Prognostic Impact of Carotid Plaque Imaging using Total Plaque Area added to SCORE2 in middle-aged subjects

The Arteris Cardiovascular Outcome (ARCO) cohort study

Corresponding Author:

Michel Romanens, MD

Vascular Risk Foundation

Spitalstr. 9, CH-4600 Olten, Switzerland

michel.romanens@gmail.com

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Abstract

A large number of cardiovascular events occur in seemingly healthy individuals. Atherosclerosis imaging can improve the outcome and treatment regime of such subjects.

We aim to assess the predictive value of atherosclerosis imaging beyond cardiovascular risk calculators in subjects aged 40-65 years.

We compared PROCAM, SCORE and SCORE2 with carotid ultrasound (total plaque area, TPA) in subjects without known cardiovascular diseases. Follow-up was obtained by phone or mail.

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. PROCAM risk was 5±6%, SCORE risk 1.3±1.6% and SCORE2 5±3%. Both for the primary outcome (AMI, STROKE=MACE) and the secondary outcome (adding CABG, CAD and PTCA=ASCVD) hazards increased significantly for TPA 3rd tertile (MACE 6.7, ASCVD 22.5) and for SCORE2ptp Code 3 (MACE 7.7, ASCVD 10.1) after adjustment for risk factors (age, smoke, sex, systolic BP, lipids, medication). Model performance was statistically improved regarding model fit in all models using TPA. Net reclassification improvement (NRI) for SCORE2ptp increased significantly by 32% for MACE ($p=0.0001$) and 44% for ASCVD ($p<0.00001$).

TPA posttest risk integrated into SCORE2 added prognostic information to SCORE2 alone, supporting the assessment of ASCVD risk with carotid ultrasound in subjects aged 40-65 years.

One Sentence Summary

Total Plaque Area adds significant prognostic information to the SCORE2 risk estimates supporting the additional value imaging carotid arteries in a primary prevention setting.

Keywords

Carotid plaque; cardiovascular outcome; cardiovascular risk equations; arterial age; atherosclerosis imaging; atherosclerosis.

List of Abbreviations

3D	three dimensional
AMI	fatal or non-fatal myocardial infarction
AUC	area under the curve
ASCVD	atherosclerotic cardiovascular disease
BP	blood pressure
CABG	coronary bypass grafting
CAD	coronary artery disease on an invasive coronary angiogram with luminal narrowing of 50% or more
cAGE	chronological age
CI	confidence interval
Code	used in SCORE2ptp, 1= low, 2=intermediate, 3=high risk and used for TPA, 1= 0 plaque or 1st tertile, 2=2nd tertile, 3=3rd tertile
EAS	European Atherosclerosis Society
ESC	European society of cardiology
FAM	family history of premature myocardial infarction or stroke
HDL	high-density lipoprotein
HL	Hosmer & Lemeshow test
JASE	Journal of American Society of Echocardiography
LDL	low-density lipoprotein
MACE	fatal or nonfatal acute myocardial infarction or stroke
NRI	Net reclassification improvement
PESA	Progression of Early Subclinical Atherosclerosis Study
ROC	receiver operating curves
PROCAM	Prospective Cardiovascular Münster Study for fatal and non-fatal myocardial infarction
PROCAMcvd	Prospective Cardiovascular Münster Study for fatal and non-fatal myocardial infarction and stroke

PTCA	percutaneous transluminal coronary angioplasty
TPA	Total plaque area (carotid plaque)
SCORE	SCORE Risk charts and equations, European Society of Cardiology, for fatal cardiovascular events
SCORE2	SCORE Risk charts and equations, European Society of Cardiology, for fatal and non-fatal cardiovascular events
SCORE2ptp	Posttest risk of SCORE and TPA based on the Bayes theorem
SD	standard deviation
STROKE	fatal or nonfatal stroke

Introduction

The SCORE2 working group and European Society of Cardiology (ESC) Cardiovascular risk collaboration has published new prediction algorithms for estimating 10-year risk of cardiovascular disease in Europe in January 2021 (1). Previously, the ESC and European Atherosclerosis Society (EAS) have issued a guideline for dyslipidemia treatment and suggested to use arterial (carotid and/or femoral) plaque burden with ultrasound as a risk modifier in individuals at low or moderate risk (2). This recommendation was based on the performance of SCORE, a risk algorithm for cardiovascular mortality only (3). With SCORE2, risk classification has been extended to include non-fatal cardiovascular events (myocardial infarction and stroke) and risk categories have also been modified according to an individual's age at the time of the risk assessment. In subjects aged below 50 years, <2.5% risk is defined as low and ≥7.5% is defined as high risk, whereas in subjects aged 50-69 years the cut-offs are < 5.0% and ≥10.0% respectively. This important modification allows to account for life-time risks. In view of the SCORE2 modifications, additional ultrasound imaging tests to detect carotid or femoral plaque as risk category modifiers may not be necessary anymore.

In order to address the question, whether additional ultrasound plaque imaging in carotid arteries may still be indicated as a risk modifier in primary care, we performed a joint German and Swiss (central Europe) cohort study in subjects aged 40-65 years. Specifically, we addressed the questions, (1) whether SCORE2 outperforms other risk prediction algorithms used in Germany and Switzerland (PROCAM (4), SCORE) regarding calibration, discrimination and reclassification, and (2) whether carotid plaque per se or integrated into posttest risk calculations into SCORE2 added additional information above and beyond SCORE2.

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.

We calculated minimum sample size of N=252 with 12 cases for ROC analysis, N=2208 with 138 cases for comparative ROC analysis. Patients with known ASCVD or diabetes mellitus were excluded. Consecutive patients aged 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 after public advertisements approved by the local ethical committee. In the German Centre in Koblenz, subjects were referred within a working medicine setting. Subjects were free of cardiovascular symptoms, disease or diabetes mellitus and between 40 to 65 years of age. Laboratory values, systolic blood pressure (measured in the sitting position after a brief resting period with a plethysmographic method) and medical history were obtained locally and entered into a spread-sheet (Excel, Microsoft, Richmond, USA).

Patient information

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 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).

