All ASCVD deaths had a TPA above the 3rd tertile, except for one with TPA in the 2nd tertile (average TPA for all ASCVD deaths 136 mm^2).

In the Koblenz cohort, there were 10 deaths, of which 8 were attributed to myocardial infarction and 2 to stroke. In all these patients, TPA was within the 3rd tertile (range 62–260 mm^2, average 149 mm^2).

The average follow-up time was 5.9 ± 2.9 years (range 3–144 months) and the ASCVD event rate was 5.4% or, by linear extrapolation, 9.2% in 10 years.

Table 1 shows the clinical baseline characteristics and cardiovascular risks of those with and without a cardiovascular event and both groups combined. When the group with events (both primary and secondary outcome) was compared with the group without events, all clinical and risk variables showed adverse characteristics for the event group regarding the frequency of smoking, sex and continuous variables such as systolic blood pressure, lipid levels, TPA, arterial age and results from cardiovascular risk equations. By extrapolation, ASCVD risk was 9.2% in the Arteris cohort over 10 years and almost all patients reported not having taken statins despite knowledge of the imaging results.

Table 2 shows the hazard ratios (and 95% confidence intervals) for cardiovascular endpoints according to TPA. Significant prediction improvements of cardiovascular risk factors (model 1) and risk charts (model 2) were realised for the outcomes in the 2nd (TPA 22–61 mm^2) and 3rd TPA tertile (TPA ≥62 mm^2).

Table 3 shows models for test performance regarding outcomes, where a model fit by chi-square was significantly improved beyond risk equations (PROCAM, SCORE) when TPA was also included. Discrimination was significantly improved by about >4% with TPA, and calibration was generally improved when imaging was added.

Table 4 shows the net reclassification improvements using TPA, which was statistically significant for the outcome (>30% reclassifications when compared with PROCAM and SCORE).

Table 1: Baseline characteristics, results from risk scores and imaging.

No.	2842
Female, n (%)	1080 (38%)
Age (years), mean ± SD	50 ± 8
Smoker, n (%)	609 (21%)
Systolic blood pressure (mm Hg), mean ± SD	126 ± 16
BMI (kg/m^2), mean ± SD	26 ± 4
Cholesterol (mmol/l), mean ± SD	6.0 ± 1.1
HDL (mmol/l), mean ± SD	1.5 ± 0.4
LDL (mmol/l), mean ± SD	3.7 ± 0.9
Triglycerides (mmol/l), mean ± SD	1.6 ± 1.1
TPA (mm^2), mean ± SD	42 ± 54
SCOREca (%), mean ± SD	1.3 ± 1.6
PROCAMca (%), mean ± SD	4.8 ± 6.4
AGLAca (%), mean ± SD	3.3 ± 4.5

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; TPA = total plaque area

Table 2: Hazard ratios (95% confidence intervals) for cardiovascular end points associated with total plaque area (TPA) tertiles adjusted for traditional cardiovascular risk factors (model 1) and for PROCAMca, SCOREca, and FRAMca (model 2).

	No Atherosclerosis	Tertile 1	Tertile 2	Tertile 3	p-value (trend)
Model 1	1.0 (ref)	1.7 (0.3–9.1)	5.3 (1.2–22.9)	23.4 (5.5–98.5)	<0.0001
Model 2	1.0 (ref)	1.9 (0.4–10.1)	6.9 (1.6–29.3)	33.7 (8.2–138.6)	<0.0001

Plaque area in tertiles: 1st tertile (<22 mm^2); 2nd tertile (22–61 mm^2); 3rd tertile (≥62 mm^2). Variables used for adjustment in model 1 were age, smoke, sex, systolic blood pressure, lipids, body mass index, medication use (antihypertensive and lipid lowering drugs separately).

Table 5 shows the patient characteristics stratified by no atherosclerosis (reference) and presence of atherosclerosis by TPA tertiles. In all groups, AGLA average risk was below 10% (6.7%), and SCORE showed intermediate risk in the 3rd tertile high-risk cohort, where an event rate of 38.2% was expected by linear extrapolation of the 5 observed years.

