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Prediction of cardiovascular events with traditional risk equations and total plaque area of carotid atherosclerosis
The Arteris Cardiovascular Outcome (ARCO) cohort study

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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 traditional risk calculators in subjects aged 40–65 years.

We compared PROCAM, SCORE and FRAM with carotid ultrasound (total plaque area, TPA) and arterial age (AA) was calculated 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 FRAM 10 ± 6%. Both for the primary outcome (AMI, STROKE/TIA, CABG) and the secondary outcome (adding CAD and PTCA) hazards increased significantly for TPA tertiles and AA groups between 1.4 (0.1–16.1) and 21.4 (2.8–163.6) after adjustment for risk factors (age, smoke, sex, systolic BP, lipids, BMI, medication in Model 1) and after adjustment for results from PROCAM, SCORE and FRAM (Model 2). Model performance was statistically improved regarding model fit in all models using TPA and AA. Net reclassification improvement (NRI) for PROCAM and SCORE using TPA tertiles or AA age groups increased significantly between 30% to 48%.

TPA and AA added prognostic information to conventional risk equations, supporting the assessment of ASCVD risk with carotid ultrasound in subjects aged 40–65 years.

1. Introduction

The European (ESC/EAS) guideline for dyslipidemia suggest to use arterial (carotid and/or femoral) plaque burden with ultrasound as a risk modifier in individuals at low or moderate risk (Mach et al., 2020).

However, any test introduced into medicine is only as valuable as the associated outcome (Romanens et al., 2010). Criteria for screening test quality are: 1. Independent comparison with a gold standard; 2. Large spectrum of pretest probabilities; 3. Ability to change clinical decisions; 4. High reproducibility; 5. Validation in several populations; 6. High accuracy to discriminate individuals with and without disease discrimination.

In this study we compare predictors of ASCVD using carotid atherosclerosis quantified by TPA (and from TPA derived arterial age (Romanens et al., 2014)) with more traditional methods (cardiovascular

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Abbreviations

AA	arterial age
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

risk calculators, namely PROCAM, SCORE, FRAMINGHAM, PCE). We hypothesize, that arterial age and TPA are superior to cardiovascular risk calculators and clinical characteristics of patients in prediction of ASCVD in subjects aged 40–65 years.

2. 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.

2.1. 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 and 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).

2.2. Patient information

Smoking status, family history for premature coronary disease and presence of diabetes mellitus were self-reported.

2.3. 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. 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.

2.4. 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.

2.5. 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.

2.6. 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) (Romanens et al., 2017). All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously reported (Romanens et al., 2014). 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. 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 was present in this population.

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

2.7. 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 (Mach et al., 2020)) and the German PROCAM risk. (Voss et al., 2002) Further, we calculated risk based on FRAMINGHAM cardiovascular disease risk using lipids and body-mass-index (D'Agostino et al., 2008) and also calculated risk based on the POOLED COHORT EQUATION (PCE). (Pylypchuk et al., 2018) 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 (Romanens et al., 2010).

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

	Outcome group								
	Primary		Secondary (all events)		No event		P value Event vs no event	All	
N, %	78	2.7	154	5.4	2688			2842	
Male	72		141		1636			1765	
Female	6	8	13	5.8	1068	40	<0.00001	1081	38
Age + SD	55	6	55	6	50	8	<0.0001	50	8
Arterial age + SD	70	17	71	17	40	21	<0.0001	42	22
Smoker, %	37	47	72	47	537	20	<0.00001	609	21
BP mm Hg, systolic + SD	136	20	133	18	125	15	<0.0001	125.7	15.5
BMI + SD	27	4	27	4	26	4	NS	26	4
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	2.0	1.4	2.0	1.3	1.6	1.1	<0.0001	1.6	1.1
TPA + SD, mm2	131	98	134	85	39	47	<0.0001	42	54
FRAMca + SD, %	22	10	22	11	10	8	<0.001	11.0	8.5
FRAMbmi + SD, %	23	11	22	11	10	8	<0.001	11.1	8.7
SCOREca + SD, %	3.4	2.5	3.2	2.3	1.2	1.5	<0.0001	1.3	1.6
PCEca + SD, %	12	6	12	5	5	5	<0.0001	5.3	5.2
PROCAMca + SD %	12	8	13	9	4	6	<0.0001	**4.8**	6.4
PROCAMpt TPA + SD, %			45	25	8	13	<0.0001		
PROCAMpt AA + SD, %			32	23	7	13	<0.0001		
SCOREpt TPA + SD, %			19.9	14.7	2.8	4.4	<0.0001		
SCOREpt AA + SD, %			17.3	20.2	2.2	4.8	<0.0001		