Sensitivity Analysis

Because 18% 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. Subjects were entered into an anonymized study registry, for which current legislation in Switzerland and Germany does not require formal ethical committee consent.

Carotid imaging

Burden of longitudinal carotid plaque surface was imaged with a high-resolution ultrasound linear transducer probe (7.5–12.0 MHz), which identified plaques with intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed up to the total plaque area (TPA) in mm^2. 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 areas of shadowing were rarely seen in subjects aged 40-65 years, therefore, this was not a significant problem. 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)(5). All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously reported (6). Arterial age was calculated from average values of TPA derived from 5-year intervals for men and women aged 35 to 79 years were plotted against the chronological age in 1'500 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 point score system for low risk populations in Switzerland and for intermediate risk in Germany (SCORE2, (1)) and calculated the German PROCAM risk for myocardial infarction and stroke online (7). Further, we calculated risk based on the SCORE risk equation (3). For NRI calculations we calculated sensitivity and specificity of TPA tertiles and derived posttest risk calculations for SCORE2 using the Bayes theorem as described elsewhere (8). The sensitivities and specificities for the Bayes formula are displayed in Table 7 (for TPA tertiles) and a negative test was defined as TPA: 1. tertile (<22 mm^2); a positive test was defined as presence of 2. tertile (22-61 mm^2) or 3. tertile ($\geq$ 62 mm^2).

Statistics

We used MedCalc® Statistical Software version 20.014 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org) to calculate Cox proportional-hazards regressions, and ROC curves and their comparisons (9). Groups were compared using a t-test for continuous variables and CHI^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere (10): 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."

We used Cox proportional-hazards regression after adjustment for clinical variables and risk algorithms both for MACE and ASCVD. Further we assessed model performance using model fit (χ^2), discrimination (ROC analysis) and calibration (Hosmer & Lemeshow test).

The level of statistical significance was set at $p < 0.05$.

Results

The ARTERIS cohort is composed of subjects of the cardiological practice KARDIOLAB in Olten, (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 predominantly Caucasian 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 due to age. The remaining 3452 subjects were eligible for study entry and follow-up could be obtained for 2842 (82.3%) subjects, who were dominantly visited in Koblenz, Germany (80%) and the German cohort contributed to the total of ASCVD event in 123 out of 154 cases (80%). Events are confirmed by medical records in 75% and by telephone interview in 25%.

In the VARIFO cohort, 16 deaths occurred, of which 5 were of unknown cause 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 (MACE) was 41 AMI and 16 STROKES (total 57 MACE), other events were 21 CABG, 41 PTCA and 35 CAD (adding another 97 events to the total of events of 154 ASCVD 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. 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.

Table 1 shows clinical baseline characteristics and cardiovascular risks of those with and without a cardiovascular event. Patients with MACE and ASCVD were statistically significant more males (92% and 94% respectively), were older (55 versus 50 years) and were more frequently smokers (56% and 47% versus 20% in those without ASCVD). The lipid profile in those with ASCVD was less favourable with higher triglycerides, high total and LDL cholesterol and lower HDL cholesterol. Average TPA was 127 in MACE and 134 mm^2 in ASCVD versus 39 mm^2 in those without ASCVD. Assessment with risk algorithms placed patients with ASCVD into the moderate risk category, while those without ASCVD were usually in the low-risk category when assessed with PROCAM, SCORE and SCORE2.

Table 2 displays the discrimination of MACE and ASCVD using AUC for PROCAM, PROCAMcvd, SCORE, SCORE2, SCORE2ptp and TPA. For the discrimination of MACE, all AUC were between 0.83 and 0.86 with significant better discrimination for SCORE2ptp vs SCORE2 and vs TPA. For the discrimination of ASCVD, we found PROCAM vs PROCAMcvd p=0.0002; PROCAM vs SCORE2PTP p=0.0001; PROCAM vs TPA p=0.0006, PROCAMcvd vs SCORE2PTP p=0.0008, PROCAMcvd vs TPA p=0.0049; SCORE ~ SCORE2PTP p<0.0001, SCORE vs TPA p=0.0004; SCORE2 vs SCORE2ptp p<0.0001; SCORE2 vs TPA p=0.0001; all others o=NS. **Figure 1** shows the AUC für ASCVD.

Table 3a shows the sensitivity and specificity to detect ASCVD for PROCAMcvd, SCORE, SCORE2, SCORE2ptp intermediate and high risk or for TPA 2nd and 3rd tertile. For the discrimination of intermediate risk, PROCAMcvd showed only a moderate result (66%) compared to SCORE, SCORE2 and TPA (88% to 95%), while specificity was best for PROCAMcvd (84%) and significantly lower for SCORE, SCORE2 and TPA (48%-60%). For

the discrimination of high risk, PROCAMcvd, SCORE and SCORE2 showed only a low result (18%-31%) compared to SCOREptp and TPA (72% to 82%), while specificity was best for PROCAMcvd, SCORE and SCORE 2 (95%-98%) and significantly lower for SCORE2ptp and TPA (78%-79%). These results are visualized in **Figure 2** (for ASCVD only)**. Table 3b** shows the observed MACE and ASCVD numbers stratified by risk category and risk assessment tools. Compared to PROCAM, where 46% MACE and 49% ASCVD events were observed in the low-risk category, such events occurred only rarely in persons at low risk defined by SCORE (12% and 10% respectively), by SCORE2 (7% and 12%), but in the risk tools using TPA, only 5% of event occurred. Only 19% of MACE and 20% of ASCVD occurred in the PROCAM high risk category, whereas almost all events occurred in the 3rd tertile of TPA (74% and 82% respectively) and in the high risk group of SCORE2ptp (84% and 85% respectively).

Table 4 shows a logistic regression of the various risk prediction tools as a measure of model fit to determine calibration. Goodness of fit was not significant regarding PROCAM, PROCAMcvd, SCORE and SCORE2 for MACE and ASCVD outcomes. Only with the addition of carotid plaque information derived from TPA, model fit became significant both for MACE and ASCVD. **Figure 3** shows examples of the graphical representation of ASCVD using the Hosmer & Lemeshow test for PROCAM, SCORE, SCORE2, and SCORE2ptp.