Table 6 shows the cost-efficacy analysis (using the SMB model) for the whole group of patients with direct costs (model 1) and total costs defined as direct and indirect costs (model 2), further stratified for multiplicative and

additive QALYs [14], for 5 or 10 years and for relative risk reduction per 1.0 mmol/l LDL reductions of 22% and 29%, respectively. The range of cost/QALY (ICER) was between CHF 144,469 and CHF −128,328.

Table 7 shows cost effects of a "treat them all" strategy versus "treat only patients within the 3rd TPA tertile" at screening, with costs of CHF 75 per patient to determine TPA. Even if costs for fatal events that could be avoided are minimised to CHF 8500, the imaging strategy leads to a return on investment of CHF 8158 (or CHF 23,514 if case fatality is included with CHF 1.5 million over 10

Table 3: Model performance regarding global chi-square, discrimination and calibration.

Model	Model fit		Discrimination	Calibration	
	χ^2	p-value	C-index (95% CI)	χ^2	p-value
PROCAMca	140.114	<0.0001	0.831 (0.816–0.844)	53.5126	<0.0001
PROCAMca + TPA	232.964	<0.0001	**0.869 (0.856–0.881)**	44.8182	<0.0001
SCOREca	137.836	<0.0001	0.824 (0.809–0.838)	38.0416	<0.0001
SCOREca + TPA	199.707	<0.0001	**0.866 (0.853–0.879)**	61.3254	<0.0001

CI = confidence interval; TPA = total plaque area

Table 4: Net reclassification improvement (NRI) using post-test risk of PROCAM and SCORE based on TPA tertiles derived sensitivities and specificities for observed outcome.

	NRI	95% CI	p-value
PROCAM	**Ref model**		
PROCAM + Bayes TPA	0.421	0.356–0.486	<0.0001
SCORE	**Ref model**		
SCORE + Bayes TPA	0.373	0.307–0.439	<0.0001

CI = confidence interval

Table 5: Characteristics of patients stratified by atherosclerosis presence (TPA tertiles), effect of statin therapy (with relative risk reduction of 22% and 29%), 50% LDL lowering for daily costs of CHF 1.00 and numbers needed to treat for various risk scores and 10-year risk derived from TPA.

	All	Zero plaque	Carotid plaque tertiles (TPA)		
TPA groups		0	1	2	3
n (%)	2842 (100)	728 (26)	688 (24)	719 (25)	707 (25)
Age (years), mean ± SD	50.1 ± 7.6	44.3 ± 6.4	49.8 ± 7.0	51.8 ± 6.8	54.7 ± 5.9
LDL (mmol/l), mean ± SD	3.7 ± 0.9	3.4 ± 0.8	3.6 ± 0.9	3.8 ± 0.9	4.1 ± 1.0
FU (years), mean ± SD	5.9 ± 2.9	5.1 ± 2.8	6.2 ± 2.8	5.8 ± 2.8	4.7 ± 2.9
Event (%)	5.4	0.3	0.7	2.9	17.8
Event 10 (%)	9.2	0.5	1.2	5.0	38.2
SCORE (%), mean ± SD	1.3 ± 1.6	0.5 ± 0.6	0.9 ± 1.0	1.4 ± 0.9	2.6 ± 2.2
SCORE SMB (%), mean ± SD	7.3 ± 8.8	2.5 ± 3.5	5.0 ± 5.2	7.6 ± 5.0	14.1 ± 12.0
PROCAM (%), mean ± SD	4.8 ± 6.4	1.8 ± 2.9	3.0 ± 4.0	4.9 ± 2.8	9.5 ± 8.7
AGLA (%), mean ± SD	3.3 ± 4.5	1.2 ± 2.0	2.1 ± 2.8	3.4 ± 5.5	6.7 ± 6.1
RRR 22%					
LDL treat	1.9	1.7	1.8	1.9	2.0
RRR	41.2	37.8	39.8	42.0	45.0
ARR SMB %	3.0	1.0	2.0	3.2	6.4
NNT SMB	33.3	104	50	31	16
ARR AGLA %	1.4	0.5	0.8	1.4	3.0
NNT AGLA	72.7	212	121	70	33
ARR ARCO %	4.1	0.2	0.5	2.1	17.2
NNT ARCO	24	488	215	47	6
RRR 29%					
LDL treat	1.9	1.7	1.8	1.9	2.0
RRR	54.3	49.9	52.5	55.4	59.3
ARR SMB %	4.0	1.3	2.6	4.2	8.4
NNT SMB	25	79	38	24	12
ARR AGLA %	1.8	0.6	1.1	1.9	4.0
NNT AGLA	55	161	92	53	25
ARR ARCO %	5.4	0.3	0.6	2.8	22.7
NNT ARCO	19	370	163	36	4

