

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 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 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. Mislabeling should be avoided.

Introduction

Preventive medicine is a pillar of basic health care and is essential to avoid disease expansion¹. 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 in Switzerland. 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 regulated in the Medical Products Act⁵, 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 and other preventable cardiovascular disease's risk changes the risk category from low to intermediate or high or from intermediate to high.

For the purpose of this study, we tested the predicting ability of SCORE, AGLA and HerzCheck using the recently published ARCO cohort study observations for outcome⁶ and cost-effectiveness of carotid imaging⁷ and calculated calibration factors for various outcomes as well as the occurrence of myocardial infarction and other cardiovascular events.

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
NRI	Net reclassification improvement
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 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. 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 ($\geq 50\%$) 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 r^2 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)⁸. All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously reported⁹: 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 (SCORE¹⁰) and the German PROCAM risk for myocardial infarction and for stroke multiplied with a correction factor of 0.7.¹¹ Further, we calculated point scores for HerzCheck and PROCAM with associated 10 year risk estimates and we calculated PROCAM using the original formula¹². 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.¹³

Statistics

We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons.¹⁴ Groups were compared using a t-test for continuous variables and CHI^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere¹⁵: 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: $\text{NRI} = P(\text{up}|\text{event}) - P(\text{down}|\text{event}) + P(\text{down}|\text{non-event}) - P(\text{up}|\text{non-event})$. The null hypothesis for $\text{NRI} = 0$ 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: $(PV \times SE) / [PV \times SE + (1 - PV) \times (1 - SP)]$

PTP negative: $[PV \times (1 - SE)] / [PV \times (1 - SE) + SP \times (1 - PV)]$

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 mm²). 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 mm², average 149 mm²).

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. 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 mm²), 2nd (TPA 22-61 mm²) and 3rd TPA tertile (TPA \geq 62 mm²) 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.

Table 8 shows the cumulative incidence of cardiovascular events with myocardial infarction as the reference observed in the DETECT¹⁶ and in the ARCO study. For every AMI, 1.8 AMI+STR occur in the combination of DETECT with ARCO; when adding revascularisation 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 mm²).

Discussion

The goals of this study were to test calibration and discrimination 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 and was to test the relative incidence of myocardial infarction (CHD) with other cardiovascular endpoints (CVD), because in Switzerland CHD risk estimates are repeatedly labeled as CVD risk estimates.

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 – for Switzerland – it may be justified to multiply the ARCO risk by 0.7 (Table 2b), where risk by AGLA CHD is still underestimated by 15%. If we assess the calibration factors of AGLA for CHD+STR and for all CVD events, then risk is underestimated by 55% and by 245% (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 extremely poor. Therefore, to calculate CVD risk, it is important to add additional risk elements, e.g., from PROCAM Stroke or by direct calculation of 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 our multivariate 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.

When we stratify observed events by zero plaque and TPA tertiles (table 7, 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 SCORE, PROCAM and AGLA showed intermediate (SCORE) or average low-risk.

In order to verify our ARCO observation, we compared event rates from the DETECT study cohort (N=4044, FU 5 years)¹⁶ and we summed the observations from ARCO and DETECT as shown in table 8 (34'340 patient observation years). From these contemporary observations we can expect that for every AMI another 0.8 STR occur (TIA excluded), therefore AMI+STR risk is AGLA or PROCAM multiplied by 1.8; for all cardiovascular events, the multiplication factor is 4.1. From these observations it becomes clear that CHD is about a quarter of CVD incidence in these contemporary cohort observations. As an example, an AGLA_{CHD} risk of 5% may represent an AGLA_{CVD} risk of 20%.

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.¹⁷ 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,^{18,19} 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.^{20,21} 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 claim to use AGLA CHD and HerzCheck CHD as a cardiovascular assessment tool for CVD misleads patients in their risk perception and conflicts with the correct labeling of these calculators. Further, at the discretion of physician and pharmacists, communicated risk should be recalculated using PROCAM STROKE or SCORE CVD to avoid miscommunication of low risk where in fact intermediate or even high risk was present.