Table 5 shows a multivariate Cox proportional Hazards model which included using a foreward step approach regarding clinical variables (age, sex, family history, BP, smoking, and lipids) for the MACE and the ASCVD outcome. For MACE, significant predictors were sex, smoking, family history, blood pressure and intermediate or high posttest SCORE2 risk (which includes results from TPA). For ASCVD, significant predictors were age, sex, smoking, family history, LDL and intermediate or high posttest SCORE2 risk.

Table 6 shows a multivariate Cox proportional Hazards model which included using a

foreward step approach regarding risk algorithms (PROCAM, PROCAMcvd, SCORE, SCORe2) for the MACE and the ASCVD outcome. For MACE, significant predictors were the SCORE calculators only. For ASCVD, significant predictors were PROCAMcvd and the SCORE calculators. **Figure 4** displays the adjusted Cox proportional Hazards models as calculated in Tables 5 and 6 and **Figure 5** shows a Forest plot of ASCVD predicting clinical variables.

We performed NRI statistics for SCORE2ptp. For MACE, NRI was 32% ($p=0.001$) and for ASCVD, NRI was 44% ($p<0.0001$).

Table 7 displays the sensitivities and specificities of TPA tertiles to detect MACE and ASCVD.

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

As we published recently, TPA added prognostic information to conventional risk equations available for PROCAM, SCORE, and FRAMINGHAM, supporting the joint assessment of ASCVD risk with carotid ultrasound in subjects aged 40–65 years (11) and we found this approach to be cost-effective (12).

The SCORE2 algorithm is a major step ahead in cardiovascular risk prediction for two reasons: (1) Lowering the risk threshold for intermediate risk from 5.0% to 2.5% in subjects aged <50 years accounts for the increased life-time risk by expecting (with linear extrapolation), that a risk of e.g., 4.0% in 10 years will translate into a risk of 12% in 30 years. Therefore, apparently low-risk, as known from previous risk charts is not trivial in younger age. (2) The trade-off between poor sensitivity and high specificity at the 10% intermediate risk threshold was lowered to 2.5% in subjects aged below 50 and lowered to 5.0% in subjects aged 50-69 years, which is expected to increase sensitivity (desired preventive effect), but may decrease specificity (unwanted effect because of treatment allocated to patients who will not experience an event in 10 years). By increasing the perception of risk to 30 instead of 10 years, patients cannot become healthier (e.g., true negative will remain true negative, if no event happens: the number of true negatives cannot increase). However, events occurring in the period between 11-30 years will change true negatives to false negatives. Let us consider the case of 50 true positives, 50 false positives, 50 false negatives and 850 true negatives. In this case, sensitivity is 50% and specificity is 94%, a situation traditionally known from calculators such as PROCAM. Let us consider, that over 30 years true positives will occur in 150 instead of 50 patients, which reduces the number of true negatives, then we count 750 true negatives and 150 true positives, which increases sensitivity from 50% to 75% while specificity is preserved at 94% at an increase of disease prevalence from 9% to 19%.

Based on this background, it may be argued, that additional tests like TPA may not be necessary with SCORE2. In order to test this hypothesis, we analysed our cohort study data. First, we performed sensitivity and specificity analysis and found that SCORE and SCORE2, when compared to PROCAM to detect ASCVD at the intermediate risk threshold, was significantly higher for sensitivity, but significantly lower for specificity and at the high-risk threshold results were comparable for PROCAM, SCORE and SCORE2 regarding specificity. Therefore, the higher sensitivity for SCORE2 when compared to PROCAM could be reproduced, however, SCORE and SCORE2 sensitivity performance was very similar, and this again is most likely due to the low threshold for intermediate risk in SCORE, which was chosen to be 1.0% for cardiovascular mortality, instead of, e.g., 2.5%. Therefore, lower risk thresholds increase sensitivity at the trade-off regarding specificity, as expected and reproduced by our data.

The major finding of our study, when adding the information from carotid plaque ultrasound quantification using the TPA method and associated sensitivities and specificities for posttest risk calculations into SCORE2 (SCORE2ptp) was the significant improvement of discrimination and calibration when compared to PROCAM, SCORE and SCORE2. Further, reclassification was significantly improved with SCORE2ptp when compared to SCORE2 by 32% for MACE and by 44% for ASCVD. Regarding discrimination for MACE, SCORE2ptp was a significantly better predictor with an AUC of 0.86 ($p=0.003$) when compared to SCORE and SCORE2 (Table 2). For the prediction of ASCVD, SCORE2ptp and TPA, discrimination (0.87 and 0.88 respectively) was significantly higher than for the risk assessment tools not incorporating TPA. Furthermore, over 70% MACE and ASCVD occurred in the high-risk group of SCORE2ptp and TPA (PROCAM 19% and 20% respectively, Table 3b). Reliability of discrimination is improved with TPA and associated posttest risk in our study. Reliability of calibration is also significantly improved using model fit (logistic regression model, Table 4, Figure 3). When TPA was used to define SCORE2ptp

we observed a significantly better result in the Cox proportional Hazards model for MACE and ASCVD when compared to PROCAM and SCORE (Table 6, Figure 4).

Statistical procedures should be introduced in order to reclassify subjects not just based upon presence / absence of plaques. Based upon TPA tertiles and outcome for cardiovascular events, sensitivities and specificities are evidence based (11) and can be used to calculate the posttest risk based upon the Bayes theorem (8). Based upon our observations, more than 30% of subjects aged 40-65 years can be reclassified using the pretest calculator SCORE and the posttest risk calculations (3). In this study, the net reclassification index (NRI) was 32% for SCORE2ptp and MACE and 44% for ASCVD. As an example, the reclassification process would take place in a person aged 48 years with a SCORE2 result of 2.2% and a TPA within the 3rd tertile, where for MACE sensitivity is 74% and specificity is 76%, which results in a Bayes posttest risk of 6.5%, which shifts this person from low to intermediate MACE risk.