ARCO = the Arteris cohort; ARR = absolute risk reduction; FU = follow-up; LDL = low-density lipoprotein; NNT = number needed to treat; RRR = relative risk reduction; SD = standard deviation; SMB = Swiss Medical Board; TPA = total (carotid) plaque area

years). The "treat them all" strategy is also associated with a substantial return on investment; however, a screening strategy with carotid imaging is more cost effective (ICER between −2.97 and −7.86). Further, the imaging strategy would prevent more events than the treat them all strategy (241,261 vs 230,221) over 10 years.

Table 8 shows the distribution of patients and events by risk groups of AGLA and SCORE. Events were 154 over 5.9 years, of which 66% occurred in in the low-risk segment of AGLA (10% for SCORE) and 92% of patients were categorised as having low AGLA risk. The distribution of events in the high-risk segments was 7% for AGLA and 18% for SCORE.

Supplementary table S1 in the appendix shows cost-effectiveness results for several base-case cardiovascular risks. As expected, cost/QALY showed a large variation (depending on duration of therapy, value of a statistical life values, additive or multiplicative QALY), with ranges for

CHF/QALY (ICER) between 485,663/QALY to −93,483/QALY.

Table S2 shows insignificant changes in the cost-effectiveness results of table 7 when the relation of fatal to nonfatal events was changed from 1:45 (SMB assumption in table 7) to 1:6.3 as observed in the Arteris cohort.

Table S3 displays the assumptions of the economic model of the SMB regarding QALY and base-case risk. Base-case risk over 5 years was 2 deaths and 9 nonfatal events in 1000 persons treated with statins. Therefore, there were 1.1% at risk over 5 years or – with linear extrapolation – 2.2% in 10 years. The effect of multiplicative QALYs is also shown. The model assumes that all events occur at half time of the total treatment period, e.g., after 2.5 years when treatment duration is 5 years, or after 5 years when treatment duration is 10 years.

Table 6: Cost per QALY (ICER) using a 16 model sensitivity analysis.

QALY	RRR	5 years		10 years	
		Model 1	**Model 2**	**Model 1**	**Model 2**
Multiplicative	0.22	144,496	32,285	62 774	−2805
Additive	0.22	144,496	32,285	125,548	−5610
Multiplicative	0.29	100,725	−90 433	40,889	−64 164
Additive	0.29	100,725	−90 433	81,777	−128 328

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RRR = relative risk reduction **Model 1 costs:** CHF 8500 for a fatal event, CHF 25,000 for a nonfatal event in the first year, CHF 8000 for a nonfatal event in subsequent years (baseline model of the Swiss Medical Board [13], reflecting direct cost per event based on assumptions by Pletscher et al. [26]. **Model 2 costs:** CHF 150,000 per year per fatal event, CHF 50,000 for a nonfatal event in the first year, CHF 16,000 for a nonfatal event in subsequent years (reflecting direct and indirect costs per event)

Table 7: Cost effects comparing a "treat them all" strategy with a "treat 3rd TPA tertile only" strategy in the Swiss population (age 30–65), stratified further for avoidable costs per fatal case of either CHF 1.5 million in 10 years or once CHF 8500 (treatment costs according to the Swiss Medical Board).