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 (%)	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, mm ²	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	AMISTR CABG	ALL events
Event Rate (%)		1.44	2.01	2.7	5.4
		10 year			
Outcome		AMI	AMISTR	AMISTR CABG	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	AMISTR CABG	ALL events
Event Rate (%)		1.44	2.01	2.7	5.4
		10 year			
Outcome		AMI	AMISTR	AMISTR CABG	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			
SCOREcvd	L	1601	16	0	870	3.06122449	-27.5510204
	M	823	240	71		30.6122449	
	H	15	32	44		Kappa	0.28
		PROCAMas			N	%	
		L	M	H			
SCOREcvd	L	1597	17	3	734	4.57424349	-21.252639
	M	706	318	110		25.8268825	
	H	1	27	63		Kappa	0.37
		HerzCheck			N	%	
		L	M	H			
SCOREcvd	L	1597	20	0	934	1.47783251	-31.3863476
	M	867	245	22		32.8641802	
	H	19	48	24		Kappa	0.25
		AGLA			N	%	
		L	M	H			
SCOREcvd	L	1612	5	0	1048	0.70372977	-36.1717101
	M	975	144	15		36.8754398	
	H	33	40	18		Kappa	0.16
		PROCAMpoint			N	%	
		L	M	H			
SCOREcvd	L	1612	5	0	988	1.19634061	-33.5679099
	M	926	179	29		34.7642505	
	H	18	44	29		Kappa	0.21
		PROCAMpoint			N	%	
		L	M	H			
PROCAMAS	L	2301	3	0	363	0.17593244	-12.5967628
	M	243	117	2		12.7726953	
	H	12	108	56		Kappa	0.50
		AGLA			N	%	
		L	M	H			
PROCAMAS	L	2304	0	0	449	0	-15.7987333
	M	306	56	0		15.7987333	
	H	10	133	33		Kappa	0.35
		HerzCheck			N	%	
		L	M	H			
PROCAMAS	L	2249	55	0	358	2.07600281	-10.52076
	M	224	134	4		12.5967628	
	H	10	124	42		Kappa	0.47
		PROCAM			N	%	
		L	M	H			
PROCAMAS	L	2304	0	0	195	0	-6.86136524
	M	134	228	0		6.86136524	
	H	1	60	115		Kappa	0.76
		PROCAMpoint			N	%	
		L	M	H			
PROCAM	L	2423	16	0	193	0.77410274	-6.01688951
	M	130	152	6		6.79099226	
	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), and estimates of myocardial infarction (PROCAM, AGLA) oder cardiovascular risk (SCORE)

TPA Groups	ALL	Zero Plaque		Carotid Plaque Tertiles (TPA)					
		0	26	1	2	3	25	707	25
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			

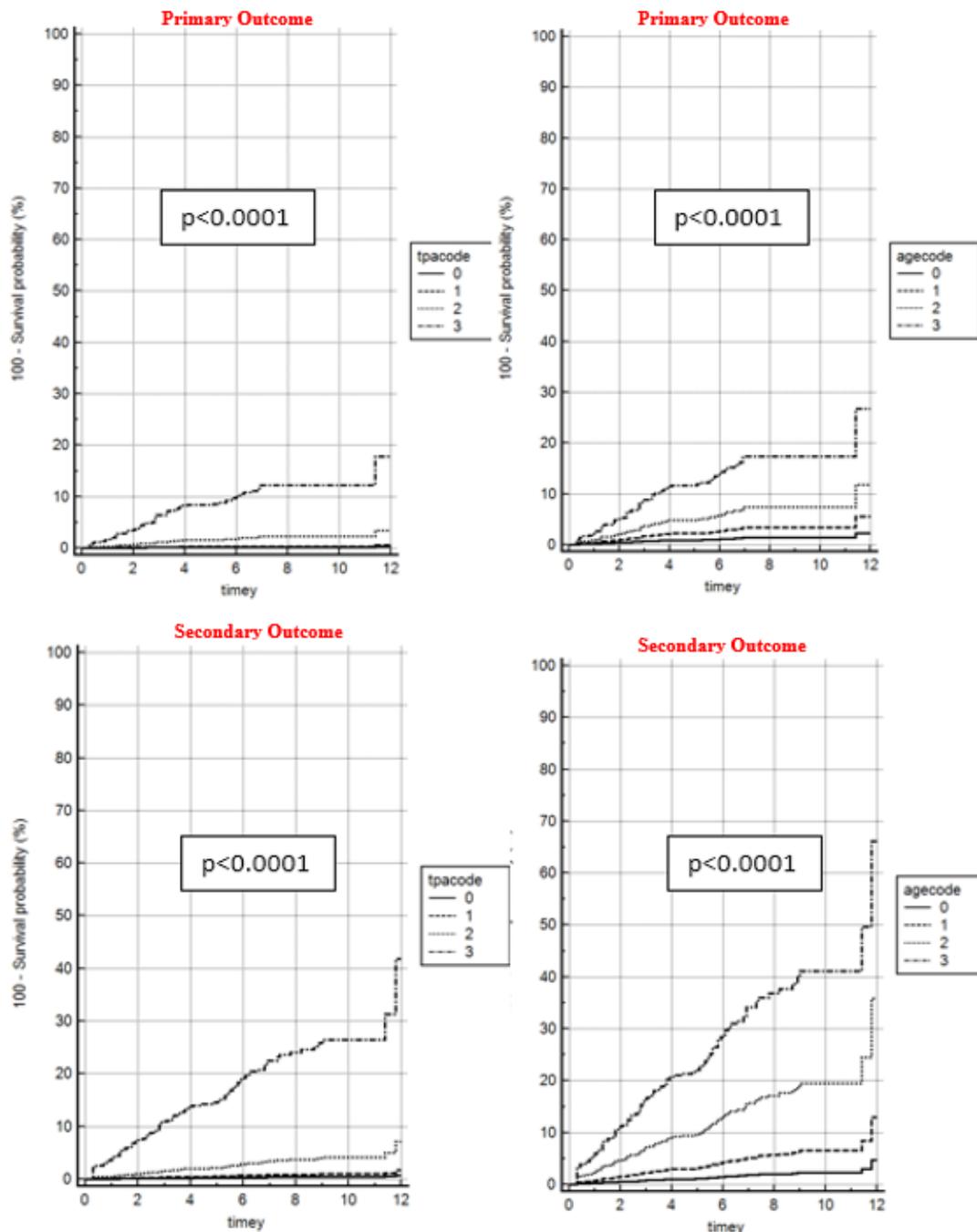
Table 8: Incidence of cardiovascular endpoints in DETECT²² (N=4044) and ARCO (N=2842) and combination of both studies with 34'340 observed patient years (29 TIA from DETECT were excluded from this analysis)