Recently, a writing group by Johri et al of the American Society of Echocardiography (JASE) recommended against the use of TPA for cardiovascular risk assessment, mainly due to the problem to correctly identify the best imaging plane of a plaque (13). This view has been contradicted by Spence et al in a letter to JASE, pointing out to the excellent reproducibility of the TPA method (xx). Furthermore, TPA is a full carotid vessel measurement and the recommended 3D-approach by the JASE writing group for plaque quantification suffers from the acknowledged problem of overlapping plaque images, where a plaque may be quantified twice. Further, JASE recommended for measurements of carotid intima-media thickness (CIMT), although CIMT measurement is even more dependent of the imaging plane than TPA due to the small structures quantified. JASE also recommended measurements of maximum plaque thickness, which is problematic, because it does not directly quantify total plaque burden of the carotid arteries (e.g., the length of two plaques may differ, while hight might be the same, therefore area and volume would be different).

TPA has an excellent prognostic power, as we have shown in our cohort study and in a review (14), is rapidly performed, reproducible and can be tracked over time. Available 3D technology for the presence and volume of carotid plaque has also been tested with an automated 3D probe in the PESA study (15). The prevalence of carotid plaques in men aged 50-54 was 48%, whereas we found a prevalence for any plaque of 86% and a prevalence of plaque with a total plaque area > 21 mm^2, which corresponds to the cutoff of the second tertile, of 66% (11). This apparent difference is attributable to two important technical differences. First, carotid plaque volume was measured in PESA with the use of the Philips iU 22 ultrasound system equipped with a single sweep volumetric VL 13-5 transducer, which covers only a volume of 38 mm x 30° of the carotid artery (16) and visualises the distal part of the common carotid artery, the bulb and the proximal parts of the internal carotid artery (14). Off-line software then calculates the plaque areas from all obtained cross-sectional images in order to produce the total plaque volume (TPV), a time-consuming method when compared to TPA. Since the field of view is only 38 mm x 30°, some plaques proximal or distal to the transducer are missed and these plaques are included in the total plaque area derived from longitudinal carotid images (17). Second, the definition of plaque up from a intima-media-thickness (IMT) of >1.5 mm is likely to miss substantial amounts of atherosclerosis and associated cardiovascular risk, as is known form IMT studies, where risk substantially increases with IMT > 1.0 mm (18). The advantage of the longitudinal plaque imaging (TPA technique) is its high reproducibility (19), vendor independence (no additional costs for surface tracings) and the possibility to obtain the results without additional software. TPA is measured easily within the whole tree of the carotid / subclavian arteries and does not require the exposure of the Inguina region, which may create a source of discomfort for examiners and patients. Since the TPA measurement has been validated in numerous studies and the prognostic significance of this measurement has been proven beyond doubt (14), it is sufficient to first sonicate the carotids in a sequential test procedure. We suggest however, to

perform additional imaging tests in subjects, where pretest risk is substantial (e.g., SCORE2 risk > 7.5%) and no carotid plaque is found. In this case, femoral, subclavian, aortic arch, abdominal aorta plaque or coronary calcium may be used to assess the presence and extent of atherosclerosis. In contrast to the Calcium Score (20), TPA is also able to track the effects of preventive efforts over time, which is especially attractive and motivating for patients, since good control of cardiovascular risk factors in patients with advanced atherosclerosis is not only likely to reduce cardiovascular events (21) but also the amount of TPA (22–24) and arterial age (11).

We believe that risk prediction should focus on the detection of ASCVD rather than MACE, since we have shown, that most events occur in those patients who were within the 3rd tertile of TPA and many patients with 2nd or 3rd tertile TPA can be captured for effective preventive therapies before MACE occurs. In fact, ultrasound-based imaging of ASCVD risk meets virtually all quality requirements. This knowledge is available. The problem is not the lack of scientific knowledge but the insufficient application of this knowledge in daily preventive practice.

Addressing the limitations of our study, and similar to other studies (25,26) we were able to assess only a limited number of follow-up (82%), which excludes derivation of *absolute* risk; however, limited number of follow-ups does not bias the *relative* diagnostic power of risk markers and our sensitivity analysis makes a selection bias unlikely. We were able to include only a limited number of women and a limited number of cardiovascular events from the Olten Centre, however, previous studies assessed also sufficiently high numbers of women and found similar predictive strengths in women (14,27). Further, we did not use an independent outcome committee, however, 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.

Conclusions

SCORE2, like SCORE, performs well in categorizing patients with events as medium- or high risk when compared to PROCAM. Additional information regarding calibration and discrimination of SCORE2 compared to PROCAM and SCORE was small. The addition of the TPA-Bayes criterion to SCORE2 as well as TPA itself outperformed other risk models that did not use the Bayes posttest information of TPA regarding MACE and ASCVD. SCORE2ptp risk groups maintain important clinical information, significantly improves risk classification by 44% regrading ASCVD also perform above and beyond SCORE2. SCORE2 and TPA should be used jointly in order to allocate preventive resources as soon and as personalised as possible.

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

	TYPE OF OUTCOME								
Patient characteristics	**MACE**		**ASCVD (A)**		**NO ASCVD (NA)**		**p A vs NA**	**ALL**	
N	57		154		2688			2842	
Male (%)	54	92	141	94	1636	60	<0.00001	1765	62
Female (%)	3	8	13	6	1068	40	<0.00001	1081	38
Age + SD	55	6	55	6	50	8	<0.0001	50	8
Smoker, %	32	56	72	47	537	20	<0.00001	609	21
BP mm Hg, systolic + SD	139	20	133	18	125	15	<0.0001	125,7	15,5
BMI + SD	27	4	27	4	26	4	NS	26	4
Lipids									
Cholesterol + SD, mmol/l	6,3	1,1	6,3	1,1	6,0	1,1	<0.01	6,0	1,1
HDL + SD, mmol/l	1,3	0,3	1,3	0,3	1,5	0,4	<0.0001	1,5	0,4
LDL+ SD, mmol/l	4,1	0,9	4,1	0,9	3,7	0,9	<0.0001	3,7	0,9
Triglyceride + SD, mmol/l	1,8	1,3	2,0	1,3	1,6	1,1	<0.0001	1,6	1,1
Imaging									
TPA + SD, mm2	127	98	134	85	39	47	<0.0001	42	54
Risk algorithms									
PROCAM + SD %	13	8	13	9	4	6	<0.0001	5	6
PROCAMcvd + SD %	16	9	16	10	6	7	<0.0001	6,0	8,0
SCORE + SD, %	3,8	3,0	3,0	2,0	1,2	1,5	<0.0001	1,3	1,6
SCORE2 + SD, %	9	4	8	4	4	3	<0.0001	5,0	3,0
SCORE2ptp + SD, %	21	10	22	10	6	8	<0.0001	7,0	9,0

Table 2: AUC for MACE and ASCVD using predictors of discrimination from risk algorithms, ultrasound plaque imaging and posttest risk of SCORE2 derived from TPA.

