Do PROCAM based Swiss risk tools (AGLA and HerzCheck ®) predict cardiovascular events? A classification using cardiovascular outcome data from the Swiss / German ARCO Study.

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Abstract

Background

For the purpose of this study, we tested the predicting ability of AGLA and HerzCheck using the ARCO cohort study observations and calculated calibration factors for various outcomes.

Methods

We performed a cohort outcome study and compared PROCAM derived AGLA and HerzCheck to SCORE and TPA for calibration, discrimination and survival.

Results

In 2842 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 disease defined by invasive angiography) during a mean follow-up time of 5.9 (1-12) years. AGLA CHD risk was well calibrated (15% underreported risk), but was poorly calibrated for CVD (like stroke, CABG, PTCA or CAD) with underreported risk up to 345%. Substantial misclassifications occurred with AGLA and HerzCheck compared to SCORE. 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 or AA age groups increased significantly between 30% to 48%.

Conclusions

PROCAM derived risk calculators are well calibrated for the risk of myocardial infarction (CHD). For CVD, important underestimation occurs. Labeling AGLA and HerzCheck as CVD risk calculators is regulated in the Medical Product Act. By consequence, all available patients should be recalculated for their CVD risk, if CVD risk was reported instead of CHD risk.

Introduction

Preventive medicine is a pillar of basic health care and is essential to avoid disease expansion[1]. Regarding cardiovascular disease prevention, it has become a sort of malpractice for almost 10 years to label heart infarction (CHD) risk as cardiovascular (CVD) risk. Several publications[2,3], the AGLA website, the AGLA pocket guide and HerzCheck ®[4] show such confounding since 2013. The result of such risk calculators is subject is regulated in the Medical Products Act[5], since risk calculators are a medical product.

PROCAM based calculators have been published by the Assmann Foundation (https://www.assmann-stiftung.de/procam-tests/), where risk for myocardial infarction and risk for stroke may be calculated separately. The clinical problem arises, when risk for myocardial infarction is low or intermediate and when the addition of stroke risk changes the risk category from low to intermediate or high or from intermediate to high. In a Swiss Broadcasting[6], the risk of a patient (Mr. Roos) was reported to be around 15% for myocardial infarction according to AGLA and the calculate stroke risk according to PROCAM is 12% or corrected for Switzerland by a factor of 0.7 of 8%. Therefore, Mr. Roos is a high-risk patient (15% + 8% = 23%) and should be treated accordingly. This is also verified by the SCORE test for low-risk populations, which places Mr. Roos into the high-risk segment (8% risk for fatal cardiovascular events in 10 years).

For the purpose of this study, we tested the predicting ability of AGLA and HerzCheck using the ARCO cohort study observations and calculated calibration factors for various outcomes.

List of Abbreviations

ASCVD	atherosclerotic cardiovascular disease
AMI	fatal or nonfatal acute myocardial infarction
AUC	area under the curve
FRAM	Framingham risk equation for fatal and non-fatal cardiovascular events
PCE	Pooled cohort equation, for fatal and non-fatal cardiovascular events
ROC	receiver operating curves
TPA	Total plaque area (carotid plaque)
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

Materials and Methods

We used the cohort method in order 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 spread-sheet (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. 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 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 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).

We decided to add CABG to the primary endpoint in order 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)[7]. All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously reported [8]: 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 spread-sheet. We used the European Society of Cardiology risk equation for low risk populations (SCORE [9]) and the German PROCAM risk for myocardial infarction and for stroke multiplied with a correction factor of 0.7. [10] Further, we calculated point scores for HerzCheck and PROCAM with associated 10 year risk estimates and we calculated PROCAM using the original formula[11]. 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. [12]

Statistics

We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons. [13] Groups were compared using a t-test for continuous variables and CHI^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere[14]: 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 analyzed 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

The ARTERIS 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 center in KOBLENZ, Germany (N=3326). All patients lived in central Europe or Switzerland with a dominant white population.

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 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 3719 subjects were eligible for study entry and follow-up could be obtained for 2842 (79.8) subjects, who were dominantly visited in Koblenz, Germany (80%) and the German cohort contributed to the total of ASCVD event in 133 out of 154 cases (86%). 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 PTCA (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. 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.