2.8. Statistics

We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons (Delong et al., 1988). Groups were compared using a *t*-test for continuous variables and CHI^2 for categorical variables. Net reclassification improvements were calculated as described elsewhere (Melander et al., 2009): 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 after adjustment for cardiovascular risk factors in Model 1 (sex, age, smoke, BMI, total cholesterol, HDL, LDL, triglycerides, systolic blood pressure, use of hypertensive and lipid lowering drugs) and after adjustment for risk charts (Model 2) both for the primary and secondary outcome. Further we assessed model performance using model fit (χ^2), discrimination (ROC analysis) and calibration (Hosmer & Lemeshow test). Patients were split according to TPA into those without atherosclerosis (reference group) and tertiles of TPA; as well as being 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:

$$\text{PTP positive} : (PV \times SE)/[PV \times SE + (1\text{–}PV) \times (1\text{–}SP)]$$

$$\text{PTP negative} : [PV \times (1\text{–}SE)]/[PV \times (1\text{–}SE) + SP \times (1\text{–}PV)]$$

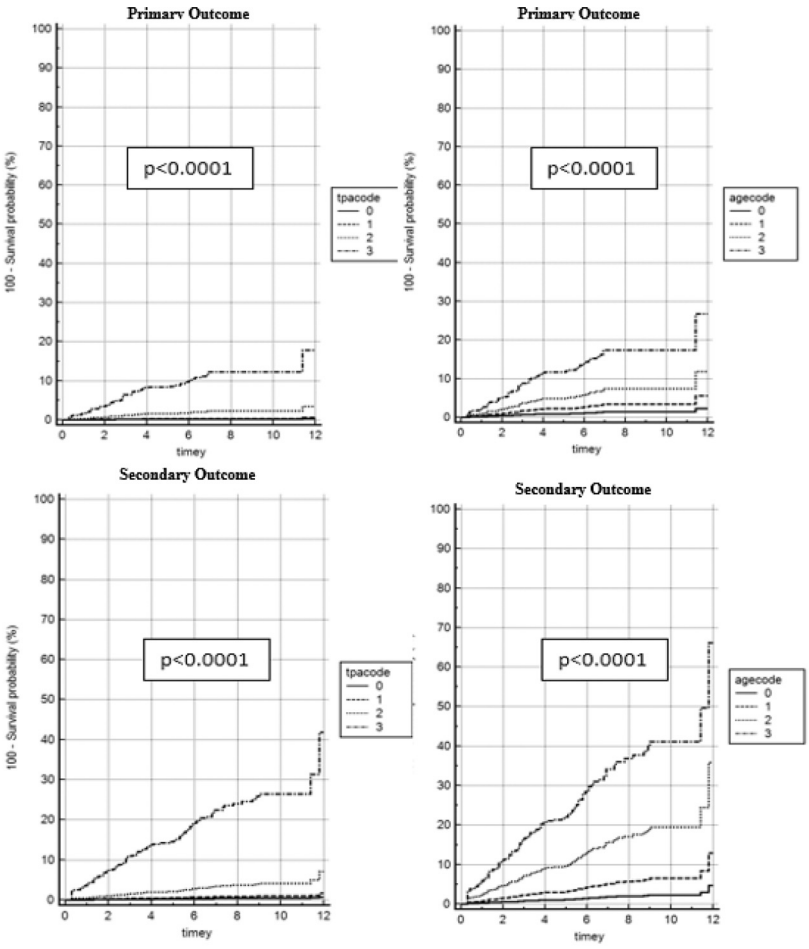
where PTP denotes posttest probability, PV denotes prevalence, SE denotes sensitivity, SP denotes specificity, positive denotes test positivity and negative denotes test negativity. A TPA below the first tertile was considered as a negative test. An arterial age below chronological age was considered as a negative test. The level of statistical significance was set at $p < 0.05$.