	MACE		ASCVD	
Variable	**AUC**	**95% CI**	**AUC**	**95% CI**
PROCAM	0,83	0,819 to 0,847	0,83	0,811 to 0,839
PROCAMcvd	0,84	0,830 to 0,857	0,84	0,824 to 0,851
SCORE	0,83	0,814 to 0,842	0,82	0,809 to 0,838
SCORE2	0,83	0,813 to 0,842	0,82	0,805 to 0,833
SCORE2PTP	**0,86**	**0,846 to 0,872**	**0,87**	**0,861 to 0,885**
TPA	0,83	0,815 to 0,843	**0,88**	**0,865 to 0,890**

P for MACE: SCORE2 vs SCORE2PTP: p=0.03; SCORE2PTP vs TPA: p=0.02, all others p=NS

P for ASCVD: PROCAM vs PROCAMcvd p=0.0002; PROCAM vs SCORE2PTP p=0.0001; PROCAa vs TPA p=0.0006, PROCAMcvd vs SCORE2PTP p=0.0008, PROCAMcvd vs TPA p=0.0049; SCORE ~ SCORE2PTP p<0.0001, SCORE vs TPA p=0.0004; SCORE2 vs SCORE2ptp p<0.0001; SCORE2 vs TPA p=0.0001; all others o=NS.

Table 3a: Sensitivity (SENS) and Specificity (SPEC) of risk categories for intermediate or high ASCVD risk

	Cutoff for intermediate risk				Cutoff for high risk			
Risk tool	**SENS, 95%-CI**		**SPEC, 95%-CI**		**SENS, 95%-CI**		**SPEC, 95%-CI**	
PROCAMcvd	65,58	57,5 - 73,0	83,74	82,3 - 85,1	28,57	21,6 - 36,4	95,09	94,2 - 95,9
SCORE	89,61	83,7 - 93,9	59,56	57,7 - 61,4	18,18	12,4 - 25,2	97,66	97,0 - 98,2
SCORE2	88,31	82,2 - 92,9	47,73	45,8 - 49,6	30,52	23,4 - 38,4	95,09	94,2 - 95,9
SCOREptp	94,81	90,0 - 97,7	55,88	54,0 - 57,8	72,08	64,3 - 79,0	78,98	77,4 - 80,5
TPA score	95,45	90,9 - 98,2	52,42	50,5 - 54,3	81,82	74,8 - 87,6	78,39	76,8 - 79,9

Table 3b: Observed MACE and ASCVD by risk category (low, medium, high) and risk assessment tool (PROCAM, SCORE, SCORE2, SCORE2ptp, TPA tertiles)

	MACE	**%**	**ASCVD**	**%**
N=	**57**	**100**	**154**	**100**
PROC low	26	46	76	49
PROC med	20	35	47	31
PROC high	11	19	31	20
SCORE low	7	12	16	10
SCORE med	34	60	110	71
SCORE high	16	28	28	18
SCORE2 low	4	7	18	12
SCORE2 med	30	53	89	58
SCORE2 high	23	40	47	31
SCORE2ptp low	3	5	8	5
SCORE2ptp med	6	11	15	10
SCORE2ptp high	48	84	131	85
TPA 0-1	3	5	7	5
TPA 2	12	21	21	14
TPA 3	42	74	126	82

Table 4: Model fit based on logistic regression for MACE and ASCVD

Logistic Regression Coefficients and Standard Errors								
	MACE				**ASCVD**			
Variable	**Coefficient**	**Std. Error**	**Wald**	**P**	**Coefficient**	**Std. Error**	**Wald**	**P**
PROCAM	0,034396	0,10236	0,1129	0,7368	0,0093995	0,076332	0,01516	0,902
PROCAMcvd	-0,05124	0,10135	0,2556	0,6132	0,0038108	0,074856	0,002592	0,9594
SCORE	0,04495	0,094698	0,2253	0,635	-0,065648	0,080755	0,6609	0,4163
SCORE2	0,049788	0,12904	0,1489	0,6996	-0,090538	0,096034	0,8888	0,3458
SCORE2ptp	0,093332	0,043528	4,5975	**0,032**	0,11324	0,031809	12,6732	**0,0004**
TPA	0,0054614	0,0021587	6,4007	**0,0114**	0,010778	0,0019269	31,2897	**<0,0001**
Constant	-5,68804	0,37657	228,1624	**<0,0001**	-4,65204	0,25037	345,2385	**<0,0001**

Table 5: Cox proportional Hazards model using clinical variables and posttest risk categories of SCORE2 for MACE and ASCVD

	Coefficients and Standard Errors for MACE					
Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
cAge	0,05236	0,02137	6,0039	0,0143	1,0538	1,0105 to 1,0988
Sex_Code	-1,6124	0,577	7,8099	0,0052	0,1994	0,0644 to 0,6178
SMOKE_Code	1,4975	0,2837	27,859	<0,0001	4,4704	2,5636 to 7,7954
Fam_Code	0,6265	0,2803	4,9951	0,0254	1,871	1,0801 to 3,2408
BPs	0,03067	0,00754	16,555	<0,0001	1,0311	1,0160 to 1,0465
SCORE2ptpCode=2	1,9659	0,7207	7,4406	0,0064	7,1412	1,7390 to 29,3252
SCORE2ptpCode=3	2,0354	0,6282	10,497	0,0012	7,6554	2,2347 to 26,2253