	Treatment strategy			
	All	**All**	**TPA 3rd Tert**	**TPA 3rd Tert**
30–65 (2017)	RRR 0.29	RRR 0.29	RRR 0.29	RRR 0.29
No.	4,260,524	4,260,524	1,065,131	1,065,131
Events in 10 years	424,344	424,344	406,933	406,933
Avoided	230,221	230,221	241,261	241,261
Avoided nonfatal events	188,362	188,362	197,395	197,395
Avoided fatal	41,858	41,858	43,866	43,866
Direct and indirect costs per nonfatal event over 10 years	200,000	200,000	200,000	200,000
Direct and indirect costs per fatal event over 10 years	**1,500,000**	**8500**	**1,500,000**	**8500**
Avoided nonfatal costs in CHF million	37,672	37,672	39,479	39,479
Avoided fatal costs in CHF million	62,787	356	65,798	373
Total avoided costs in CHF million	100,460	38,028	105,277	39,852
Treatment cost	19,104	19,104	4776	4776
Screening costs (CHF 75 per case) in CHF million	0	0	320	320
Treatment and screening costs in CHF million	19,104	19,104	5096	5096
Extra costs in 10 years in CHF million	−81,356	−18,924	−100,182	−34,756
Cost / savings per person in CHF	−19,095	−4442	−23,514	−8158
ICER			−2.97	−7.86

ICER = incremental cost-effectiveness ratio; RRR = relative risk reduction; TPA = total plaque area

Table 8: Distribution of patients and events across risk categories of AGLA and SCORE.

	Patients (%)	Event rate	Events %
AGLA <10%	92.2	3.9	66.2
AGLA 10–19%	6.7	22.2	27.3
AGLA ≥20%	1.2	30.3	6.5
SCORE <1.0%	56.9	1.0	10.4
SCORE 1.0–4.9%	39.9	9.7	71.4
SCORE ≥5.0%	3.2	30.8	18.2

Discussion

Our patient-level dual-centre cohort study shows that the population is at a 10-year risk of 9.2% for cardiovascular diseases such as myocardial infarction, stroke, coronary artery bypass surgery, stenting, or presence of coronary artery disease defined as a coronary stenosis of >50% detected by an invasive coronary angiogram.

Risk prediction with TPA, AGLA, and SCORE

Stratification of the cohort based on TPA from ultrasound imaging into four groups with either no carotid plaque (reference group) or carotid TPA tertiles led to extrapolated 10-year event rates of 0.3%, 0.7%, 2.9% and 38.2%, respectively. Only 7% of patients with events had an AGLA risk above 20% and only 34% had an AGLA risk above 10%; SCORE risk of over 5% was present in only 18% of subjects with events. Over all TPA tertiles, AGLA risk remained on average within the low-risk category, as did SCORE risk, which did not exceed an average of 2.6%.

Our first hypothesis can be accepted, since cardiovascular events did occur in those patients stratified into the low-risk group by AGLA or into the low- or intermediate-risk group by SCORE. A strategy that treats healthy patients with statins, based on a high-risk AGLA or high-risk SCORE alone, does not reach the vast majority of target patients, namely those who will develop atherosclerotic disease and hence an increased life-time risk for higher morbidity, mortality and costs.

Cost-effectiveness analysis (CEA) using QALYs

We performed a sensitivity analysis based on the SMB QALY model by varying the numbers for costs of death and the relative risk reduction of a statin per 1 mmol/l LDL reduction (either 22% or 29%). Thus, by assuming an average 50% LDL reduction with the use of 80 mg of generic atorvastatin or 20 mg of generic rosuvastatin (daily prices are less than CHF 1.00, but we used the SMB assumption of daily costs of CHF 1.00) computed from individual patient level data and using additive and multiplicative QALYs [27]. Therefore, the sensitivity analysis produced 16 possible results. We applied the calculation to the average data of the entire population observed and found that statins were cost effective for any input chosen. Based on an aggregate of individual patient level data with real events in a low risk population, statins at current prices (CHF 1.00 per day to lower LDL by 50% [10]) were cost effective, even when all patients would be treated, using CEA and a cost-effectiveness level less than CHF 150,000 per QALY.