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

In the VARIFO cohort, 16 deaths occurred, of which 5 were of unknown 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 was 41 AMI, 16 STROKES, 21 CABG (total 78 events) and number of events in the secondary



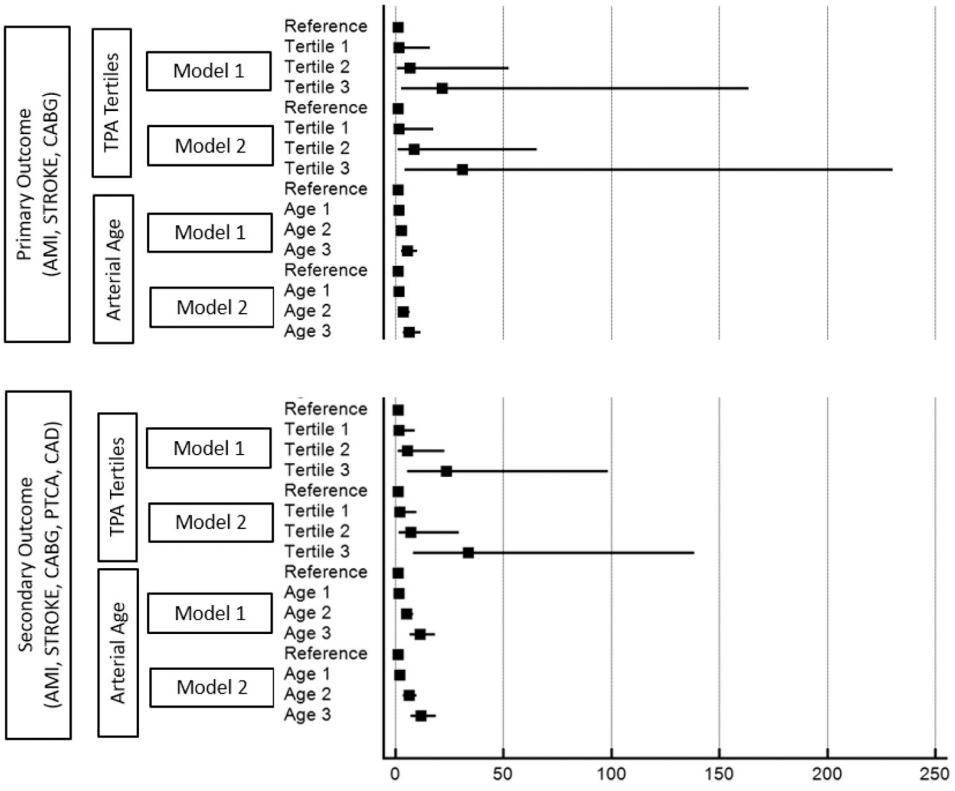
aacode: arterial age code (0=below cAge, 1=1-10 years older than cAge, 2=11-20 years older than Age, 2=>20 years older than cAge). tpacode: Total Plaque Area Code (0=no atherosclerosis, 1=1st tertile, 2=2nd tertile, 3=3rd tertile)

Fig. 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).

Table 2
Hazard ratios (and 95% CI) for primary and secondary outcome associated with TPA tertiles and AA (difference in arterial age), adjusted for traditional cardiovascular risk factors (model 1) and for PROCAMca, SCOREca, and FRAMca (model 2).