Excluded: CHOL, HDL, LDL, TG

	Coefficients and Standard Errors for ASCVD					
Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
cAge	0,06947	0,01394	24,844	<0,0001	1,0719	1,0431 to 1,1016
Sex_Code	-1,332	0,3237	16,938	<0,0001	0,2639	0,1400 to 0,4977
SMOKE_Code	1,071	0,1712	39,126	<0,0001	2,9182	2,0863 to 4,0819
Fam_Code	0,6247	0,1718	13,219	0,0003	1,8678	1,3337 to 2,6157
LDL	0,165	0,07513	4,8235	0,0281	1,1794	1,0179 to 1,3665
SCORE2ptpCode=2	1,6346	0,4412	13,728	0,0002	5,1276	2,1596 to 12,1746
SCORE2ptpCode=3	2,3154	0,3892	35,399	<0,0001	10,129	4,7239 to 21,7187

Excluded: BP, CHOL, HDL, TG

Table 6: Cox proportional Hazards model using risk algorithms and posttest risk categories of SCORE2 for MACE and ASCVD

	Coefficients and Standard Errors for MACE					
Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
SCORE2	0,2419	0,03643	44,0731	<0,0001	1,2736	1,1859 to 1,3679
SCORE2ptpCode=2	1,9635	0,7077	7,6969	0,0055	7,1244	1,7795 to 28,5227
SCORE2ptpCode=3	2,2638	0,6269	13,0402	0,0003	9,6193	2,8153 to 32,8671

Excluded variables: PROCAM, PROCAMcvd, SCORE

	Coefficients and Standard Errors for ASCVD					
Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
PROCAMcvd	0,01749	0,01022	2,9293	0,087	1,0176	0,9975 to 1,0382
SCORE2	0,1551	0,03618	18,3714	<0,0001	1,1677	1,0878 to 1,2535
SCORE2ptpCode=2	1,8342	0,438	17,5376	<0,0001	6,2602	2,6532 to 14,7710
SCORE2ptpCode=3	2,5721	0,3835	44,9762	<0,0001	13,0937	6,1744 to 27,7672

Excluded variables: PROCAM, SCORE

Table 7: Sensitivities and Specificities of TPA tertiles to detect MACE and ASCVD, respectively

MACE, TPA tertiles

Criterion	Sensitivity	95% CI	Specificity	95% CI
≥0	100	93,7 - 100,0	0	0,0 - 0,1
>0	98,25	90,6 - 100,0	26,1	24,5 - 27,8
>1	94,74	85,4 - 98,9	50,74	48,9 - 52,6
>2	73,68	60,3 - 84,5	76,12	74,5 - 77,7
>3	0	0,0 - 6,3	100	99,9 - 100,0

ASCVD, TPA Tertiles

Criterion	Sensitivity	95% CI	Specificity	95% CI
≥0	100	97.6 - 100.0	0	0.0 - 0.1
>0	98,7	95.4 - 99.8	27,01	25.3 - 28.7
>1	95,45	90.9 - 98.2	52,42	50.5 - 54.3
>2	81,82	74.8 - 87.6	78,39	76.8 - 79.9
>3	0	0.0 - 2.4	100	99.9 - 100.0

Plaque area in tertiles: 1. tertile (<22 mm^2); 2. tertile (22-61 mm^2); 3. tertile (≥ 62 mm^2)

Figures:

Figure 1: AUC for ASCVD using discrimination predictors from risk algorithms (PROCAM, SCORE), from ultrasound imaging (TPA) and from posttest risk (SCORE2ptp)

