PROCAM based myocardial infarction risk in relation to global vascular disease risk: observations from the ARCO cohort study

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Abstract

Background

In Switzerland, risk for acute myocardial infarction (AMI) has been labelled as risk for atherosclerotic cardiovascular disease (ASCVD). This may lead to an underestimation of ASCVD risk and prevent adequate preventive measures.

Methods

We calculated correction factors for AMI risk to obtain ASCVD risk, tested predicting abilities of PROCAM/AGLA, SCORE, HerzCheck® and carotid plaque imaging (TPA) for ASCVD events in this cohort study and calculated survival curves, calibration and discrimination for ASCVD outcomes derived from PROCAM/AGLA, SCORE and TPA.

Results

In 2 842 subjects (age 50±8, 38% women) 154 (5.4%) cardiovascular events occurred (ASCVD: 41 myocardial infarctions, 16 strokes or TIA, 21 CABG, 41 PTCA, 35 coronary artery diseases defined by invasive angiography) during a mean follow-up time of 5.9 (1-12) years. AGLA-AMI risk was well calibrated for AMI (15% underreported risk for the risk of acute myocardial infarction), but was poorly calibrated for ASCVD (STROKE, CABG, PTCA or CAD, which contributed to the secondary outcome variables) with underreported risk resulting in a correction factor of 3.45. Discrimination was comparable for all risk calculators, but TPA outperformed risk calculators for survival using Cox proportional survival functions. Net reclassification improvement (NRI) for PROCAM and SCORE using TPA tertiles groups increased significantly between 30% to 48%.

Conclusions

PROCAM derived risk calculators are well calibrated for the risk of myocardial infarction (AMI). PROCAM-AMI should be multiplied by a factor of 4 to obtain ASCVD. PROCAM-AMI does not represent global cardiovascular risk. Corresponding adjustments in the AGLA communication of risk appear necessary.

List of Abbreviations

AA	arterial age
AGLA	national working group on lipids and atherosclerosis of the Swiss Society of Cardiology
AGLA-AMI	AGLA risk for myocardial infarction
AUC	area under the curve in ROC analysis
ASCVD	atherosclerotic cardiovascular disease
AMI	fatal or nonfatal acute myocardial infarction
AMISTR	risk for AMI and stroke
AMISTRCABG	risk for AMI, stroke and coronary artery bypass grafting
AUC	area under the curve
CABG	coronary artery bypass grafting
CAD	coronary artery disease defined as > 50% narrowing of an epicardial coronary artery detected by invasive coronary angiography
CVD	cardiovascular disease
FHS	Framingham heart study
FRAM	Framingham risk equation for fatal and non-fatal cardiovascular events
HerzCheck®	Registered by the Swiss Heart Foundation: a Procam based risk calculator for myocardial infarction only
HerzCheck-AMI	Risk of HerzCheck for AMI
NRI	Net reclassification improvement
PAD	peripheral occlusive artery disease causing claudication
PCE	Pooled cohort equation, for fatal and non-fatal cardiovascular events
PTCA	peripheral transluminal coronary angioplasty
ROC	receiver operating curves (discrimination analysis)
STR	fatal or non-fatal stroke

TPA	Total plaque area (carotid plaque)
PROCAM	Prospective Cardiovascular Münster Study for fatal and non-fatal myocardial infarction
PROCAM-AMI	PROCAM risk for myocardial infarction
PROCAM-AMISTR	PROCAM risk for myocardial infarction and stroke
PROCAMpoint-AMI	PROCAM risk for myocardial infarction based upon a point scoring system developed by the PROCAM investigators
SCORE	SCORE Risk charts and equations, European Society of Cardiology, for fatal cardiovascular events
SCORE-ASCVD	SCORE risk for ASCVD