Primary outcome					
TPA	No atherosclerosis	Tertile 1	Tertile 2	Tertile 3	P-value (trend)
Model 1	1.0 (ref)	1.4 (0.1–16.1)	6.7 (0.9–52.2)	21.4 (2.8–163.6)	<0.0001
Model 2	1.0 (ref)	1.6 (0.1–17.5)	8.5 (1.1–65.4)	31.1 (4.2–230.3)	<0.0001
Arterial age	Below cAge	1–10 y older	11–20 years older	>20 years older	P-value (trend)
Model 1	1.0 (ref)	1.4 (0.6–3.0)	2.8 (1.4–5.3)	5.4 (2.8–10.3)	<0.0001
Model 2	1.0 (ref)	1.7 (0.8–3.8)	3.4 (1.8–6.5)	6.3 (3.4–11.9)	<0.0001
Secondary outcome					
TPA	No atherosclerosis	Tertile 1	Tertile 2	Tertile 3	P-value (trend)
Model 1	1.0 (ref)	1.7 (0.3–9.1)	5.3 (1.2–22.9)	23.4 (5.5–98.5)	<0.0001
Model 2	1.0 (ref)	1.9 (0.4–10.1)	6.9 (1.6–29.3)	33.7 (8.2–138.6)	<0.0001
Arterial age	Below cAge	1–10 y older	11–20 years older	>20 years older	P-value (trend)
Model 1	1.0 (ref)	1.7 (0.9–3.2)	5.1 (3.1–8.3)	11.2 (6.8–18.5)	<0.0001
Model 2	1.0 (ref)	2.1 (1.1–4.0)	6.1 (3.7–9.8)	11.7 (7.2–18.8)	<0.0001

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



Model 1 includes clinical variables (age, sex, systolic blood pressure, lipids, use of antihypertensive medication, use of lipid lowering medication, BMI) and Model 2 includes PROCAM, SCORE and FRAM. All p-values for trend < 0.0001

Fig. 2. Adjusted hazard ratios (95% CI) for primary and secondary outcome associated with TPA and difference in arterial age (for detailed numbers refer to Table 2). Model 1 includes clinical variables (age, sex, systolic blood pressure, lipids, use of antihypertensive medication, use of lipid lowering medication, BMI) and Model 2 includes PROCAM, SCORE and FRAM. All p-values for trend <0.0001.

outcome was 41 PTCA and 35 CAD (adding another 76 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 clinical baseline characteristics and cardiovascular risks of those with and without a cardiovascular event. All clinical and risk variables showed adverse characteristics for the event groups regarding smoking, sex, systolic blood pressure, lipids, TPA, arterial age and risk estimates. By extrapolation, ASCVD 10-year risk was 9.2%. Use of statins was rare.

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.

Fig. 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 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 2 and Fig. 2 show the HR (and 95% CI) for primary and secondary end points associated with TPA and difference in arterial age. Significant prediction improvements of cardiovascular risk factors (Model 1) and risk charts (Model 2) were realized for both primary and secondary outcomes in the 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.

Table 3 shows models for test performance regarding primary and secondary outcomes, where model fit by χ^2 was significantly improved for TPA and AA beyond risk equations (regarding PROCAM, SCORE, FRAM age and FRAMbmi), discrimation was comparable between TPA/AA and risk equations for the primary outcome, but significantly improved discrimination by about 2% to 5% percent with TPA and AA, whereas calibration was improved, when imaging was added for both the primary and the secondary outcome only for the Framingham risk equation. When the Bayes theorem was used for posttest risk calculations, discrimination improved significantly for the primary and for the secondary outcome using either TPA or AA.

Table 4 shows NRI for TPA and AA categories, which are statistically significant for the primary outcome and the secondary outcome with improvement of 30% to 48%.

The crude distribution of secondary outcome events (N = 154) across risk stratification with TPA and PROCAM was assessed. While the 3rd TPA tertile allocates 82% of events correctly as highest risk, PROCAM classifies 80% of events as low or intermediate risk (SCORE 81%).

Supplemental Table 1 shows sensitivities and specificities of TPA tertiles and arterial age groups for the primary and the secondary

Table 3
Model performance regarding global χ^2, discrimination and calibration.

Primary outcome					
Model	Model fit		Discrimination	Calibration	
	χ2	P-value	C-index (95% CI)	χ2	P-value
PROCAMca	57.885	***	0.834 (0.820–0.847)	39.329	***
PROCAMca + tpa	104.370	***	0.866 (0.853–0.879)	27.362	P = 0.0006
PROCAMca + aa	92.915	***	0.841 (0.827–0.855)	25.348	P = 0.0014
SCOREca	67.500	***	0.819 (0.804–0.833)	22.272	P = 0.0023
SCOREca + tpa	92.460	***	0.859 (0.845–0.871)	38.390	***
SCOREca + aa	78.319	***	0.837 (0.822–0.850)	29.584	P = 0.0003
FRAMca	94.650	***	0.843 (0.829–0.856)	19.971	P = 0.0104
FRAMca + tpa	144.968	***	0.868 (0.855–0.881)	10.453	P = 0.2346
FRAMca + aa	118.602	***	0.852 (0.838–0.865)	19.496	P = 0.0124
FRAMbmi	89.318	***	0.835 (0.821–0.849)	21.380	P = 0.0062
FRAMbmi + tpa	146.228	***	0.869 (0.856–0.881)	9.899	P = 0.1944
FRAMbmi + aa	119.976	***	0.852 (0.839–0.865)	23.109	P = 0.0032