A health technology assessment cost-effectiveness analysis using aggregated data for risk categories will be unable to detect patients who would benefit from statins and withholding statin treatment in this risk category is unable to positively influence the atherosclerotic epidemic. On the other hand, stratification of patients with SCORE, but not with AGLA (due to calibration and labelling problems [AGLA risk is risk for myocardial infarction only]) extended by additional clinical information, e.g., from medical imaging of carotid atherosclerosis or calcified coronary plaque (using computed tomography) is likely to reveal patients who benefit the most from statins. We showed a wide range of results using CEA, which points to the problem that QALY models can be easily used to calculate desired cost efficacies. We showed that the variability of CEA using the QALY concept is high, with costs per QALY ranging between CHF 144,496 and −128,328. The second study hypothesis is thus accepted and QALYs should not be used to guide medical decisions.

As a rule of thumb, we found a cardiovascular risk of 4% in 10 years (which may correspond to an AGLA risk of 1–2%) to be cost effective in primary care patients on statin treatment. This is in line with the health technology assessment report on statins of the Federal Office of Public health [28]), where in male patients up to age 55 statins are cost-effective at an AGLA risk of 1% (women: up to age 65). Therefore, statins are very cost effective even at very low AGLA risk.

Cost-effectiveness analysis (CEA) using direct and indirect cost estimates

The "treat them all with statins" strategy is not only cost-effective, but will save lives and avoid morbidity in the Swiss population aged 30–65 years. Annually, 4186 cardiovascular deaths and 18,836 cardiovascular events could be avoided with cost savings of CHF 1.4 to 7.0 million (direct and indirect costs). The efficacy of statins will increase with more selective use resulting from personalised clinical stratification using TPA, with cost savings of CHF 3.4 to 10.0 million annually. Therefore, this CEA shows that statins are cost effective in primary care and this lends support to our third study hypothesis, that statins should be reimbursed in primary care. Cost optimisation with carotid imaging is possible with an ICER of −2.97 to −7.86, if the imaging costs are 75 CHF per patient.

Using more sophisticated QALY models with inclusion of life-time calculations, discounted QALY and adding pill-taking disutility (which in fact is very disputable), a statin treatment regardless of LDL even for patients at borderline risk (7.5% ASCVD risk in 10 years) would be likely to be very cost effective [29, 30].

Our ratio of direct to indirect cost was found to be 61/39, others have found a ratio of 1:1 [31]; further, we calculated risk for myocardial infarction and stroke only, but during cardiovascular disease prevention using statins a ratio of 1 myocardial infarction to 3 other cardiovascular events occurs (stroke, peripheral artery disease, coronary obstructive disease, CABG, PTCA) [32, 33]. Therefore, our calculations about the beneficial effects of statins in primary care regarding direct and indirect costs represent a very conservative estimate.

Should we "QALY"?

Health economists like to "qaly" medicine. In this context, "I qaly" the healthcare system is the expression of an evolving mathematical machinery [34] that aims to give answers to the question of whether a medical therapy is indicated or not. Health economists claim that the QALY is a reliable metric like body size or weight. However, QALYs are influenced by cultural, social, individual, extrinsic or intrinsic observations and factors, and experience of life quality based upon physical, psychological, interpersonal, socioeconomic and spiritual dimensions that are never constant over time. The constancy of the multiplicative utility function over time is not evidence-based, and can never be

evidence-based at the individual level. Too many variables influence utility and, therefore, QALYs are expressing a fixed utility over time [35], which creates an axiomatic expression [27] of what is claimed to be real and is completely unrelated to human life quality, despite the claims of health economists who measure life quality. QALYs are not reproducible as a metric, being hampered by several biases (especially response shift and recall bias), and they lack a gold standard [36, 37].

Target patient identification

Preventive medicine should target those patients who will develop a cardiovascular event in the future. Conventionally, risk equations such as SCORE and AGLA stratify patients into risk categories from which the intensity of preventive medication was derived. If such an approach serves as the prior probability for CEA, the precision to identify target patients may not be sufficient to make recommendations, especially when calibration problems occur [38]. Today we are confronted with the fact that most target patients (82% for SCORE and 93% for AGLA in our study) are stratified into low- or intermediate-risk levels, despite being in the 3rd TPA tertile where 85% of all events occurred, and thus should have been placed in the high-risk group.