Introduction

Preventive medicine is a pillar of basic health care and is essential to avoid disease expansion (1). In order to detect healthy subjects at risk for cardiovascular events, several calculators are based upon cardiovascular risk factors with the Framingham Heart Study (FHS) as the pioneering epidemiologic study. FHS was begun in 1948 with 5,209 men and women (2) and identified major independent cardiovascular risk factors such as age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. The Framingham Heart Study defines CVD as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure (2). In Germany, PROCAM-based calculators have been published by the Assmann Foundation (https://www.assmann-stiftung.de/procam-tests/), where risk for fatal or non-fatal myocardial infarction (AMI) and risk for fatal or non-fatal ischemic stroke (STR) can be calculated with two different risk calculators. In Switzerland, the national working group on lipids and atherosclerosis (AGLA) has recommended the PROCAM risk calculator for fatal and non-fatal myocardial infarction with a calibration factor of 0.7, because international epidemiological data (3) and results from a Swiss imaging study (4) suggested that the Swiss population is at low risk for cardiovascular events. Further, the Swiss Heart Foundation has adopted a PROCAM based score system for myocardial infarction in their HerzCheck® risk calculator (5).

In this study we address the question, how many other cardiovascular diseases such as ischemic stroke, peripheral artery disease, coronary obstruction on an invasive coronary angiogram or coronary revascularisation (ASCV) do occur per one myocardial infarction. Since such diseases are all preventable, reporting only the risk for myocardial infarction may underestimate the risk for the afore mentioned cardiovascular diseases. The reason for this

exercise is due to the fact that it has become a sort of malpractice for almost 10 years to label myocardial infarction (AMI) risk as atherosclerotic cardiovascular (ASCVD) risk in Switzerland. Such mislabeling occurs, to the best of our knowledge, in Switzerland only. Several publications (6,7), the AGLA website, the AGLA pocket guide and HerzCheck® (5) show such confounding between the risk for AMI versus ASCVD since 2013.

The frequency relation between AMI and ASCVD was assessed in Germany using the DETECT study (8), where for every AMI another 4.6 ASCVD events occurred.

In this study we first present own outcome data from the ARCO cohort study, where we assessed the occurrence of AMI, stroke (STR), peripheral transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) and obstructive coronary artery disease (CAD) and compared our results with the DETECT study. Second, we calculated calibration and discrimination as well as survival curves for the occurrence of myocardial infarction (AMI) and other cardiovascular events (ASCVD) using various risk assessment tools such as HerzCheck®, PROCAM-AMI, SCORE-ASCVD and carotid total plaque area (TPA). Third, we compared these risk assessment tools regarding the frequency of low, intermediate and high-risk results.

Materials and Methods

We used the cohort method to detect cardiovascular events and used medical imaging (total carotid plaque area, TPA) compared to coronary / cardiovascular risk equations as predictors.

Patients with known ASCVD or diabetes mellitus were excluded. Consecutive patients aged 40-65 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 or diabetes mellitus and should be within the age range of 40 to 65 years. Laboratory values, blood pressure (measured one in the sitting position after a brief resting period with a plethysmographic method for measuring the systolic blood pressure) and medical history were measured locally and entered into a spreadsheet (Excel, Microsoft, Richmond, USA).

Patient information

Blood pressure was measured in the imaging centers and a blood sample 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.

Follow-up information

We contacted patients by telephone, email or post mail and asked patients to inform us about the occurrence of cardiovascular events (either fatal or non-fatal myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), fatal or non-fatal stroke or transient ischemic attack, or presence of a significant

(≥50%) 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 endpoint 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).

We decided to add CABG to the primary endpoint to improve the statistical power with additional 21 CABG events, thus summing up to 78 primary events (total events could be nearly doubled with PTCA and CAD to 154 events). CABG is almost uniquely performed in severe coronary artery disease (left main stem or triple vessel disease) and is therefore a diagnosis related to advanced atherosclerosis and inherent cardiovascular risk."

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, since no medical intervention was performed within the study design.

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. The sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as total plaque area. Large calcified carotid plaques creating large areas of shadowing were rarely seen in subjects aged 40-65 years, therefore, this was not a significant problem when TPA was measured. Intraobserver reproducibility (MR)was tested for the right carotid artery in 57 patients with a correlation coefficient of r2 0.964 (left carotid artery: r^2 0.944, both arteries r^2 0.986). For the cutoff of TPA 0–9 mm^2, 10–49 mm^2, 50–99 mm^2 and ≥100 mm^2 Kappa value was 0.69 (0.54–0.84 95% CI) (9). All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously reported (10): we published a paper about arterial age for 1500 men and women separately and calculated arterial age as follows: mean values of TPA derived from 5-year intervals for men and women aged 35 to 79 years were plotted against the chronological age. An exponential function was added, which connected these 5-year intervals, and the equation of the line was displayed along with the 95% confidence intervals (CIs). These two exponential equations describing TPA (y) as a function of age (x) were solved for x in order to determine the age at which such an amount of TPA is generally found in the population, i.e., the arterial age, for men and women separately."