Secondary outcome					
Model	Model fit		Discrimination	Calibration	
	χ2	P-value	C-index (95% CI)	χ2	P-value
PROCAMca	140.114	***	0.831 (0.816–0.844)	53.513	***
PROCAMca + tpa	232.964	***	0.869 (0.856–0.881)	44.818	***
PROCAMca + aa	243.789	***	0.866 (0.853–0.879)	33.928	***
SCOREca	137.836	***	0.824 (0.809–0.838)	38.042	***
SCOREca + tpa	199.707	***	0.866 (0.853–0.879)	61.325	***
SCOREca + aa	210.262	***	0.867 (0.854–0.879)	44.490	***
FRAMca	192.486	***	0.843 (0.829–0.856)	28.825	P = 0.0003
FRAMca + tpa	332.605	***	0.887 (0.874–0.898)	9.316	P = 0.3164
FRAMca + aa	278.368	***	0.872 (0.860–0.884)	21.793	P = 0.0053
FRAMbmi	180.177	***	0.838 (0.824–0.852)	30.921	***
FRAMbmi + tpa	333.224	***	0.887 (0.875–0.899)	8.408	P = 0.2980
FRAMbmi + aa	286.460	***	0.875 (0.862–0.887)	26.985	P = 0.0007

*** $P < 0.0001$.

outcome measure along with their respective 95% confidence intervals and likelihood ratio ranges.

Supplemental Table 2 shows an analysis of sensitivity, specificity and predictive values for PROCAM and SCORE and with the Bayes based addition of TPA and AA information for intermediate and high risk cutoff of risk detection tools further stratifying for the primary and the secondary outcome. By adding results from imaging, there were improvements in sensitivities at maintained specificities and negative likely hood ratios could be improved.

Table 4
Net Reclassification Improvement (NRI) using posttest risk of PROCAM and SCORE based on TPA tertiles and arterial age categories derived sensitivities and specificities for the primary and the secondary outcome.

Model	Reclassification	
	NRI	(95% CI)
Impact of model performance for prediction of primary outcome		
PROCAM	Ref model	
PROCAM + Bayes TPA	0.480	(0.385 to 0.576)**
PROCAM + Bayes AA	0.343	(0.253 to 0.434)**
SCORE	Ref model	
SCORE + Bayes TPA	0.381	(0.288 to 0.473)**
SCORE + Bayes AA	0.308	(0.211 to 0.405)*

	Reclassification	
	NRI	(95% CI)
Impact of model performance for prediction of secondary outcome		
PROCAM	Ref model	
PROCAM + Bayes TPA	0.421	(0.356 to 0.486)**
PROCAM + Bayes AA	0.408	(0.344 to 0.472)**
SCORE	Ref model	
SCORE + Bayes TPA	0.373	(0.307 to 0.439)**
SCORE + Bayes AA	0.459	(0.387 to 0.530)**

* $P < 0.001$.
** $P < 0.0001$.

Prediction was also tested for fatal or non-fatal myocardial infarction only (N = 41). Using ROC analysis, each test (TPA, PROCAM, SCORE) performed equally well, where AUC for PROCAMca was 0.836 (0.822 to 0.850, $p < 0.0001$), for SCOREca was 0.797 (0.781 to 0.811, $p < 0.0001$) and for TPA was 0.802 (0.787 to 0.817, $p < 0.0001$; all p for comparisons of AUC > 0.05). Using Cox proportional-hazards regression with clinical data and risk equations, only sex (Wald 5.5, $p = 0.019$), PCEca (Wald 12.6, $p = 0.0004$) and TPA (Wald 21.9, $p < 0.0001$) were significant predictors, whereas chronological age, systolic blood pressure, lipids, BMI, medication codes, SCOREca, FRAMca, FRAMbmi and PROCAMca were not. Using Kaplan-Meier survival analysis with TPA tertiles, and PROCAMca and SCOREca risk categories (low, intermediate, high risk), prediction was highly statistically significant for all ($p < 0.0001$), however, myocardial infarctions occurred in the high-risk categories for PROCAMca, SCOREca and TPA, in 15%, 27% and 71%, respectively.