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 AA regarding primary outcome after 11 years, and secondary high-risk outcome was reached with TPA 3rd tertile after 6 years and was reached with AA 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.

Table 2a shows the 10-year extrapolation of observed ARCO risk by different outcomes and observed risks for PROCAM and AGLA with applied calibration factors. As an example, a patient with a 6% CHD risk changed risk between 6.9% to 29.6%, according to the cardiovascular risk factors.

Table 2b adds a calibration factor to ARCO 10-year risk of 0.7. By consequence, AGLA underestimates CHD risk by only 15%, but cardiovascular risk (secondary outcome) is undercalibrated by 245%.

Table 3 shows the discrimination comparison of HerzCheck, AGLAold and AGLA to detect primary and secondary outcomes. AGLA outperformed HerzCheck and AGLAold

significantly (p=0.02 for AUC difference.

Table 5 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 + STR + CABG), only TPA was a significant predictor. For the secondary outcome, TPA and HerzCheck were significant predictors, but PROCAM and SCORE were not in both models.

Table 6 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 7 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.

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 goal of this study was to test calibration and discrimation as well as survival prediction using various risk calculators from PROCAM CHD, PROCAM STROKE and SCORE CVD for low-risk populations as well as the HerzCheck scoring system in a low-risk population of patients aged 40 – 65 years.

Regarding calibration for myocardial infarction (CHD), 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 it is justified to multiply the ARCO risk by 0.7 (Table 2b), where risk by AGLA CHD is still underestimated by 15%. If we follow the calibration factors of AGLA for CHD+STR, then risk is underestimated by 55% and by 245% for all cardiovascular events (Table 2b). AGLA risk appears appropriate to detect CHD risk in a contemporary population with good calibration in Switzerland, however, regarding other cardiovascular outcomes such as stroke, CABG, PTCA and coronary artery disease (defined by a coronary angiogram), calibration is poor or even very poor. Therefore, in order to calculate CVD risk, it is important to add additional risk elements, e.g., from PROCAM Stroke or by directly calculation SCORE CVD. Moreover, as presented in Table 4, many patients at low risk with PROCAM based calculators have intermediate risk with SCORE CVD.

Regarding discrimination using receiver operating curves (ROC) analysis, similar results were found for HerzCheck, PROCAM old and PROCAM with slightly better performance for PROCAM 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 nor SCORE added prognostic information over TPA in the Cox proportion hazards model.

Our reclassification model using risk derived from the BAYES theorem in conjunction

with PROCAM and SCORE 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.

Finally, an impression about the effect of statins based on observed LDL values and cardiovascular risk, stratified by TPA tertiles, showed that patients can be selected based upon TPA and observed NNT. This is an important point, because the lack of carotid plaque information in a low-risk population on average may create a wrong impression about statin effects based on NNT (Table 7).

Our study reveals, that cardiovascular events and diseases occur mainly in those with diseased carotid arteries and not in those with high cardiovascular risk detected by risk equations such as PROCAM or SCORE. This lends support to the paradigm postulated by Spence 10 years ago: “treat arteries, not risk factors” [16]. The ESC lipid guidelines 2019 recommend carotid plaque imaging, which should be used to further stratify patients with low or intermediate SCORE risk. [9] However, no consent as to when imaging results should be considered as a high cardiovascular risk finding, has been reached. Based upon our results, a TPA above the third tertile (≥ 62 mm^2) is an information, that may close this information gap. This finding was associated with an event rate of near 20% for the primary outcome after 12 years of follow-up and with an event rate of 20% for the secondary outcome after 6 years.

From a lifetime perspective, the secondary outcome is probably as important as the primary outcome in younger subjects. TPA is readily measured within 2-3 minutes, which allows for a low-cost and cost-efficient [17] estimate of cardiovascular risk. Our study supports the Class IIa ESC 2019 [9] recommendation for the assessment of ASCVD risk, “which should be considered as a risk modifier in individuals at low or moderate risk”. In subjects aged 40-65 years, arterial age is more predictive than chronological age, which confirms the results from the CAFES-CAVA study. The famous sentence by Thomas Sydenham may therefore be modified by "a *young or middle-aged* man is as old as his arteries."

