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Cost-Effectiveness-Analysis of Statins in primary care. Results from the Arteris Cohort Study

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Abstract:	Background The 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 (CEA) of high-potency statins. Results Subjects (N=2 842) were followed for 5.9 ± 2.9 years with occurrence of 154 cardiovascular events (extrapolated 10-year risk was 9.2%). Carotid plaque imaging (TPA) significantly improved cardiovascular risk prediction when compared to AGLA and SCORE regarding event-free survival prediction, test accuracy (discrimination) and calibration. Discrimation was significantly improved by about 4% percent with TPA. CEA using QALY and sensitivity analyses (based on 16 models) ranged between CHF 144’496 to -128’328 per QALY. CEA using direct and indirect costs showed that a treat-them-all strategy in the Swiss population would be cost-effective with return-on-investment per patient in 10 years between CHF 4’442 to 19’059 and the use of carotid imaging was also cost-effective (ICER -2.97 to -7.86). Conclusions Carotid ultrasound significantly improved cardiovascular risk stratification and is cost-effective. The SMB 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.
Keywords:	Primary prevention; health economics; statin therapy
Additional Information:	

Question	Response
I confirm that neither this manuscript, nor any other with substantially similar content by one or more of the same authors, has been published, accepted or is currently being assessed by another journal with a view to publication.	Yes
I certify that all authors have participated sufficiently (1) in the conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.	Yes
Trial registration number: We encourage the registration of clinical trials in a primary registry that participates in WHO's International Clinical Trial Registry Platform. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Please include the trial registration number and the name of the trial registry at the end of the abstract too.	n/a
We require every article reporting results of prospective research using human subjects or samples or results of animal research to include a statement that the study obtained ethics approval, including the name of the ethics committee(s) or institutional review board(s) and the number/ID of the approval(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why.	Name of the ethics committee(s) or institutional review board(s): n/a Number/ID of the approval(s): n/a
Please specify the study design. Please note that particular forms of articles submitted to SMW should adhere to reporting guidelines as specified below:	Other
Have you obtained consent from the patient if there is an unavoidable risk of breach of privacy? (Please note that the	No - - Informed consent is not necessary for this paper.

manuscript will not be reviewed until this consent is received.)	
Have figures or tables from other publications been used? (Permission to reprint figures or tables from other publications must be obtained by the author prior to submission of the manuscript. A copy of the permission from the copyright holder has to be sent to the editorial office.)	No - No copyrighted material has been used.
Please disclose outside financial support or other financial relationships (both personal and institutional) that could be viewed as presenting a potential conflict of interest in connection with the submitted manuscript. A conflict of interest statement is published with each paper. (We do not need to receive signed copies of the authors' forms now, but if your manuscript is accepted for publication the editorial office will ask you to return the authors' forms signed by each author.)	none to disclose
Response to Reviewers:	please see file: QALY_SMW_ResponseToReviewers_032021.docx for the fully formatted version of the responses Response to Reviewers #2 SMW-D-20-00354 Cost-Effectiveness-Analysis of Statins in primary care. Results from the Arteris Cohort Study Answers by Authors in blue. Text changes in red. Reviewers' comments: Reviewer #1: The questions and comments raised by the reviewers have all been answered properly. Reviewer #3: The responses are appropriate to the reviewer's points. I would advise to spell out abbreviations CEA and TPA in the abstract. Answer 1: This has been done, thank you for the comment Reviewer #4: Thank you for your comprehensive response in addressing previous peer review comments. However, there are a few more observations that if addressed could add to the quality of the paper. Further comments 1. Lifetime horizon: Thank you for clarifying that a 5 year and 10-year horizon was reported. However, in Lin et al (2015), it was stated that "Shortening the time horizon from lifetime to 10 years (simulating limited life expectancy) considerably increased the ICER…" which may suggest that a lifetime horizon would be a suitable choice.

Answer 1: In the paper by Lin et al an increased ICER was reported in a Singapore CEA model in elderly patients with limited life expectancy (< 10 years). Our population was composed of subjects aged 50±8 years. Since all patients were free of cardiovascular diseases and diabetes at the time of study inclusion, and mortality was very low during observation time, we estimate that ICER was not artificially inflated in this cohort.