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 mmHg), 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).

4. Discussion

We compared carotid atherosclerosis with traditional risk markers as predictors of ASCVD in subjects aged 40–65 yeas. TPA and AA were significantly better predictors of ASCVD when compared to PROCAM and SCORE regarding diagnostic accuracy (AUC), reclassification index (NRI) and event-free survival (COX regression) to detect the primary and secondary endpoints.

We show that TPA/AA can efficiently identify subjects at increased cardiovascular risk: subjects without high-risk findings on imaging (e.g., TPA < 62 mm^2, arterial age < 11 years older than chronological age) had a very low (<2%) cardiovascular risk during the average follow-up time of 5.9 years (Fig. 1, unadjusted hazards). When we compared the correct allocation of secondary endpoint events to risk categories using either TPA or PROCAM or SCORE, most cases within the 3rd TPA tertiles (TPA ≥ 62 mm^2) are detected (82%), while PROCAM classifies 80% and

SCORE classifies 81% of events as low or intermediate risk. Therefore, the cutoff for cardiovascular risk categories may not be appropriate, as previously published (Romanens et al., 2017).

We compared our results with the BioImage (Sillesen et al., 2017) and the Tromso (Johnsen et al., 2007) study. In BioImage, association of 3D Plaque was weaker when adjusted for traditional risk factors. This may be due to the higher average age of studied subjects in BioImage, who were about 15 years older than in our study (the event group had an average age of 54 years, the non-event group of 49 years, Table 1). In the Tromso study, subjects were 10 years older and associations of TPA with cardiovascular risk was significantly weaker in men than in women. In our study, we could assess only a limited number of women (38%) and their event rate was very low when compared to men. Therefore, our results are mainly driven by outcome in men. The apparent difference in TPA performance with the Tromso study may be due to the fact, that in the Tromso study TPA was measured only on the right carotid artery.

Our results are congruent with the CAFES-CAVA study (Belcaro et al., 2001), where 10′000 younger subjects (average age around 51 years, age range 35–65 years) with low cardiovascular risk were followed-up over 10 years and where carotid or femoral plaque detected 86% out of 721 cardiovascular events, replicating a historical Finnish study (Salonen and Salonen, 1991).

We integrated the information from carotid atherosclerosis into cardiovascular risk calculators using the Bayes theorem approach. This led to a significantly improvement of ASCVD prediction. ESC lipid guidelines 2019 recommend carotid plaque imaging, for further risk stratification (Mach et al., 2020). Based on our results, a TPA above the third tertile ($\geq$62 mm^2) is associated with an event rate of near 20% for the primary outcome after 12 years and with an event rate of 20% for the secondary outcome after 6 years (Fig. 1). From a lifetime perspective, the secondary outcome is as important as the primary outcome in younger subjects. TPA is measured within 2–3 min, which allows for cost-efficient risk stratification (Romanens et al., 2019b).

Timely initiation of lipid-therapy has potential to improve risk (Brunner et al., 2019), however, when carotid atherosclerosis is not present and patients are reluctant to life-long statin therapies, “negative risk factors” from imaging such as carotid sonography allow to delay preventive therapies (Mortensen et al., 2019).

Similar to other studies (Baber et al., 2014; Belcaro et al., 2001) we were able to assess only a limited number of follow-up (82%), which excludes derivation of *absolute* risk; however, limited number of follow-up 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 (Johnsen et al., 2007; Romanens et al., 2019a). 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 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.

5. Conclusions

Comparing predictive value of carotid atherosclerosis imaging to traditional risk calculators in healthy subjects aged 40–65 years, we found NRI improvement of between 30% - 48%. This clinical prognostic improvement supports the assessment of ASCVD risk with carotid ultrasound.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2021.106525.