Limitations

We present a practice-based analysis and not a random-sample population-based analysis. Therefore, absolute numbers for risk may be biased. We tried to estimate indirect costs of a cardiovascular event and acknowledge, that several assumptions are completely arbitrary. One special point regards the value of a statistical life (VSL) that is used for CEA. The SMB used costs of CHF 8500 for case fatality, thus avoiding indirect costs. We used CHF 150,000 VSL/year and the dramatic effect of such differences on CEA are outlined in table 7. VSL/year was AU$ 182,000 (Australia 2014 [39]) and US$ 129,000 (USA 2009 [40]) and around EUR 150,000 in Europe [41].

As a limitation of our paper, decision making was based on a base-case only. We did not perform formal scenario analysis on the input variables, because this would go far beyond the scope of this report. However, base-case variations in prior probabilities and observed versus estimated relations between the probability of fatal versus nonfatal events did not change the results of our analysis. Because of a lack of information regarding many indirect cost assumptions in Switzerland, our calculations are preliminary and open to debate. We followed the published cost-effectiveness guidelines [42].

Another potential limitation is the absence of discount calculations in scenario analysis. Discounting effects are usually displayed as no discounting versus 3% or 6% discounting, and differential discounting (different discounts for costs and effects) have also been discussed [43]. Since statin prices are low, the application of discounts does not appear to be valid. Discounting effects (either on QALYs, cost of lost life-years and treatment costs) is also problematic for two major reasons: treatment costs tend to increase over time (Baumol cost-disease) [44] and discounting the value of life (in QALYs) appears unethical [45].

In conclusion, we can confirm that our three study hypotheses are valid: (1) with use of carotid ultrasound for imaging plaque burden, cardiovascular risk stratification is significantly improved, cost effective and cost efficient; (2) the SMB QALY model has several drawbacks, shown in our sensitivity analysis where results varied considerably, which limits its use in clinical and political decision making; (3) a "treat them all" strategy with statins in the Swiss population aged 30–65 years appears to be very cost effective, when indirect costs of avoidable cardiovascular events are included, even at an unacceptably low valuation of life. Numbers are further cost-effectively improved with personalised risk models based on carotid plaque imaging.

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Appendix

Supplementary tables

Table S1: Sensitivity for various thresholds of cardiovascular risk, duration of therapy, statin effects (RRR), and QALY model.

Sensitivity analysis based on variations of priors over 5 years RRR 0.22										
	Value of life CHF 1 × 8500					Value of life CHF 150,000 per life year lost				
Event rate for fatal or nonfatal cardiovascular event	3.6	1.3	2.5	3.8	7.1	3.6	1.3	2.5	3.8	7.1
Cost per QALY (CHF) multiplicative QALY	144,496	485,662	229,043	137,374	56,621	32,285	373,451	116,833	25,164	−55,589
Cost per QALY (CHF) additive QALY	144,496	485,662	229,043	137,374	56,621	32,285	373,451	116,833	25,164	−55,589
Sensitivity analysis based on variations of priors over 10 years RRR0.22										
	Value of life CHF 1 × 8500					Value of life CHF 150,000 per life year lost				
Event rate for fatal or nonfatal cardiovascular event	7.3	2.5	5.0	7.6	14.1	7.3	2.5	5.0	7.6	14.1
Cost per QALY (CHF) multiplicative QALY	62,774	233,357	105,048	59,213	18,837	−2805	167,778	39,469	−6366	−46,742
Cost per QALY (CHF) additive QALY	125,548	466,715	210,096	118,427	37,674	−5610	335,557	78,938	−12,731	−93,484
Sensitivity analysis based on variations of priors over 5 years RRR 0.29										
	Value of life CHF 1 × 8500					Value of life CHF150,000 per life year lost				
Event rate for fatal or non-fatal cardiovascular event	3.6	1.3	2.5	3.8	7.1	3.6	1.3	2.5	3.8	7.1
Cost per QALY (CHF) multiplicative QALY	100,725	359,540	164,864	95,322	34,061	−90,433	168,382	−26,294	−95,836	−157,097
Cost per QALY (CHF) additive QALY	100,725	359,540	164,864	95,322	34,061	−90,433	168,382	−26,294	−95,836	−157,097
Sensitivity analysis based on variations of priors over 10 years RRR 0.29										
	Value of life CHF 1 × 8500					Value of life CHF 150,000 per life year lost				
Event rate for fatal or nonfatal cardiovascular event	7.3	2.5	5.0	7.6	14.1	7.3	2.5	5.0	7.6	14.1
Cost per QALY (CHF) multiplicative QALY	40,889	170,296	72,958	38,187	7557	−64,164	65,244	−32,094	−66,865	−97,496
Cost per QALY (CHF) additive QALY	81,777	340,593	145,917	76,375	15,114	−128,328	130,488	−64,189	−133,731	−194,992