Early initiation of lipid-therapy e.g. has great potential in the combat against cardiovascular events [18], however, when carotid atherosclerosis is not present and patients are reluctant to life-long statin therapies, "negative risk factors" from medical imaging such as carotid sonography may allow to delay medical preventive therapies [19], provided that regular follow-up does not reveal a change in the risk assessments.

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. [20] 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, [21,22] we were able to assess only a limited number of follow-up (80%), 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.[18,23] 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 measures, 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.

Conclusions

AGLA CHD is well calibrated for the risk of myocardial infarction only (CHD) and

discriminates well for various outcomes (CHD and CVD). PROCAM based calculators such as AGLA and HerzCheck showed similar discriminatory power when compared to SCORE, but classification analysis showed, that AGLA cannot be used for cardiovascular (CVD) outcomes. 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. From a legal point of view, AGLA and HerzCheck risk is a medical product that has been developed for CHD only. The use of AGLA and HerzCheck as a cardiovascular assessment tool (CVD) is in conflict with the labeling of these calculators. Further, at the discretion of physician and pharmacists, communicated risk should be recalculated using PROCAM STROKE or SCORE CVD in order to avoid miscommunication of low risk where in fact intermediate or even high risk is present in our patients.

Conflict of interest:

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

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
SCOREca + SD, %	1.3±1.6
SCORE SMB + SD, %	7.2±8.8
PROCAMchd + SD %	4.8±6.4
PROCAMstr + SD %	1.6±1.7
PROCAMchdstr + SD %	6.2±7.6
AGLAchd + SD %	3.3±4.5
AGLAstr + SD %	1.0±1.2
AGLAchdstr + SD %	4.4±5.3
AGLAcvd + SD % (ARCO)	9.1±11.5
HerzCheckchd + SD %	4.1±5.1

AGLAcvd adds another 40% risk to AGLAcastr based upon the ARCO observation (added CABG and PTCA observations)

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 year			
Outcome		AMI	AMISTR	AMISTRCABG	ALL
ARCO		5.5	7.4	9.3	16.6
Baseline	Estimates	Calibration			
PROCAMchd	4.8	0.87	0.64	0.52	0.29
PROCAM chd str	6.3	1.14	0.85	0.68	0.38
AGLA chd	3.4	0.61	0.45	0.36	0.20
AGLA chd str	4.4	0.80	0.59	0.47	0.27
Correction		Correction factors			
PROCAMchd		1.15	1.55	1.94	3.45
PROCAM chd str		0.88	1.18	1.48	2.63
AGLA chd		1.65	2.22	2.77	4.93
AGLA chd str		1.26	1.69	2.11	3.76
Example		6% CHD risk multiplied by correction factor			
PROCAMchd		6.92	9.31	11.64	20.71
PROCAM chd str		5.27	7.09	8.87	15.78
AGLA chd		9.89	13.29	16.63	29.58
AGLA chd str		7.54	10.13	12.67	22.54
Discrimination		ROC AUC Analysis			
PROCAMchd			0.84	0.83	0.83
PROCAM chd str			0.85	0.84	0.84
TPA			0.83	0.85	0.89 (0.01)
Survival		Survival Analysis (Cox pro hazard model)			
PROCAMchd			N.S.	N.S.	N.S.
PROCAM chd str			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			
Outcome		AMI	AMISTR	AMISTRCABG	ALL
ARCO		3.9	5.2	6.5	11.6
Baseline	Estimates	Calibration			
PROCAMchd	4.8	1.24	0.92	0.74	0.41
PROCAM chd str	6.3	1.63	1.21	0.97	0.54
AGLA chd	3.4	0.87	0.64	0.52	0.29
AGLA chd str	4.4	1.14	0.85	0.68	0.38
Correction		Correction factors			
PROCAMchd		0.81	1.09	1.36	2.42
PROCAM chd str		0.62	0.83	1.03	1.84
AGLA chd		1.15	1.55	1.94	3.45
AGLA chd str		0.88	1.18	1.48	2.63
Example		6% risk multiplied by correction factor			
PROCAMchd		4.85	6.51	8.15	14.49
PROCAM chd str		3.69	4.96	6.21	11.04
AGLA chd		6.92	9.31	11.64	20.71
AGLA chd str		5.27	7.09	8.87	15.78

Table 3a: Discrimination Comparison of HerzCheck, AGLAold and AGLA to detect primary outcome (AMI + STR + CABG)