2. Discounting: It is established as best practice when executing a cost effectiveness analysis to discount both costs and benefits (See Drummond and Jefferson, 1996). Authors' justification on the effect of discounting being minimal cannot be held as valid.
References:
- Lin L, Teng M, Zhao YJ, Khoo AL, Seet RC, Yong QW, Yeo TC, Lim BP. Long-term Cost-effectiveness of Statin Treatment for Primary Prevention of Cardiovascular Disease in the Elderly. Cardiovasc Drugs Ther. 2015 Apr;29(2):187-97. doi: 10.1007/s10557-015-6584-7. PMID: 25860556.
- Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. British Medical Journal 313: 275-837

Answer 2: Thank you for providing the interesting paper by Drummond et al about discounting costs and benefits. Discounting in economic medical studies has been discussed by Drummond et al as being controversial. Costs of statins are likely not more discountable in the future, since prices are already very low. Discounting benefits of prevented events implies that the cost of the treatment of non-prevented events decrease over time. However, treatment cost are rather compounding than discounting. This has it's theoretical grounds in Baumol Cost Disease in Health Care, a theory, that in the meantime has been confirmed for Switzerland1. According to Dave et al, 28% of studies in health care did not use discounting, which shows, that the topic is still controversial2. As an example, The National Institute for Health and Care Excellence (NICE) guidelines for discounting (6% for costs and 1.5% for effects) were the first to prescribe differential discounting, but rather these were changed back to equal discounting (3.5% each). Brouwer et al. questioned this change, also in light of the Dutch guidelines, which were changed in the same period to prescribe differential discounting (4 and 1.5% for costs and effects respectively3. Rathi et al argued against discounting of resources needed for diseases treatments and also pointed out to the fact that the value of life should not be discounted for ethical reasons4. Certainly, it would be appropriate to discount prices of original statins (because of the decrease in costs over time, when generic statins become available). In the BAG HTA paper on statins in primary care (https://docfind.ch/H0032CHOL_Corrected%20HTA%20Report%20Statins.pdf) results of discounting are displayed in Table 8.22 (Scenario analysis). From this it becomes clear, that a uniform discount rate is in disfavour of the treatment effect and increases ICER from ≈ 48 000 (no discounting) to ≈ 85 000 (3% uniform discounting). If we apply differential discounting with 3% for costs and 1.5% for effects, ICER is reduced to ≈ 51 000 (see Table below).

New BAG HTA version
DiscountingNo3%/3%6%/6%3%/1.5%
Cost A10576766058597660
Cost B0000
Effect A0.220.0870.03890.15
Effect B0000
ICER480738804615061751067
In view of the Baumol cost-disease effect it appears prudent to use differential discounting or no discounting for effects at all. We propose to add a text in the limitation section as follows:
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 discussed3. Since statin prices are low, application of discounts does not appear to be valid. Discounting effects (either on QALY, cost of lost life-year and treatment costs) is also problematic for two major reasons: treatment cost tend to increase over time (Baumol cost-disease)1 and discounting the value of life (in QALY) appears unethical4.

	3. Absolute risk reduction: Thank you for providing clarification on absolute risk reduction. Please include said remarks in the text. We added the following text in the methods section: 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 (ARR) is therefore reduced by an effective medical therapy, that has a certain amount of relative risk reduction (e.g., 20%). Therefore, if risk is reduced by 20% from 10% to 8%, then the ARR is 2%. NNT is 100/ARR. References to Reviewers 1. Hartwig J, Krämer H. Baumolsche Kostenkrankheit im schweizerischen Gesundheitswesen. Schweizerische Ärztezeitung EMH Swiss Medical Publishers, Ltd.; 2018;99:874–877. 2. Smith Dave, Gravelle Hugh. The Practice of Discounting EconomicEvaluation of Health Care Interventions. Pract. Discount. Econ. Eval. Heal. Care Interv. 2020. https://www.researchgate.net/profile/M-Krahn/publication/14697308_Discounting_in_the_Economic_Evaluation_of_Health_Care_Interventions/links/59fb18a8aca272347a1d07ba/Discounting-in-the-Economic-Evaluation-of-Health-Care-Interventions.pdf (8 March 2021) 3. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. Pharmacoeconomics. Springer International Publishing; 2018. p. 745–758. 4. Hemant Rathi, George Papadopoulos. Should discount rates be selectively applied in health economic evaluations? Skyward Anal. Pte. Ltd., Singapore Lucid Heath Consult. Pty. Ltd., Aust. Univ. New South Wales, Sch. Med. Aust. 2020. https://lucidhealthcon.com/should-discount-rates-be-selectively-applied-in-health-economic-evaluations/ (8 March 2021)

Response to Reviewers #2

SMW-D-20-00354

Cost-Effectiveness-Analysis of Statins in primary care. Results from the Arteris Cohort Study

Answers by Authors in blue. Text changes in red.