QALY = quality-adjusted life year; RRR = relative risk reduction

Table S2: Sensitivity analysis using Arteris ratio of fatal to nonfatal cases (1:6.3). The analysis using the Swiss Medical Board ratio is presented in table 7.

	Treatment strategy			
	All	**All**	**TPA 3rd tertile**	**TPA 3rd tertile**
30–65 (2017)	RRR 0.29	RRR 0.29	RRR 0.29	RRR 0.29
No.	4,260,524	4,260,524	1,065,131	1,065,131
Events 10 y	424,344	424,344	406,933	406,933
Avoided	230,221	230,221	241,261	241,261
Avoided non-fatal events	188,362	188,362	197,395	197,395
Avoided fatal	41,858	41,858	43,866	43,866
Direct and indirect costs per nonfatal event 10 years	200,000	200,000	200,000	200,000
Direct and indirect costs per fatal event 10 years	1,500,000	8,500	1,500,000	8,500
Avoided nonfatal costs in CHF millions	37,672	37,672	39,479	39,479
Avoided fatal costs in CHF millions	62,787	356	65,798	373
Total avoided costs in CHF millions	100,460	38,028	105,277	39,852
Treatment cost	19,104	19,104	4776	4776
Screening costs (CHF 75 per case) in CHF million	0	0	320	320
Treatment and screening cost in CHF million	19,104	19,104	5096	5096
Extra costs in 10 years in CHF million	−81,356	−18,924	−10,0182	−34,756
Cost / savings per person in CHF	−19,095	−4442	−23,514	−8158
ICER			−2.91	−7.69

ICER = incremental cost-effectiveness ratio; RRR = relative risk reduction; TPA = total plaque area

Table S3: Base-case assumptions of the Swiss Medical Board (SMB).

Ratio of fatal to nonfatal events	1:4.5	SMB report 2014 [13]
Cost of a fatal cardiovascular event (CHF)	8500	Pletscher SMW 2013 [46]
Cost of a nonfatal cardiovascular event (CHF), 1st year	2000	Pletscher SMW 2013
Cost of a nonfatal cardiovascular event (CHF), after 1st year	8000	Pletscher SMW 2013
Annual statin and monitoring cost per patient (CHF)	470	SMB report 2014
QALY reduction for nonfatal cardiovascular event	0.2	SMB report 2014
QALY reduction for fatal event over 5 years in n = 1000 (2 × 2.5)	5.0	SMB report 2014
QALY reduction for nonfatal event over 5 years in n = 1000 (9 × 2.5 × 0.2)	4.5	SMB report 2014
Risk of fatal or nonfatal event in 5 years in n = 1000 (2 fatal, 9 nonfatal)	11	SMB report 2014
Statin effect per person in 5 years	0.0095	SMB report 2014
QALY reduction for fatal event over 10 years in n = 1000 (4 × 5)	20.0	Felder 2013 [14]
QALY reduction for nonfatal event over 10 years in n = 1000 (18 × 5 × 0.2)	18.0	Felder 2013
Risk of fatal or nonfatal event in 10 years in n = 1000	22	Felder 2013
Statin effect per person in 10 years	0.038	Felder 2013
Statin effect over 10 instead of 5 years, multiplicative QALY (38/9.5)	4	Felder 2013
LDL reduction 50% (individual data computation)		Karlson [10]
LDL = low-density lipoprotein; QALY = quality-adjusted life year		