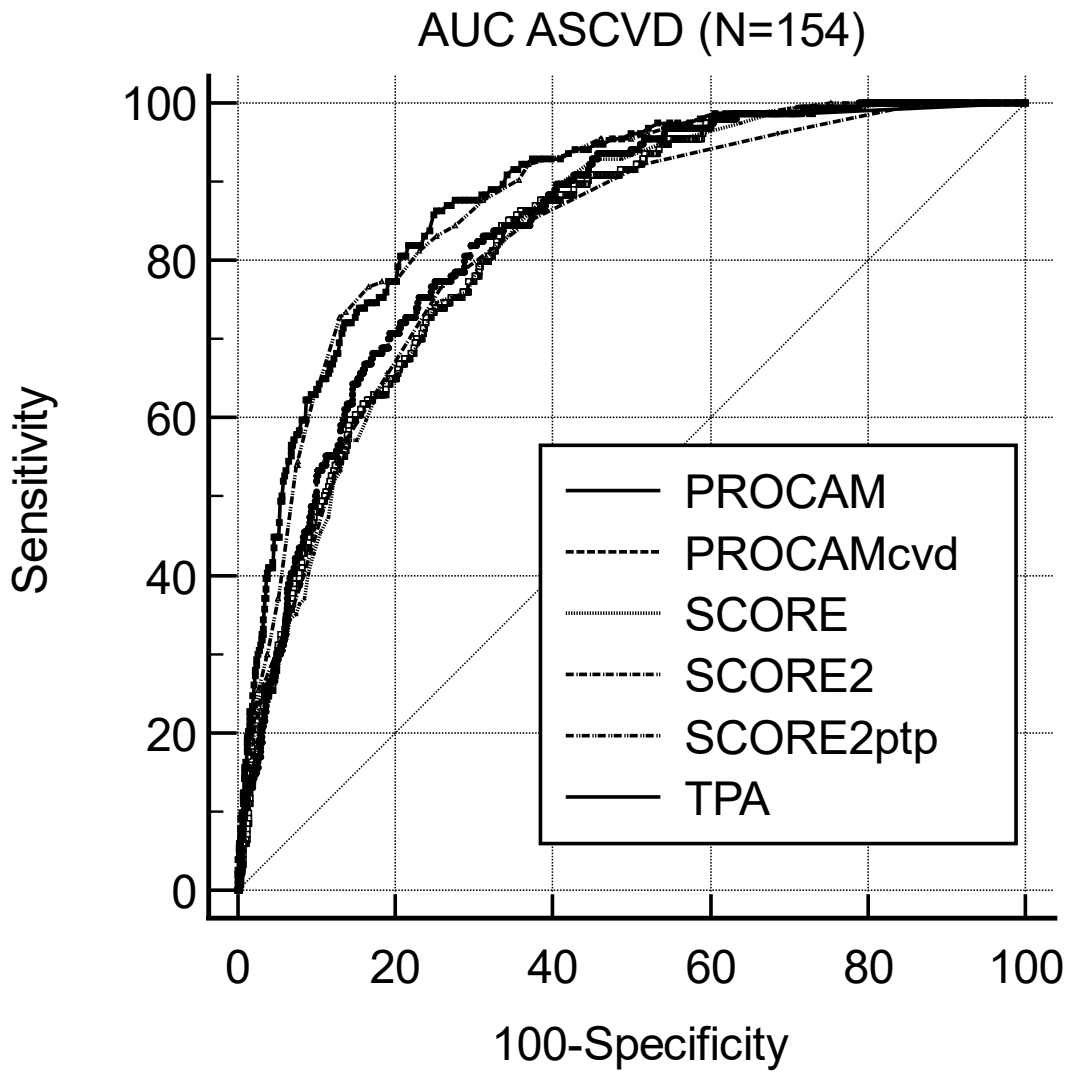

Figure 2: Forest plot of Sensitivity (SENS) and Specificity (SPEC) and 95% confidence intervals of risk tools to detect ASCVD at the high-risk cutoff

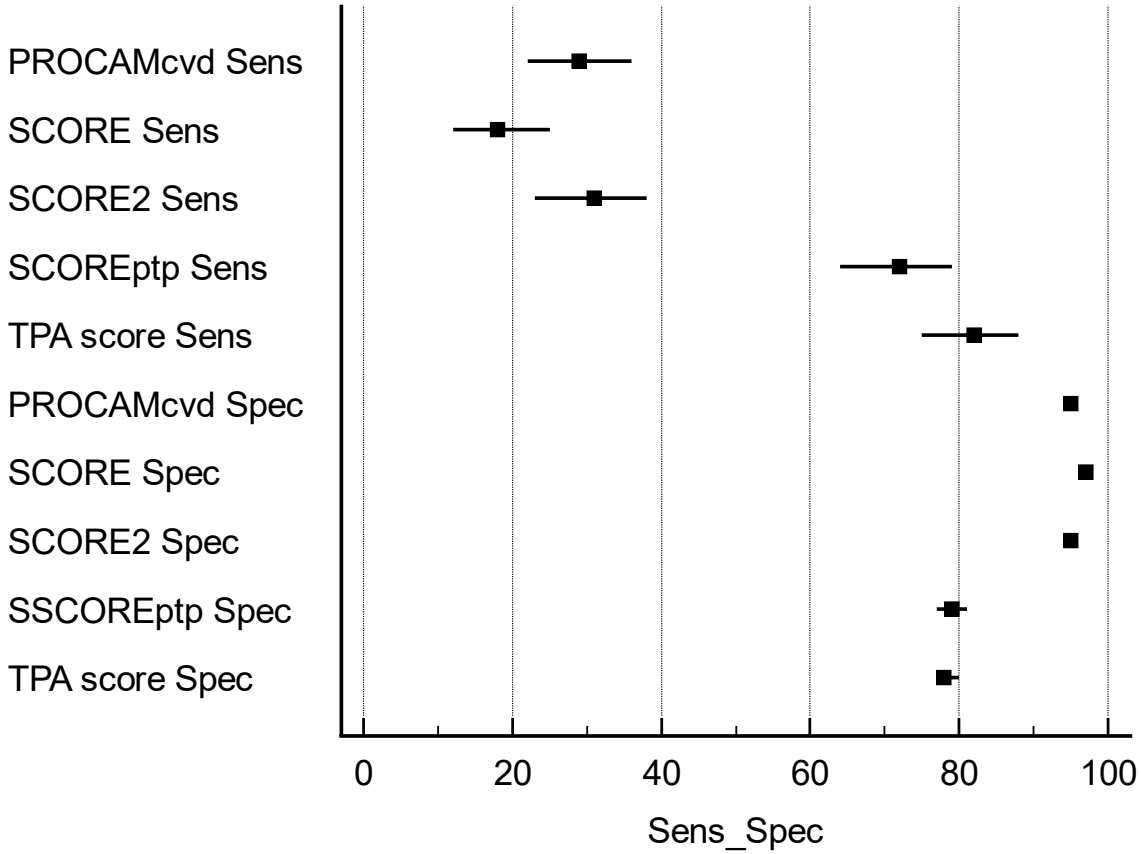

Figure 3: Model fit using the Hosmer & Lemeshow test regarding observed and expected cumulative ASCVD events.