Reviewers' comments:

Reviewer #1:

The questions and comments raised by the reviewers have all been answered properly.

Reviewer #3:

The responses are appropriate to the reviewer's points. I would advise to spell out abbreviations CEA and TPA in the abstract.

Answer 1: This has been done, thank you for the comment

Reviewer #4:

Thank you for your comprehensive response in addressing previous peer review comments. However, there are a few more observations that if addressed could add to the quality of the paper.

Further comments

1. Lifetime horizon: Thank you for clarifying that a 5 year and 10-year horizon was reported. However, in Lin et al (2015), it was stated that "Shortening the time horizon from lifetime to 10 years (simulating limited life expectancy) considerably increased the ICER…" which may suggest that a lifetime horizon would be a suitable choice.

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New BAG HTA version

Discounting	No	3%/3%	6%/6%	3%/1.5%
Cost A	10576	7660	5859	7660
Cost B	0	0	0	0
Effect A	0.22	0.087	0.0389	0.15
Effect B	0	0	0	0
ICER	48073	88046	150617	51067

In view of the Baumol cost-disease effect it appears prudent to use differential discounting or no discounting for effects at all. We propose to add a text in the limitation section as follows:

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References to Reviewers

1. Hartwig J, Krämer H. Baumolsche Kostenkrankheit im schweizerischen Gesundheitswesen. *Schweizerische Ärztezeitung* EMH Swiss Medical Publishers, Ltd.; 2018;**99**:874–877.
2. Smith Dave, Gravelle Hugh. The Practice of Discounting EconomicEvaluation of Health Care Interventions. Pract. Discount. Econ. Eval. Heal. Care Interv. 2020. https://www.researchgate.net/profile/M-Krahn/publication/14697308_Discounting_in_the_Economic_Evaluation_of_Health_Care_Interventions/links/59fb18a8aca272347a1d07ba/Discounting-in-the-Economic-Evaluation-of-Health-Care-Interventions.pdf (8 March 2021)
3. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. Pharmacoeconomics. Springer International Publishing; 2018. p. 745–758.
4. Hemant Rathi, George Papadopoulos. Should discount rates be selectively applied in health economic evaluations? Skyward Anal. Pte. Ltd., Singapore Lucid Heath Consult. Pty. Ltd., Aust. Univ. New South Wales, Sch. Med. Aust. 2020. https://lucidhealthcon.com/should-discount-rates-be-selectively-applied-in-health-economic-evaluations/ (8 March 2021)

Cost-Effectiveness-Analysis of Statins in primary care. Results from the Arteris Cohort Study

Authors:

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wordcount: 4’980 (incl. abstract)

Abstract

Background

The 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 (CEA) of high-potency statins.

Results

Subjects (N=2 842) were followed for 5.9 ± 2.9 years with occurrence of 154 cardiovascular events (extrapolated 10-year risk was 9.2%). Carotid plaque imaging (TPA) significantly improved cardiovascular risk prediction when compared to AGLA and SCORE regarding event-free survival prediction, test accuracy (discrimination) and calibration. Discrimation was significantly improved by about 4% percent with TPA. CEA using QALY and sensitivity analyses (based on 16 models) ranged between CHF 144'496 to -128'328 per QALY. CEA using direct and indirect costs showed that a treat-them-all strategy in the Swiss population would be cost-effective with return-on-investment per patient in 10 years between CHF 4'442 to 19'059 and the use of carotid imaging was also cost-effective (ICER -2.97 to -7.86).

Conclusions

Carotid ultrasound significantly improved cardiovascular risk stratification and is cost-effective. The SMB 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.