HerzCheck	0.809	0.0206	0.794 to 0.823
PROCAMold	0.815	0.0195	0.800 to 0.829
PROCAM	0.835	0.0182	0.821 to 0.848

p = 0.022 for PROCAM versus HerzCheck

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

HerzCheck	0.817	0.0148	0.802 to 0.831
PROCAMold	0.816	0.0146	0.801 to 0.830
PROCAM	0.832	0.0139	0.818 to 0.846

p = 0.020 for PROCAM versus HerzCheck

Table 4: Reclassification of risk, kappa statistics and net reclassification improvements

		PROCAM			N	%	Net %
		L	M	H	87	3.06122449	-27.5510204
SCOREcvd	L	1601	16	0	870	30.6122449	
	M	823	240	71			
	H	15	32	44		**Kappa**	**0.28**
		PROCAMas			N	%	
		L	M	H	130	4.57424349	-21.252639
SCOREcvd	L	1597	17	3	734	25.8268825	
	M	706	318	110			
	H	1	27	63		**Kappa**	**0.37**
		HerzCheck			N	%	
		L	M	H	42	1.47783251	-31.3863476
SCOREcvd	L	1597	20	0	934	32.8641802	
	M	867	245	22			
	H	19	48	24		**Kappa**	**0.25**
		AGLA			N	%	
		L	M	H	20	0.70372977	-36.1717101
SCOREcvd	L	1612	5	0	1048	36.8754398	
	M	975	144	15			
	H	33	40	18		**Kappa**	**0.16**
		PROCAMpoint			N	%	
		L	M	H	34	1.19634061	-33.5679099
SCOREcvd	L	1612	5	0	988	34.7642505	
	M	926	179	29			
	H	18	44	29		**Kappa**	**0.21**
		PROCAMpoint			N	%	
		L	M	H	5	0.17593244	-12.5967628
PROCAMAS	L	2301	3	0	363	12.7726953	
	M	243	117	2			
	H	12	108	56		**Kappa**	**0.50**
		AGLA			N	%	
		L	M	H	0	0	-15.7987333
PROCAMAS	L	2304	0	0	449	15.7987333	
	M	306	56	0			
	H	10	133	33		**Kappa**	**0.35**
		HerzCheck			N	%	
		L	M	H	59	2.07600281	-10.52076
PROCAMAS	L	2249	55	0	358	12.5967628	
	M	224	134	4			
	H	10	124	42		**Kappa**	**0.47**
		PROCAM			N	%	
		L	M	H	0	0	-6.86136524
PROCAMAS	L	2304	0	0	195	6.86136524	
	M	134	228	0			
	H	1	60	115		**Kappa**	**0.76**
		PROCAMpoint			N	%	
		L	M	H	22	0.77410274	-6.01688951
PROCAM	L	2423	16	0	193	6.79099226	
	M	130	152	6			
	H	3	60	52		**Kappa**	**0.65**

Table 5a: Cox proportional hazards model survival analysis for the primary outcome using HerzCheck, PROCAM, SCORE and TPA

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
HerzCheck	0.0573	0.03131	3.3497	0.0672	1.059	0.9959 to 1.1260
PROCAMca	-0.0008	0.02159	0.001445	0.9697	0.9992	0.9578 to 1.0424
SCOREca	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 5b: Cox proportional hazards model survival analysis for the secondary outcome using HerzCheck, PROCAM, SCORE and TPA

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
HerzCheck	0.05855	0.02236	6.8572	**0.0088**	1.0603	1.0148 to 1.1078
PROCAMca	0.00674	0.01487	0.2056	0.6503	1.0068	0.9779 to 1.0365
SCOREca	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 6: Net Reclassification Improvement (NRI) using posttest risk of PROCAM and SCORE based on TPA tertiles derived sensitivities and specificities for observed outcome