Patient status was known to A.A. and M.R. in all cases.

Computation of cardiovascular risk

Cardiovascular risk was computed using the published risk formulae in an Excel spreadsheet. We used the European Society of Cardiology risk equation for low risk populations (SCORE (11)) and the German PROCAM risk for myocardial infarction and for stroke multiplied with a correction factor of 0.7 (12). Further, we calculated point scores for HerzCheck® and PROCAM with associated 10 year risk estimates and we calculated PROCAM using the original formula (13). For NRI calculations we calculated sensitivity and specificity of TPA tertiles and arterial age (AA) classes and derived posttest risk calculations for PROCAM and SCORE using the Bayes theorem as described elsewhere (14).

Statistics

We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons (15). Groups were compared using a t-test for continuous variables and CHI^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere (16): The Net Reclassification Improvement (NRI) is a statistical tool proposed to assess improvement in model performance offered by a new method of classification compared to a reference one. The NRI indicates how much more frequently appropriate reclassification occurs than inappropriate reclassification with the use of a new model of classification. The NRI is based on reclassification tables constructed separately for participants with and without the interest event, and quantifies the correct movement in categories, upwards for events and downwards for non-events. Define upward movement (up) as a change into higher category based on the new algorithm and downward movement (down) as a change in the opposite direction. The NRI is defined as a proportion P as follows: NRI= P(up|event)−P(down|event)+P(down|non-event)−P(up|non-event). The null hypothesis for NRI = 0 is tested using Z statistic following McNemar asymptotic test for correlated proportions."

Survival analysis was performed with Kaplan Meier survival analysis and Cox proportional-hazards regression both for the primary and secondary outcome. Further we assessed model performance using discrimination (ROC analysis). Patients were split according to TPA in those without atherosclerosis (reference group) and tertiles of TPA; and were split regarding arterial age below chronological age (reference group), and those with arterial age 1-10, 11-20, and > 20 years over chronological age. Sensitivity and specificity of TPA tertiles and AA age groups 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 positive: (PV x SE) / [PV x SE+(1 –PV) x (1 –SP)]

PTP negative: [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. An arterial age below chronological age was considered as a negative test. The level of statistical significance was set at $p < 0.05$.

Results

Our cohort is built by 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 centre in KOBLENZ, Germany (N=3326). All patients lived in central Europe or Switzerland with a dominant white population.

Therefore, the original cohort is built of 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, VARIFO subjects were excluded for age below 40 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 for age reasons. 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).

Number of events in the primary outcome was 41 AMI, 16 STROKES, 21 CABG (total 78 events) and number of events in the secondary outcome was 41 PTCA and 35 CAD (adding another 74 events to the total of events of 154 cases).

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 the 2842 observed subjects, 38% were women, average age was 50±8 years, 21% were smokers, average systolic blood pressure was 126 mm Hg, average total Cholesterol was 6.0 mmo/l (HDL 1.5 mmol/l, LDL 3.7 mmol/l) and the average total plaque area (TPA) was 42±5 mm^2. Subjects were at an average intermediate risk with SCORE (1.3%) and at low risk for PROCAM-AMI (4.8%), AGLA-AMI (3.3%), HerzCheck-AMI (4.1%) and PROCAM-AMISTR (6.2%).

Based upon our imaging results, definition of risk categories for TPA and arterial age were as follows: 1st (TPA 1-21 mm^2), 2nd (TPA 22-61 mm^2) and 3rd TPA tertile (TPA ≥62 mm^2) and in subjects with arterial age older than chronological age by 11-20 or 21 years or more. The distribution of TPA among no plaque patients was N=728 and for tertile 1,2 and 3 was N=720, N=687 and N=707 respectively.

Figure 1 shows unadjusted risk prediction results for TPA tertiles and arterial age groups for the primary and secondary outcome. A 20% risk was reached for arterial age regarding primary outcome after 11 years, and secondary high-risk outcome was reached with TPA 3rd tertile after 6 years and was reached with arterial age high risk after 4 years.