List of Abbreviations

ASCVD	atherosclerotic cardiovascular disease
AMI	fatal or nonfatal acute myocardial infarction
AUC	area under the curve
BMI	body mass index
BP	blood pressure (systolic)
CABG	coronary artery bypass grafting
cAge	chronological age
CEA	cost-effectiveness analysis
CI	confidence interval
HR	hazard ratio
ICER	incremental cost-efficiency ratio
LR	likelihood ratio
NRI	net reclassification improvement
PT	posttest
PTCA	percutaneous transluminal coronary angioplasty
PTP	posttest probability
PV	prevalence
ROC	receiver operating curves
SD	standard deviation
SE	sensitivity
SP	specificity
TPA	Total plaque area (carotid plaque)
tpacode	Total Plaque Area Code (0=no atherosclerosis, 1=1st tertile, 2=2nd tertile, 3=3rd tertile)
PROCAM	Prospective Cardiovascular Münster Study for fatal and non-fatal 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

Introduction

Statins reduce cardiovascular risk by 22% per 1 mmol/l LDL reduction in secondary prevention [1] and by 29% in primary prevention [2]. Shared decision to treat patients with statins is based on evidence and guidelines, e.g. the European Lipid Guidelines 2019 [3].

According to The Swiss Federal Office of Public Health (FOPH), the prescription of statins in primary care may not be cost-effective and should be evaluated in a health technology assessment (HTA) 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].

Due to a possible restriction of reimbursement for statin therapy in the population at low or at intermediate risk we designed and conducted an individual-level cohort study using outcome data to test the hypothesis, that the patient who will experience a cardiovascular event in the future cannot be correctly stratified by AGLA and SCORE risk categories. This is due to a substantial portion of cardiovascular events occurring in patients with low and intermediate risk, whereas carotid plaque presence may allow for a substantially improved risk stratification. We use the Swiss Medical Board 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 CEA. We calculate 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 calculate on 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) to coronary / cardiovascular risk equations as predictors.

For sample size estimation, we calculated N=252 with 12 cases for ROC analysis, N=2208 with 138 cases for comparative ROC analysis. Patients with known 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 pseudonymization.

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 ethical 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, diabetes mellitus and be within the age range of 30 to 65 years. Laboratory values, blood pressure and medical history were measured locally and entered into a spread-sheet (Excel, Microsoft, Richmond, USA).

Patient information

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

Follow-up information

We contacted patients by telephone, email or post mail and asked patients to inform us about occurrence of cardiovascular events (either fatal or non-fatal myocardial infarction, PTCA, coronary artery bypass grafting (CABG), fatal or non-fatal stroke or transient ischemic attack, or presence of a significant stenosis assessed by 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 end-point was adjudicated to myocardial infarction. The primary endpoint was a composite of acute myocardial infarction, stroke/TIA or CABG. The secondary endpoint included the primary endpoint plus PTCA

and coronary artery disease. Results were further compared to a single outcome measure (fatal or non-fatal myocardial infarction only).

Sensitivity Analysis

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

Ethical aspects

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

Carotid imaging

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 up to the total plaque area (TPA) in mm^2. All TPA measurements were made by A.A. in Koblenz and by M.R. 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 NRI calculations we calculated sensitivity and specificity of TPA tertiles and AA classes and derived posttest risk calculations for PROCAM and SCORE using the Bayes theorem as described elsewhere [9].

Effect estimates of LDL Lowering

For each of the 4 TPA groups (no plaque, TPA tertiles), average LDL levels are presented with the expected risk reduction achievable with Statins (Atorvastatin ~~40~~ 80 mg or Rosuvastatin ~~10~~ 20 mg per day at daily cost < 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 (ARR) is therefore reduced by an effective medical therapy, that has a certain amount of relative risk reduction (e.g., 20%). Therefore, if risk is reduced by 20% from 10% to 8%, then the ARR is 2%. NNT is 100/ARR. From that, absolute risk reduction, either with an RRR of 22% or 29%, was calculated and the numbers-needed-to-treat derived for each individual. Computation of risks associated with TPA tertiles and comparison to no plaque as the comparator is a standard procedure to stratify risk cohort [11,12].

Effect model of the SMB

The SMB model [13] for calculating cost/QALY (ICER) is as follows. For one fatal cardiovascular event (myocardial infarction, stroke, coronary revascularisation), 4.5 nonfatal events occur. The cost is CHF 8 500 per fatal event; and CHF 25 000 per nonfatal event in the first year and CHF 8 000 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. 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 non-fatal 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 (multiplicative QALY [14]). The SMB based its assumptions regarding statin effects on the Cholesterol Treatment Trialists' (CTT [2,15]) study published in 2012.