References

Baber, U., Mehran, R., Sartori, S., Schoos, M., Falk, E., Sillesen, H., Muntendam, P., Garcia, M., Gregson, J., Pocock, S., Fuster, V., 2014. Detection and impact of subclinical coronary and carotid atherosclerosis on cardiovascular risk prediction and reclassification in asymptomatic us adults: insights from the high risk plaque bioimage study. J. Am. Coll. Cardiol. 63, A998.

Belcaro, G., Nicolaides, A.N., Ramaswami, G., Cesarone, M.R., De Sanctis, M., Incandela, L., Ferrari, P., Geroulakos, G., Barsotti, A., Griffin, M., Dhanjil, S., Sabetai, M., Bucci, M., Martines, G., 2001. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study). Atherosclerosis 156, 379–387. https://doi.org/10.1016/S0021-9150(00)00665-1.

Brunner, F.J., Waldeyer, C., Ojeda, F., Salomaa, V., Kee, F., Sans, S., Thorand, B., Giampaoli, S., Brambilla, P., Tunstall-Pedoe, H., Moitry, M., Iacoviello, L., Veronesi, G., Grassi, G., Mathiesen, E.B., Söderberg, S., Linneberg, A., Brenner, H., Amouyel, P., Ferrières, J., Tamosiunas, A., Nikitin, Y.P., Drygas, W., Melander, O., Jöckel, K.-H., Leistner, D.M., Shaw, J.E., Panagiotakos, D.B., Simons, L.A., Kavousi, M., Vasan, R.S., Dullaart, R.P.F., Wannamethee, S.G., Risérus, U., Shea, S., De Lemos, J.A., Omland, T., Kuulasmaa, K., Landmesser, U., Blankenberg, S., 2019. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium. Lancet. https://doi.org/10.1016/S0140-6736(19)32519-X.

D'Agostino, R.B., Vasan, R.S., Pencina, M.J., Wolf, P.A., Cobain, M., Massaro, J.M., Kannel, W.B., Agostino, R.B.D., 2008. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117, 743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579.

Delong, E., Delong, D., Clarke-Pearson, D., 1988. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44, 837–845.

Johnsen, S.H., Mathiesen, E.B., Joakimsen, O., Stensland, E., Wilsgaard, T., Løchen, M.-L. L., Njølstad, I., Arnesen, E., 2007. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. Stroke 38, 2873–2880.

Mach, F., Baigent, C., Catapano, A.L., Koskinas, K.C., Casula, M., Badimon, L., Chapman, M.J., De Backer, G.G., Delgado, V., Ference, B.A., Graham, I.M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T.R., Riccardi, G., Richter, D. J., Sabatine, M.S., Taskinen, M.-R., Tokgozoglu, L., Wiklund, O., Mueller, C., Drexel, H., Aboyans, V., Corsini, A., Doehner, W., Farnier, M., Gigante, B., Kayikcioglu, M., Krstacic, G., Lambrinou, E., Lewis, B.S., Masip, J., Moulin, P., Petersen, S., Petronio, A.S., Piepoli, M.F., Pintó, X., Räber, L., Ray, K.K., Reiner, Ž., Riesen, W.F., Roffi, M., Schmid, J.-P., Shlyakhto, E., Simpson, I.A., Stroes, E., Sudano, I., Tselepis, A.D., Viigimaa, M., Vindis, C., Vonbank, A., Vrablik, M., Vrsalovic, M., Zamorano, J.L., Collet, J.-P., Koskinas, K.C., Casula, M., Badimon, L., John Chapman, M., De Backer, G.G., Delgado, V., Ference, B.A., Graham, I.M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T.R., Riccardi, G., Richter, D. J., Sabatine, M.S., Taskinen, M.-R., Tokgozoglu, L., Wiklund, O., Windecker, S., Aboyans, V., Baigent, C., Collet, J.-P., Dean, V., Delgado, V., Fitzsimons, D., Gale, C. P., Grobbee, D., Halvorsen, S., Hindricks, G., Iung, B., Jüni, P., Katus, H.A., Landmesser, U., Leclercq, C., Lettino, M., Lewis, B.S., Merkely, B., Mueller, C., Petersen, S., Petronio, A.S., Richter, D.J., Roffi, M., Shlyakhto, E., Simpson, I.A., Sousa-Uva, M., Touyz, R.M., Nibouche, D., Zelveian, P.H., Siostrzonek, P., Najafov, R., van de Borne, P., Pojskic, B., Postadzhiyan, A., Kypris, L., Špinar, J., Larsen, M.L., Eldin, H.S., Viigimaa, M., Strandberg, T.E., Ferrières, J., Agladze, R., Laufs, U., Rallidis, L., Bajnok, L., Gudjónsson, T., Maher, V., Henkin, Y., Gulizia, M. M., Mussagaliyeva, A., Bajraktari, G., Kerimkulova, A., Latkovskis, G., Hamoui, O., Slapikas, R., Visser, L., Dingli, P., Ivanov, V., Boskovic, A., Nazzi, M., Visseren, F., Mitevska, I., Retterstøl, K., Jankowski, P., Fontes-Carvalho, R., Gaita, D., Ezhov, M., Foscoli, M., Giga, V., Pella, D., Fras, Z., de Isla, L.P., Hagström, E., Lehmann, R., Abid, L., Ozdogan, O., Mitchenko, O., Patel, R.S., 2020. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur. Heart J. 41, 111–188. https://doi.org/10.1093/eurheartj/ehz455.