The p-values for trend of TPA and arterial age as a continuous variable was highly significant (all $p < 0.0001$) with WALD values derived from a Cox proportional-hazards regression of 244 for the primary and 519 for the secondary outcome with TPA and with WALD values of 103 for the primary and 221 for the secondary outcome with arterial age.

Tables 2 show observed event rates in the ARCO study for AMI, AMISTR, AMISTRCABG and all events, the associated follow-up times and the extrapolated event rates for 10 years. From this we observed a risk for AMI of 5.5% in 10 years, of AMISTR of 7.4%, of AMISTRCABG of 9.3% and for all events of 16.6% (Table 2a). PROCAM-AMI risk was 4.8%, therefore underestimating ARCO-AMI risk by a calibration factor of 0.87 and

the associated correction factor should be 1.15, giving an underestimation of AMI risk of 15%. Further, Table 2a also shows an example of a subject with a PROCAM-AMI risk of 6% and applied correction factors for AMI (6.92%), AMISTR (9.31%), AMISTRCABG (11.64%) and all events (20.71%). Therefore, an AMI risk of 6% turns out to be an ASCVD risk of 21%.

Table 2b adds a calibration factor to ARCO 10-year risk of 0.7 in order to simulate the expected lower risk present in Switzerland. By consequence, AGLA-AMI underestimates risk which results in a correction factor of 1.15 and underestimates ASCVD risk with a correction factor of 3.45.

Table 3 shows the discrimination comparison of HerzCheck, PROCAMold (prior PROCAM version available at https://www.kardiolab.ch/MONICA-PROCAM3_RA1.html) and PROCAM to detect primary and secondary outcomes. PROCAM (AUC 0.835) outperformed HerzCheck (AUC 0.809) and PROCAMold (AUC 0.815) significantly (p=0.02 for AUC difference), whereas regarding the secondary outcome, PROCAM (AUC 0.832) outperformed only HerzCheck® (AUC 0.817) significantly (p=0.020), but not PROCAMold.

Appendix Table 1 shows the reclassification of risk categories for various risk calculator combinations, their associated Kappa (agreement) values and the net reclassification changes. As an example, PROCAM-AMI would classify 3.1% of subjects in a higher risk category than SCORE-ASCVD, but SCORE-ASCVD would classify 31.1% of subjects in a higher risk category than PROCAM-AMI, resulting in a net reclassification difference of 33.7%. The largest reclassification difference was found for AGLA-AMI versus SCORE-ASCVD (37.6%). The smallest difference regarding reclassification was 7% for PROCAM-AMI versus PROCAM-AMI-STR with an expected high Kappa value of 0.76.

Table 4 shows a Cox proportional hazards model survival analysis for the primary and the secondary outcome using HerzCheck, PROCAM, SCORE and TPA. For the primary outcome (AMI + STROKE + CABG), only TPA remained as a significant predictor. For the

secondary outcome, TPA and HerzCheck were significant predictors, but PROCAM and SCORE were not in both models.

Appendix Table 2 shows the net reclassification improvements using either TPA or arterial age categories, which are statistically significant for the primary outcome and the secondary outcome with improvement of 37% to 42%.

Table 5 shows the patient characteristics stratified by no atherosclerosis (reference group) and presence of atherosclerosis defined by TPA tertiles. In all groups, AGLA average risk was below 10% (6.7%), while SCORE showed average intermediate risk in the 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 the cumulative incidence of cardiovascular events with myocardial infarction as the reference observed in the DETECT (8) and in the ARCO study. For every AMI, 1.8 AMI+STR occur in the combination of DETECT with ARCO; when adding revascularization and peripheral or coronary artery disease, cumulative incidence increases by a factor of 4.1.

Figure 2 shows risk prediction with AGLA stratified to zero carotid plaque and TPA tertiles and observed (extrapolated) 10-year event rate in ARCO. In patients with TPA in the 3rd tertile, AGLA risk is 7% and observed risk is 38%, an underestimation of risk by a factor of 5.7.