Calculation of direct and indirect medical costs:

Direct and indirect costs of fatal and non-fatal myocardial infarction and stroke were calculated as follows. Based on the final Swiss report on NCD costs 2014 [16] for the year 2011 (www.docfind.ch/CVDCosts2011.xlsx):

- Acute myocardial infarction cost estimates Swiss Francs 4'798'000'000 (direct costs: 2'760'000'000 CHF)
- Stroke cost estimates Swiss francs 3'168'000'000 (direct costs: 2'089'000'000)
- Swiss death registers found 7'703 deaths due to ischemic heart disease in the year 2011.

Assuming that for every death there are 3 non-fatal myocardial infarctions (based on Framingham Data), we estimate the number of fatal and non-fatal myocardial infarctions to be 38'515 (Switzerland, 2011). Assuming a ratio of myocardial infarction and stroke of 3.5, which is comparable to the ratio derived from Framingham risk charts (4.5 in male and 2.6 in female, 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 estimate 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 147'995 Swiss Francs per myocardial infarction or 345'125 per stroke. Accounting for the case-mix estimate, the average costs per patient are 251'622 Swiss Francs. In view of the fact that avoidable cost was calculated over a time 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 200'000 Swiss francs per event (coronary revascularization 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 of nature and reversible [15,19–22], we did not include those 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, e.g. 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 150 000 CHF per QALY, then the threshold for the 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, e.g., 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^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere [25]. Survival analysis was performed with Kaplan Meier survival analysis and Cox proportional-hazards regression after adjustment for cardiovascular risk factors in Model 1 (sex, age, smoke, BMI, total cholesterol, HDL, LDL, triglycerides, systolic blood pressure, use of hypertensive and lipid lowering drugs) and after adjustment for risk charts (Model 2) both for the primary and secondary outcome. Further we assessed model performance using model fit (CHI2), discrimination (ROC analysis) and calibration (Hosmer & Lemeshow test). Patients were split regarding TPA in those without atherosclerosis (reference group) and tertiles of TPA. Sensitivity and specificity of TPA tertiles was analysed and used for posttest calculations with PROCAM and SCORE as the prior probabilities using the BAYES theorem.

The formula for the calculation of posttest probabilities was:

PTP pos: (PV x SE) / [PV x SE+(1 –PV) x (1 –SP)]

PTP neg: [PV x (1 –SE)] / [PV x (1 – SE) +SP x (1 –PV)]

Where PTP denotes posttest 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 data on subjects from the cardiological practice KARDIOLAB in Olten, Switzerland (N=1255), the vascular risk foundation VARIFO in Olten, Switzerland (N=1050) and the prevention center in KOBLENZ, Germany (N=3326). Therefore, the ARTERIS group contains 5631 subjects, from which the following subjects 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 dominantly visited in Koblenz, Germany (80%) and the German cohort contributed to the total of ASCVD event in 123 out of 154 cases (80%). Events are 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 these 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 N=1 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 to 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 the total of both groups. Comparing the group with events (both primary and secondary outcome) to the group without events, all clinical and risk variables showed adverse characteristics for the event groups namely regarding the frequency of smoking, sex and regarding 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 did report not having taken statins despite knowledge of

the imaging results.

Table 2 show the Hazard Ratios (and 95% CI) for cardiovascular endpoints associated with TPA. Significant prediction improvements of cardiovascular risk factors (Model 1) and risk charts (Model 2) were realized 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 model fit by CHI^2 was significantly improved for TPA beyond risk equations (regarding PROCAM, SCORE), discrimation was significantly improved by about >4% percent 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 to PROCAM and SCORE).

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

Table 6 shows cost-efficacy analysis (using the SMB model) for the whole group of patients with direct costs (Model 1) and total cost defined by direct and indirect costs (Model 2), further stratified for multiplicative and additive QALY [14], for 5 or 10 years and for relative risk reduction per 1.0 mmol/l LDL reduction 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 costs of CHF 75 per patient to determine TPA. Even if costs for fatal events, that could be avoided are minimized to CHF 8’500, the imaging strategy leads to a return on investment of CHF 8’158 (or CHF 23’514, if case fatality is included with CHF 1.5 Mio over 10 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 to -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 categorized as having low AGLA risk. The distribution of events in the high-risk segments was 7% for AGLA and 18% for SCORE.