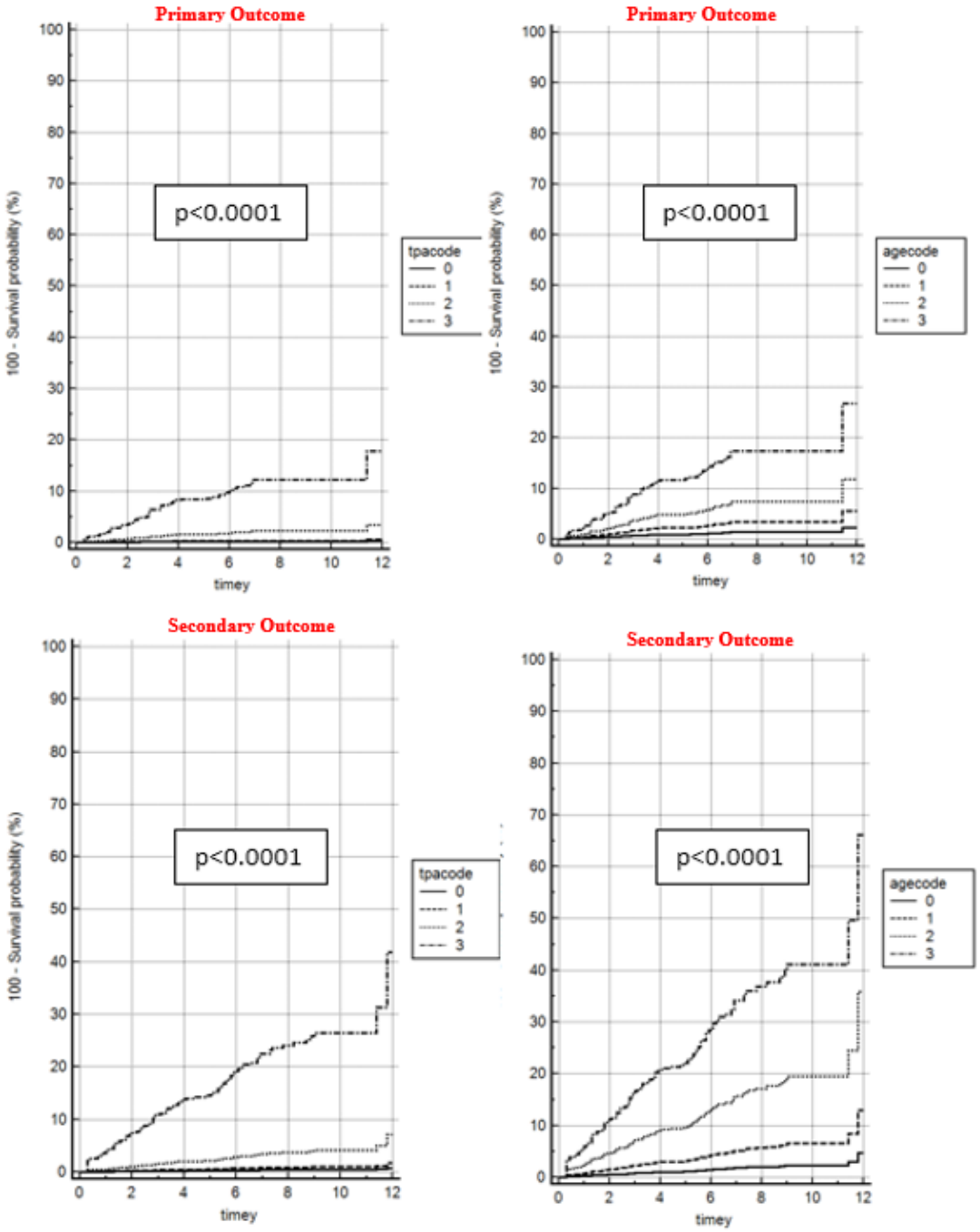
	NRI	(95% CI)	P-value
PROCAM	**Ref model**		
PROCAM + Bayes TPA	0.421	(0.356 to 0.486)	<0.0001
SCORE	**Ref model**		
SCORE + Bayes TPA	0.373	(0.307 to 0.439)	<0.0001

Table 7: 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	728 26	688 24	719 25	707 25
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	1.3 ± 1.6	0.5 ± 0.6	0.9 ± 1.0	1.4 ± 0.9	2.6 ± 2.2
SCORE SMB	7.3 ± 8.8	2.5 ± 3.5	5.0 ± 5.2	7.6 ± 5.0	14.1 ± 12.0
PROCAM	4.8 ± 6.4	1.8 ± 2.9	3.0 ± 4.0	4.9 ± 2.8	9.5 ± 8.7
AGLA	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

Figures:

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



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)

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