Melander, O., Newton-Cheh, C., Almgren, P., Hedblad, B., Berglund, G., Engström, G., Persson, M., Smith, J.G., Magnusson, M., Christensson, A., Struck, J., Morgenthaler, N.G., Bergmann, A., Pencina, M.J., Wang, T.J., 2009. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA 302, 49–57. https://doi.org/10.1001/jama.2009.943.

Mortensen, M.B., Fuster, V., Muntendam, P., Mehran, R., Baber, U., Sartori, S., Falk, E., 2019. Negative risk markers for cardiovascular events in the elderly. JACC 74. https://doi.org/10.1016/j.jacc.2019.04.049.

Pylypchuk, R., Wells, S., Kerr, A., Poppe, K., Riddell, T., Harwood, M., Exeter, D., Mehta, S., Grey, C., Wu, B.P., Metcalf, P., Warren, J., Harrison, J., Marshall, R., Jackson, R., 2018. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet 391, 1897–1907.

Romanens, M., Ackermann, F., Spence, J.D., Darioli, R., Rodondi, N., Corti, R., Noll, G., Schwenkglenks, M., Pencina, M., 2010. Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics. Eur. J. Cardiovasc. Prev. Rehab. 17, 18–23.

Romanens, M., Ackermann, F., Sudano, I., Szucs, T., Spence, J.D., 2014. Arterial age as a substitute for chronological age in the AGLA risk function could improve coronary risk prediction. Swiss Med. Wkly. 144, w13967.

Romanens, M., Mortensen, M.B., Sudano, I., Szucs, T., Adams, A., 2017. Extensive carotid atherosclerosis and the diagnostic accuracy of coronary risk calculators. Prev. Med. Rep. 6, 182–186.

Romanens, M., Sudano, I., Adams, A., Schober, E.A., 2019a. Sonographic assessment of carotid atherosclerosis: preferred risk indicator for future cardiovascular events? Swiss Med. Wkly. 149, w20142.

Romanens, M., Sudano, I., Adams, A., Warmuth, W., 2019b. Advanced carotid atherosclerosis in middle-aged subjects: comparison with PROCAM and SCORE risk categories, the potential for reclassification and cost-efficiency of carotid ultrasound in the setting of primary care. Swiss Med. Wkly. 149.

Salonen, J.T., Salonen, R., 1991. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler. Thromb. 11, 1245–1249.

Sillesen, H., Sartori, S., Sandholt, B., Baber, U., Mehran, R., Fuster, V., 2017. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. Eur. Heart J. Cardiovasc. Imaging 1–9. https://doi.org/10.1093/ehjci/jex239.

Voss, R., Cullen, P., Schulte, H., Assmann, G., 2002. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM) using neural networks. Int. J. Epidemiol. 31, 1253–1264.