Appendix Table 1 shows cost-effectiveness results for several base-case cardiovascular risks. As expected, cost / QALY show a large variation (depending on duration of therapy, VSL values, additive or multiplicative QALY), with ranges for CHF/QALY (ICER) between 485 663 / QALY to – 93 483 / QALY.

Appendix Table 2 shows insignificant changes in the cost-effectiveness results of Table 7, where the relation of fatal to non-fatal events was changes from 1:45 (SMB assumption in Table 7) to 1:6.3 as observed in the ARTERIS cohort.

Appendix Table 3 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 non-fatal events in 1 000 persons treated with statins. Therefore, there were 1.1% at risk over five years or – with linear extrapolation – 2.2% in ten years. The effect of multiplicative QALY is also shown. The model assumes, that all events occur at ½ time of the total treatment time, e.g., after 2.5 years when treatment duration is 5 years, or after 5 years when treatment duration is 10 years.

Discussion

Our patient-level dual-center 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 or stenting or presence of coronary artery disease defined by a coronary stenosis of > 50% defined by an invasive coronary angiogram.

Risk prediction with TPA, AGLA, and SCORE

Stratification of the cohort based on ultrasound imaging with TPA into 4 groups with either no carotid plaque (reference group) or carotid plaque tertiles of TPA, lead to an extrapolated 10-year event rate was 0.3%, 0.7%, 2.9% and 38.2%. Only 7% of patients with events had a risk above AGLA 20% and only 34% had an AGLA risk above 10%; SCORE over 5% was present in only 18% of subjects with events. Throughout TPA tertiles, AGLA remained on average within the low-risk category as well as SCORE, which did not exceed an average risk 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 having 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 increased life-time risk for higher morbidity, mortality and costs.

Cost-effectiveness analysis (CEA) using QALY

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 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 (where daily prices are < 1.00 CHF, but we used the SMB assumption of daily costs of 1.00 CHF) computed at individual level data and by using additive and multiplicative QALY's [26]. 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 < CHF 150’000 per QALY.

HTA cost-effectiveness analysis using aggregated data for risk categories will be unable to detect patients who would benefit from statins and a denial of any statin treatment in this risk category is unable to positively influence the atherosclerotic epidemy. On the other hand, a stratification of patients with SCORE, but not with AGLA (due to calibration and labeling 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 show a large range of results using CEA, which points to the problem, that QALY models can be easily used to calculate desired cost-efficacies. We show that the variability of CEA using the QALY concept is high with costs per QALY ranging between 144’496 and -128’328. The second study hypothesis is thus accepted and QALY 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 HTA report on statins of the FOPH[27]), 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” is not only cost-effective, but it will save lives and avoid morbidity in the Swiss population aged 30-65 years. Annually, 4’186 cardiovascular deaths and 18’836 cardiovascular events could be avoided with cost-savings of CHF 1.4 to 7.0 Mia (direct and indirect costs). The efficacy of statins will increase with a more selected use resulting from personalized clinical stratification using TPA with cost savings of CHF 3.4 to 10.0 Mia 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 optimization 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 very cost-effective [28,29].

Our ratio of direct to indirect cost was found to be 61/39, others have found a ratio of 1:1 [30]; 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)[31,32]. 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 economist like to "qaly" medicine. In this context, "I qaly" the health care system, is the expression of an evolving mathematical machinery [33], that aims to give answers to the question, whether a medical therapy is indicated or not. Health economist claim, that QALY is a reliable metric like body size or weight. However, QALY are influenced by cultural, social, individual, extrinsic or intrinsic observations and factors, and experience of life quality based upon physical, psychological, interpersonal, socio-economic and spiritual dimensions that are never constant over time. The constancy of the multiplicative utility function over time is not evidence-based, the function can never be evidence based at the individual level. Too many variables influence utility and therefore, QALY are expressing a fixed utility over time [34], which creates an axiomatic expression [26] of what is claimed to be real and is completely unrelated to human life quality despite the claims of health-economists to measure life quality. QALY are not reproducible as a metric, hampered by several biases (especially response shift and recall bias) and they lack a gold standard [35,36].

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 [37]. 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 at the high-risk level.

Limitations

We present a practice-based analysis and not a random-sample population-based analysis. Therefore, absolute numbers of 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 8'500 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 $182'000 (Australia 2014 [38]) and $ 129'000 (USA 2009 [39]) and around €150'000 in Europe [40].