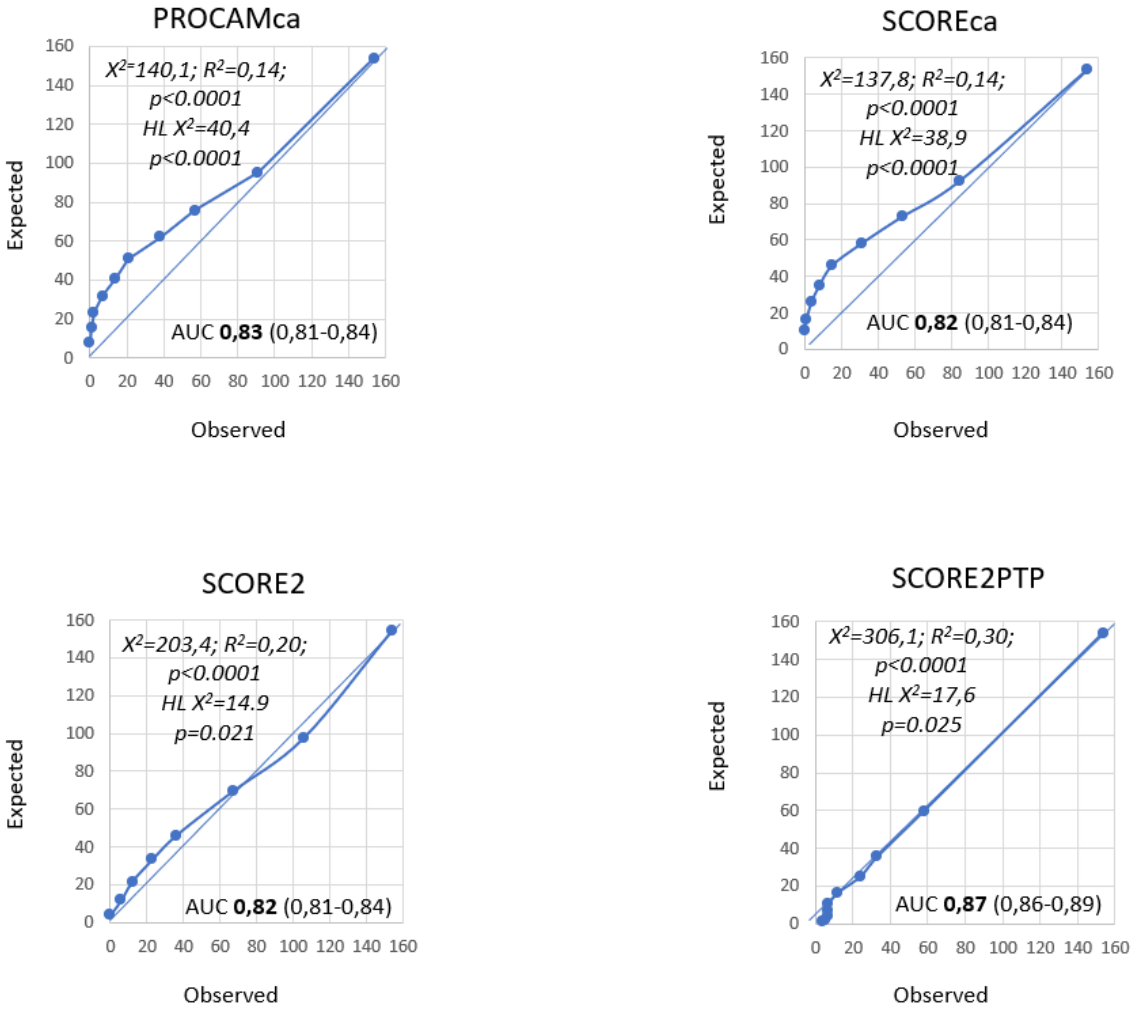

Figure 4: Display of the Cox proportional Hazards with SCORE2ptp as the categorical variable, stratified for clinical variables and risk tools according to tables 5 and 6.

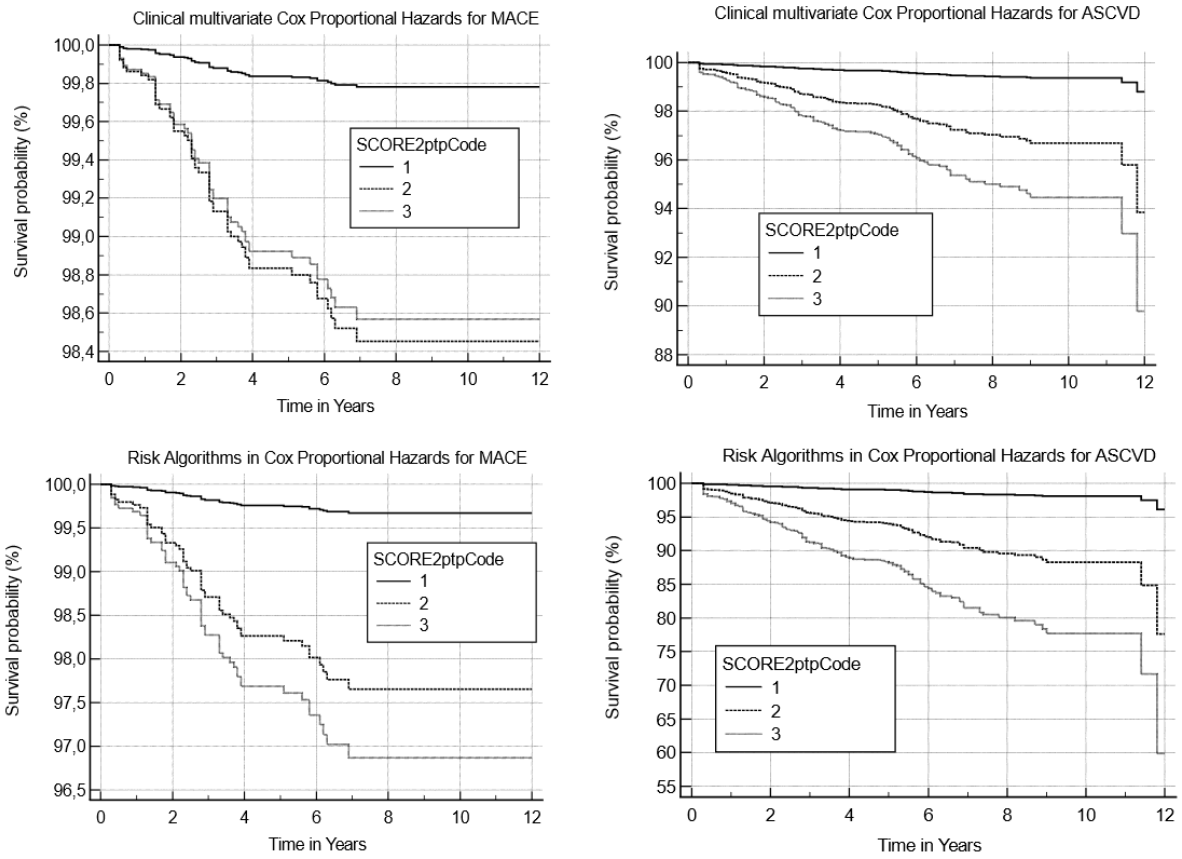

Figure 5: Forest plot of ASCVD Hazard ratios and 95%-CI predicted by clinical variables and posttest risk categories based on TPA and SCORE2 (source: Table 5).