Endpoint	DETECT	DETECT		ARCO		DETECT+ARCO	
		DETECT	Cumulative Incidence	ARCO	Cumulative Incidence	SUM EVENTS	Cumulative 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

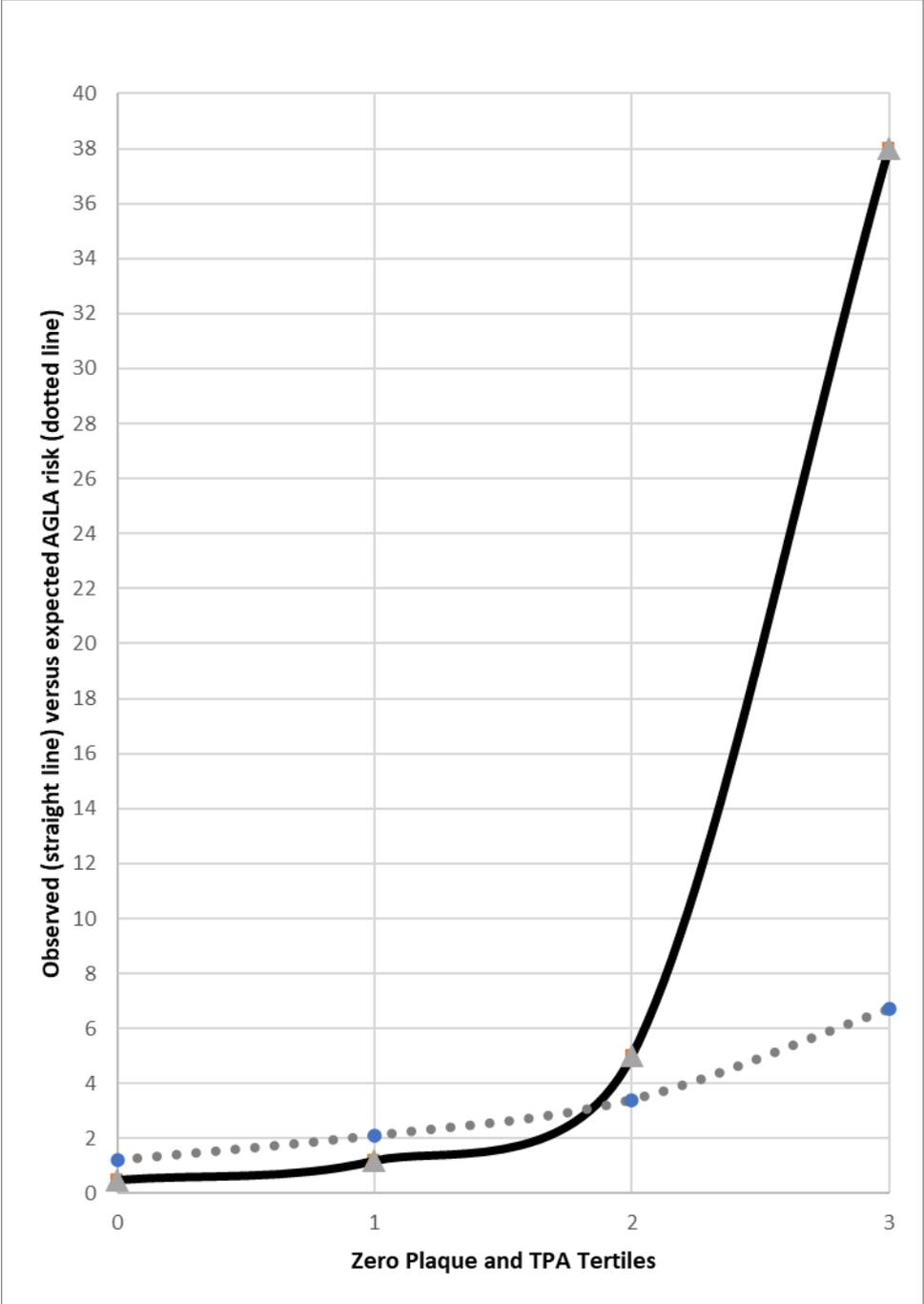
Figures:

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



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 (straight) and AGLA prediction (dotted line) plotted by zero Plaque and TPA tertiles in the ARCO study



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