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 non-fatal events did not change the results or 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 [41].

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[42]. Since statin prices are low, application of discounts does not appear to be valid. Discounting effects (either on QALY, cost of lost life-year and treatment costs) is also problematic for two major reasons: treatment cost tend to increase over time (Baumol cost-disease)[43] and discounting the value of life (in QALY) appears unethical[44].

In conclusion, we can confirm that our three study hypotheses are valid: 1. Using carotid ultrasound for imaging plaque burden, cardiovascular risk stratification is significantly improved, cost-effective and cost-efficient. 2. The SMB QALY model presents several draw backs, which are shown

in our sensitivity analysis, where results vary considerably, which limits their 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-efficiently improved with personalized risk models based on carotid plaque imaging.

Conflict of interest:

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Tables

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

N=	2 842
Female (%)	1080 (38%)
Age + SD	50±8
Smoker, %	609 (21%)
BP mm Hg, systolic + SD	126±16
BMI + SD	26±4
Cholesterol + SD, mmol/l	6.0±1.1
HDL + SD, mmol/l	1.5±0.4
LDL+ SD, mmol/l	3.7±0.9
Triglyceride + SD, mmol/l	1.6±1.1
TPA + SD, mm2	42±54
SCOREca + SD, %	1.3±1.6
PROCAMca + SD %	4.8±6.4
AGLAca + SD %	3.3±4.5

Table 2: HRs (95% CI) for cardiovascular end points associated with TPA tertiles adjusted for traditional cardiovascular risk factors (model 1) and for PROCAMca, SCOREca, and FRAMca (model 2)

TPA	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: 1. tertile (<22 mm^2); 2. tertile (22-61 mm^2); 3. tertile (≥ 62 mm^2)
Variables used for adjustment in model 1 were age, smoke, sex, systolic BP, lipids, BMI, medication use (separate for antihypertensive and lipid lowering drugs).

Table 3: Model performance regarding global CHI^2, discrimination and calibration

Model	Model fit		Discrimination	Calibration	
	chi2	P-value	C-Index (95% CI)	chi2	P-value
PROCAMca	140.114	P < 0.0001	0.831 (0.816 to 0.844)	53.5126	P < 0.0001
PROCAMca + TPA	232.964	P < 0.0001	**0.869 (0.856 to 0.881)**	44.8182	P < 0.0001
SCOREca	137.836	P < 0.0001	0.824 (0.809 to 0.838)	38.0416	P < 0.0001
SCOREca + TPA	199.707	P < 0.0001	**0.866 (0.853 to 0.879)**	61.3254	P < 0.0001

Table 4: Net Reclassification Improvement (NRI) using posttest 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 to 0.486)	<0.0001
SCORE	**Ref model**		
SCORE + Bayes TPA	0.373	(0.307 to 0.439)	<0.0001

Table 5: characteristics of patients stratified by atherosclerosis presence (TPA tertiles), effect of Statin therapy (with RRR 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 (%)	2 842 (100)	728 (26)	688 (24)	719 (25)	707 (25)
Age ± SD	50.1 ± 7.6	44.3 ± 6.4	49.8 ± 7.0	51.8 ± 6.8	54.7 ± 5.9
LDL mmol/l ± SD	3.7 ± 0.9	3.4 ± 0.8	3.6 ± 0.9	3.8 ± 0.9	4.1 ± 1.0
FU years ± 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
Event10 %	10.0	0.5	1.2	5.0	38.2
SCORE % ± SD	1.3 ± 1.6	0.5 ± 0.6	0.9 ± 1.0	1.4 ± 0.9	2.6 ± 2.2
SCORE SMB % ± SD	7.3 ± 8.8	2.5 ± 3.5	5.0 ± 5.2	7.6 ± 5.0	14.1 ± 12.0
PROCAM % ± SD	4.8 ± 6.4	1.8 ± 2.9	3.0 ± 4.0	4.9 ± 2.8	9.5 ± 8.7
AGLA % ± 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

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

		5 years		10 years	
QALY		Model 1	Model 2	Model 1	Model 2
multiplicative	RRR 0.22	144 496	32 285	62 774	-2 805
additive	RRR 0.22	144 496	32 285	125 548	-5 610
multiplicative	RRR 0.29	100 725	-90 433	40 889	-64 164
additive	RRR 0.29	100 725	-90 433	81 777	-128 328

Model 1 costs: CHF 8'500 for a fatal event, CHF 25'000 for a non-fatal event in the first year, CHF 8'000 for a non-fatal event, subsequent years (Baseline Model of the Swiss Medical Board[13], reflecting direct cost per event based on assumptions by Pletscher et al[45].