Sensitivity analysis showed, that those with complete follow-up (N=2842) compared to the whole group of patients N=5314) were comparable regarding sex (37% vs 36% women), average age (50 and 52 years), smokers (21% vs 22%), blood pressure (126 vs 126 mm Hg), total cholesterol (6.0 vs 6.0 mmol/l), HDL (1.5 vs 1.5 mmol/l), LDL (3.7 vs 3.7 mmol/l), Triglycerides (1.6 vs 1.5 mmol/l), and TPA (42 vs 46 mm^2).

Discussion

The principal result of this study in subjects aged 40 to 65 years is a correction factor of 3.8, which allows to estimate the 10-year risk for atherosclerotic cardiovascular disease (ASCVD) from the myocardial infarction (PROCAM-AMI) risk. Therefore, a subject with a PROCAM-AMI risk of 6% is expected to have an ASCVD risk of 23%.

Similarly, the German DETECTION study (8) found a correction factor of 4.6 and the combination of DETECTION and ARCO with 34'340 observed patient years resulted in a correction factor of 4.1. In clinical practice, a PROCAM risk of 5%, which is regarded as low risk for fatal and non-fatal myocardial infarction would allow to estimate an ASCVD risk of 20% in 10 years, which would probably represent a high ASCVD risk. Therefore, terms such as “global cardiovascular risk” or “cardiovascular risk” should not be used to describe AMI risk defined by PROCAM-AMI, because such a description underestimates ASCVD risk by a factor of 4 and is therefore expected to result in a frequent underestimation of ASCVD risk in Switzerland.

According to SCORE2, the new European guidelines to assess cardiovascular risk in primary care (17), a 10-year risk is available for ASCVD, defined as a composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. In subjects aged below 50 years, a SCORE2 risk below 2.5% is a low risk and above or equal 7.5% represent a high-risk situation. Cutoffs for subjects aged 50-69 years are 5% and 10% respectively. If we put our results in perspective with SCORE2 recommendations, we find a PROCAM-AMI risk of 5% to represent high ASCVD risk in a population aged 50 years on average. Therefore, we may propose to multiply PROCAM-AMI by a correction factor of 4 in order to detect ASCVD risk. We calculated SCORE2 risk in our population (data not shown) and found a SCORE2-risk of 4.5±3.0% in the ARCO study, which is very close to the PROCAM-AMI risk of this cohort (4.8%). Therefore, the European guideline investigators have chosen not to use such a correction factor, but to substantially lower the risk threshold

for high risk from 20% to 7.5%, which is 2.7 times lower (in subjects aged 50-69 years, high risk was reduced from 20% to 10%). According to a health technology assessment of the Federal Office of Public Health, the incremental cost-effectiveness ratios per quality adjusted life years for the use of statins in primary care were all cost-effective through ages 40-75 and an AGLA risk of 5% (18) and even showed a return-on-investment for AGLA risk above 15%. Therefore, also from a cost-effectiveness point of view, drastic lowering of the AGLA high-risk threshold from 20% to 7.5% or 10% (in subjects aged 50-69 years) is inevitably required in order to better address the ASCVD epidemic.

Regarding calibration for myocardial infarction (AMI), AGLA underestimated the extrapolated 10-year risk found in ARCO by 65%. However, ARCO was composed by 80% of German habitants from the Koblenz area, so – for Switzerland – it may be justified to multiply the ARCO risk by 0.7 (Table 2b), where risk by AGLA for AMI is still underestimated by 15%. If we assess the calibration factors of AGLA for AMI+STR and for all ASCVD events, then risk is underestimated by a factor of 1.55 and by 3.45, respectively (Table 2b). AGLA risk appears appropriate to detect AMI risk in a contemporary population with good calibration in Switzerland, however, regarding other cardiovascular outcomes such as stroke, CABG, PTCA and coronary artery disease (CAD, defined by a coronary angiogram), calibration is poor or even extremely poor. Therefore, to calculate ASCVD risk, it is important to add additional risk elements, e.g., from PROCAM STR or by direct calculation of SCORE ASCVD or by using the new SCORE2 risk calculator (17). Moreover, as presented in Appendix Table 1, many patients at low risk with PROCAM based calculators have intermediate risk with SCORE-ASCVD.

Regarding discrimination using receiver operating curves (ROC) analysis, similar results were found for HerzCheck®, PROCAM old and PROCAM-AMI with slightly better performance for PROCAM-AMI when looking at the primary and secondary outcome.