Model 2 costs: CHF 150'000 per year per fatal event, CHF 50'000 for a non-fatal event in the first year, CHF 16'000 for a non-fatal event, 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" in the Swiss Population (age 30-65), stratified further for avoidable costs per fatal case of either CHF 1.5 Mio in 10 years or once CHF 8'500 (treatment costs according to SMB)

	Treat			
Strategy	**ALL**	**ALL**	**TPA 3rd Tert**	**TPA 3rd Tert**
30-65 (2017)	RRR 0.29	RRR 0.29	RRR 0.29	RRR 0.29
N	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 non-fatal 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 non-fatal costs in Mio	37 672	37 672	39 479	39 479
Avoided fatal costs in Mio	62 787	356	65 798	373
Total avoided costs in Mio	100 460	38 028	105 277	39 852
Treatment cost	19 104	19 104	4 776	4 776
Screening costs per case 75 Fr. in Mio	0	0	320	320
Treatment and screening cost in Mio CHF	19104	19104	5096	5096
Extra costs in 10 years in Mio CHF	-81356	-18924	-100182	-34756
Cost / Savings per person in CHF	-19095	-4442	-23514	-8158
ICER			-2.97	-7.86

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

	N %	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
	N %	Event Rate	Events %
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

Online Appendix tables

Appendix Table 1: 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 1x 8 500					Value of life 150'000 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	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										
	Value of Life CHF 1x 8 500					Value of life 150'000 per life year lost				
Event rate for fatal or non-fatal 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	-2'805	167'778	39'469	-6'366	-46'742
Cost per QALY (CHF) additive QALY	125'548	466'715	210'096	118'427	37'674	-5'610	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 1x 8 500					Value of life 150'000 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										
	Value of Life CHF 1x 8 500					Value of life 150'000 per life year lost				
Event rate for fatal or non-fatal 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	7'557	-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

Appendix Table 2: Sensitivity analysis using SMB relation of fatal to non-fatal cases (Table 7) and ARTERIS relation (1:6.3).

1 Death in 6.33 non-fatal events scenario	Treat			
Strategy	ALL	ALL	TPA 3rd Tert	TPA 3rd Tert
30-65 (2017)	RRR 0.29	RRR 0.29	RRR 0.29	RRR 0.29
N	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 non-fatal 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 non-fatal costs in Mio	37'672	37'672	39'479	39'479
Avoided fatal costs in Mio	62'787	356	65'798	373
Total avoided costs in Mio	100'460	38'028	105'277	39'852
Treatment cost	19'104	19'104	4'776	4'776
Screening costs per case 75 Fr. in Mio	0	0	320	320
Treatment and screening cost in Mio CHF	19104	19104	5096	5096
Extra costs in 10 years in Mio CHF	-81356	-18924	-100182	-34756
Cost / Savings per person in CHF	-19095	-4442	-23514	-8158
ICER			-2.91	-7.69

Appendix Table 3: Base-case assumptions of the Swiss Medical Board (SMB)

Relation of fatal to non-fatal events	1:4.5	SMB report 2014 [13]
Cost of a fatal cardiovascular event (CHF)	8 500	Pletscher SMW 2013 [46]
Cost of a non-fatal cardiovascular event (CHF), 1st year	25 000	Pletscher SMW 2013
Cost of a non-fatal cardiovascular event (CHF), after 1st year	8 000	Pletscher SMW 2013
Annual statin and monitoring cost per patient (CHF)	470	SMB report 2014
QALY reduction for non-fatal cardiovascular event	0.2	SMB report 2014
QALY reduction for fatal event over 5 years in N=1000 (2x2.5)	5.0	SMB report 2014
QALY reduction for non-fatal event over 5 years in N=1000 (9x2.5x0.2)	4.5	SMB report 2014
Risk of fatal or non-fatal event in 5 years in N=1000 (2 fatal, 9 non-fatal)	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 (4x5)	20.0	Felder 2013 [14]
QALY reduction for non-fatal event over 10 years in N=1000 (18x5x0.2)	18.0	Felder 2013
Risk of fatal or non-fatal 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]