Regarding survival analysis for the primary outcome, only TPA remained a significant

predictor, while for the secondary outcome, HerzCheck® added a little more prognostic information to a highly significant TPA, but neither PROCAM-AMI nor SCORE-ASCVD added prognostic information over TPA in our multivariate Cox proportion hazards model.

Our reclassification model (Appendix Table 2) using risk derived from the BAYES theorem in conjunction with PROCAM-AMI and SCORE-ASCVD significantly reclassified patients in the correct outcome category. This finding shows that the addition of carotid plaque information adds to the correct allocation of patients into risk categories and assessments of carotid plaques is also recommended by the ESC (11).

When we stratify observed events by zero plaque and TPA tertiles (table 5, figure 2), we find that patients in the 3rd tertile of TPA (regarding 25% of the ARCO population) had a remarkably high extrapolated then year risk of 38%, whereas PROCAM and AGLA in average remained low and SCORE remained in intermediate risk category on average.

Our prognostic results over an average of 5.9 years might be biased by preventive interventions, especially with statins, since lipids appear to be the strongest population-attributable risk factor for cardiovascular events worldwide. (19) Our study cohort was mainly statin naïve because we found, although only anecdotally and not formally studied, that most patients with atherosclerosis were not offered statins.

Similar to other studies (20,21), we were able to assess only a limited number of follow-up (82%), which excludes the derivation of *absolute* risk in our cohort associated with the used risk markers; however, limited number of follow-up does not bias the *relative* diagnostic power of the risk markers used and our sensitivity analysis renders a selection bias unlikely. Third, we were able to include only a limited number of women and only a limited number of subjects / cardiovascular events from the Olten Centre, however, previous studies assessed also sufficiently high numbers of women and found similar predictive strengths in women (22,23). Further, we could not use the help of an independent outcome committee, however the results of singular risk factors and risk estimators significantly detected events,

therefore, misclassification in our records is very unlikely. Because TIA may be regarded as a difficult outcome measure, we excluded patients with Stroke/TIA and found that TPA significantly improved AUC by 4.8% (p=0.0048) when compared to PROCAM and significantly improved AUC by 6.1% (p=0.0002) for the secondary outcome. Finally, the non-population-based selection process for the two cohorts may reduce the generalizability of our results.

Several questions remain. Recalibration of the existing instruments or replacement of the AGLA score by SCORE2 or recommendation to measure the total plaque area (TPA) as a primary preventive measure? Which endpoint or event should be chosen for a recalibration in order to indicate e.g., the use of a statin (PTCA or CAD stenosis?). What would this mean for education (specialists who can reliably determine TPA), for the indication of statins (with the current calibration and with an adjusted calibration) and for the health care costs of the total population in Switzerland (24)?

From the literature it appears that preventive therapies should be targeted as soon as possible: according to a Markov Model from Germany (25) projections of disease burden will be massive until the year 2060 and the only cost-effective way to deal with this epidemy is intensified preventive medicine. We have found Statins and TPA to be cost-effective in primary care in a recent study (26). Disease compression (27–30) and effective prevention (31,32) are indispensable tools to avoid unaffordable healthcare costs in the future.

Conclusions

PROCAM based calculators such as AGLA and HerzCheck® showed similar discriminatory power when compared to SCORE, but classification analysis showed, that AGLA-AMI should not be interchanged for cardiovascular (ASCVD) outcomes, because it underestimates ASCVD risk by a factor of 4.

We show that the use of carotid TPA helps to further stratify patients into correct risk categories and may be used more frequently in clinical practice.

As an alternative to PROCAM, SCORE2 risk might show promising results in the future in Switzerland and would eliminate the labelling problem of the AGLA risk calculator.

Conflict of interest:

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding:

Funding was provided by the Vascular Risk Foundation, VARIFO, Switzerland.

Tables

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

N=	2 842
Female (%)	1077 (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
SCORE-ASCVD + SD, %	1.3±1.6
PROCAM-AMI + SD %	4.8±6.4
PROCAM-STR + SD %	1.6±1.7
PROCAM-AMISTR + SD %	6.2±7.6
AGLA_AMI + SD %	3.3±4.5
AGLA-STR + SD %	1.0±1.2
AGLA AMISTR + SD %	4.4±5.3
HerzCheck®-AMI + SD %	4.1±5.1

Table 2a: Calibration factors and performance of PROCAM and AGLA to detect events from the ARCO cohort with event rates extrapolated to 10 years for various outcomes separately (AMI, AMI + STR, AMI + STR + CABG, ALL).

Observation (ARCO) and Estimation (PROCAM, AGLA)					
FU Time	5.9	2.6	2.7	2.9	3.3
ARCO	ALL patients	AMI	AMISTR	AMISTRCABG	ALL events
Event Rate (%)		1.44	2.01	2.7	5.4
		10 years extrapolation			
Outcome		AMI	AMISTR	AMISTRCABG	ALL
ARCO		5.5	7.4	9.3	16.6
Baseline	Estimates	Calibration			
PROCAM-AMI	4.8	0.87	0.64	0.52	0.29
PROCAM-AMISTR	6.3	1.14	0.85	0.68	0.38
AGLA-AMI	3.4	0.61	0.45	0.36	0.20
AGLA- AMISTR	4.4	0.80	0.59	0.47	0.27
Correction		Correction factors			
PROCAM-AMI		1.15	1.55	1.94	3.45
PROCAM- AMISTR		0.88	1.18	1.48	2.63
AGLA-AMI		1.65	2.22	2.77	4.93
AGLA- AMISTR		1.26	1.69	2.11	3.76
Example		6% AMI risk multiplied by correction factor			
PROCAM-AMI		6.92	9.31	11.64	20.71
PROCAM- AMISTR		5.27	7.09	8.87	15.78
AGLA-AMI		9.89	13.29	16.63	29.58
AGLA- AMISTR		7.54	10.13	12.67	22.54
Discrimination		ROC AUC Analysis			
PROCAM-AMI			0.84	0.83	0.83
PROCAM- AMISTR			0.85	0.84	0.84
TPA			0.83	0.85	0.89 (0.01)
Survival		Survival Analysis (Cox pro hazard model)			
PROCAM-AMI			N.S.	N.S.	N.S.
PROCAM- AMISTR			N.S.	N.S.	N.S.
TPA			<0.0001	<0.0001	<0.0001

Table 2b: Calibration factors for PROCAM and AGLA to detect events from the ARCO cohort with event rates extrapolated to 10 years for various outcomes separately (AMI, AMI + STR, AMI + STR + CABG, ALL). Outcome was multiplied by 0.7 to reflect the expected risk in Switzerland

Observation (ARCO) and Estimation (PROCAM, AGLA) with outcome calibration of 0.7					
FU Time	5.9	2.6	2.7	2.9	3.3
ARCO	ALL Patients	AMI	AMISTR	AMISTRCABG	ALL events
Event Rate (%)		1.44	2.01	2.7	5.4
		10-year extrapolation			
Outcome		AMI	AMISTR	AMISTRCABG	ALL
ARCO		3.9	5.2	6.5	11.6
Baseline	Estimates	Calibration			
PROCAM-AMI	4.8	1.24	0.92	0.74	0.41
PROCAM-AMISTR	6.3	1.63	1.21	0.97	0.54
AGLA-AMI	3.4	0.87	0.64	0.52	0.29
AGLA- AMISTR	4.4	1.14	0.85	0.68	0.38
Correction		Correction factors			
PROCAM-AMI		0.81	1.09	1.36	2.42
PROCAM-AMISTR		0.62	0.83	1.03	1.84
AGLA-AMI		1.15	1.55	1.94	3.45
AGLA- AMISTR		0.88	1.18	1.48	2.63
Example		6% AMI risk multiplied by correction factor			
PROCAM-AMI		4.85	6.51	8.15	14.49
PROCAM-AMISTR		3.69	4.96	6.21	11.04
AGLA-AMI		6.92	9.31	11.64	20.71
AGLA-AMISTR		5.27	7.09	8.87	15.78

Table 3a: Discrimination (ROC analysis) Comparison of HerzCheck, PROCAMold and PROCAM to detect primary outcome (AMI + STR + CABG)

HerzCheck®-AMI (AUC and SD)	0.809	0.0206	0.794 to 0.823
PROCAMold-AMI (AUC and SD)	0.815	0.0195	0.800 to 0.829
PROCAM-AMI (AUC and SD)	0.835	0.0182	0.821 to 0.848

p = 0.022 for PROCAM-AMI versus HerzCheck®-AMI

Table 3b: Discrimination Comparison of HerzCheck, AGLAold and AGLA to detect secondary outcome (all cardiovascular events)

HerzCheck®-AMI (AUC and SD)	0.817	0.0148	0.802 to 0.831
PROCAMold-AMI (AUC and SD)	0.816	0.0146	0.801 to 0.830
PROCAM-AMI (AUC and SD)	0.832	0.0139	0.818 to 0.846

p = 0.020 for PROCAM-AMI versus HerzCheck®-AMI

Table 4a: Cox proportional hazards model survival analysis for the primary outcome using the covariates HerzCheck®, PROCAM, SCORE and TPA

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
HerzCheck®-AMI	0.0573	0.03131	3.3497	0.0672	1.059	0.9959 to 1.1260
PROCAM-AMI	-0.0008	0.02159	0.001445	0.9697	0.9992	0.9578 to 1.0424
SCORE-ASCVD	0.07514	0.04367	2.9606	0.0853	1.078	0.9896 to 1.1744
TPA	0.01042	0.0009197	128.2606	**<0.0001**	1.0105	1.0086 to 1.0123

Table 4b: Cox proportional hazards model survival analysis for the secondary outcome using the covariates HerzCheck®, PROCAM, SCORE and TPA

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
HerzCheck®-AMI	0.05855	0.02236	6.8572	**0.0088**	1.0603	1.0148 to 1.1078
PROCAM-AMI	0.00674	0.01487	0.2056	0.6503	1.0068	0.9779 to 1.0365
SCORE-ASCVD	0.04122	0.03287	1.5721	0.2099	1.0421	0.9771 to 1.1114
TPA	0.0108	0.0006211	302.3675	**<0.0001**	1.0109	1.0096 to 1.0121

Table 5: characteristics of patients stratified by atherosclerosis presence (TPA tertiles), and estimates of myocardial infarction (PROCAM, AGLA) or cardiovascular risk (SCORE)

	ALL	Zero Plaque	Carotid Plaque Tertiles (TPA)		
TPA Groups		0	1	2	3
N	2 842	728	688	719	707
Age	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	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-ASCVD	1.3 ± 1.6	0.5 ± 0.6	0.9 ± 1.0	1.4 ± 0.9	2.6 ± 2.2
PROCAM-AMI	4.8 ± 6.4	1.8 ± 2.9	3.0 ± 4.0	4.9 ± 2.8	9.5 ± 8.7
AGLA-AMI	3.3 ± 4.5	1.2 ± 2.0	2.1 ± 2.8	3.4 ± 5.5	6.7 ± 6.1

Table 6: Incidence of cardiovascular endpoints in DETECT (8) **(N=4044) and ARCO (N=2842) and combination of both studies with 34'340 observed patient years (29 TIA from DETECT were excluded from this analysis)**

		DETECT		ARCO		DETECT+ARCO
		Cumulative		Cumulative	SUM	Cumulative
Endpoint	DETECT	Incidence	ARCO	Incidence	EVENTS	Incidence
AMI	30	1.00	41	1.00	71	1.00
STR	40	2.33	16	1.39	56	1.79
PTCA/CAGB	36	3.53	62	2.90	98	3.17
CAD/ PAD	32	4.60	35	3.76	67	4.11
ALL	138		154		292	

AMI = fatal or non-fatal myocardial infarction; STR = Stroke; PTCA / CABG = coronary transluminal angioplasty / bypass grafting; CAD = obstructive coronary artery disease; PAD = peripheral artery disease with symptomatic claudication.

Figures:

Figure 1: unadjusted HRs for primary (hard events) and secondary (all events) outcome associated with TPA and differences in arterial age

(ARCO-AGLA_Figure1.jpg)

Figure 1 legend, aacode: arterial age code (0=below cAge, 1=1-10 years older than cAge, 2=11-20 years older than Age, 2=>20 years older than cAge). tpacode: Total Plaque Area Code (0=no atherosclerosis, 1=1st tertile, 2=2nd tertile, 3=3rd tertile)

Figure 2: Observed events (solid) and AGLA-AMI prediction (dotted line) plotted by zero Plaque and TPA tertiles in the ARCO study

(ARCO-AGLA_Figure2.jpg)

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