Diagnostic and therapeutic differences in cardiovascular risk assessment using SCORE2/-OP, carotid plaques and coronary calcifications

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Abstract

Background

There is evidence, but no comparative data in Switzerland, that carotid atherosclerosis is more common than coronary calcium.

Methods and Results

Age and sex specific prevalence of carotid total plaque area (cTPA) and coronary calcium Agatston scores (CAC) were measured in 907 patients and cardiovascular risk (SCORE2/-OP and posttest risk based on imaging) was calculated in a subset of 608 of 907 patients.

In 907 patients (age 59.9 ± 9.4, 34% female), the prevalence of atherosclerosis (cTPA>21mm^2; CAC>10) increased with age. cTPA>21mm^2 / CAC=0 versus cTPA=0 / CAC>10 was 23.4% versus 2.5% in women (p<0.0001) and was 17.2% versus 2.9% in men (p<0.0001), and the difference in prevalence was statistically higher in women (p=0.02).

In 608 patients with SCORE2/-OP data, the indication for LDL lowering was understimated in women through all age classes (p<0.05). Risk mismatch based upon SCORE2/-OP and imaging modalities was found in 57 (9.4%) with high carotid derived risk associated with smoking (Odds ratio 2.0 [p=0.01, 95%CI 1.1-3.5] and HDL, p=0.02, Odds ratio 0.4 [95%CI 0.2-0.8]), and was found in 50 (8.2%) with high CAC derived risk, associated with SCORE2 risk (p=0.02, Odds ratio 1.8 [95%CI 1.1-3.0].

Conclusion

In cardiology patients, carotid atherosclerosis is more common than coronary calcium. Indication for LDL lowering is often missed with SCORE2/-OP or CAC in women, and to a lesser extent, in men, as compared to cTPA. The atherosclerosis risk mismatch is 0% in patients with a SCORE2/-OP risk < 2.5% and gradually increases by small amounts in higher risk groups. Our data support the use of cTPA as the first imaging test, especially in women.

Introduction

Prevention of cardiovascular events is accomplished by primary care physicians using cardiovascular risk stratification with the Swiss AGLA guidelines, which are essentially based on the SCORE2/-OP risk calculator [1]. However, it has been shown that numerically most cardiovascular events occur in the low or intermediate risk range [2]. Accordingly, European guidelines recommend additional tests, such as calcium score or, if not available, carotid ultrasound, when the situation is unclear [3]. Recent studies have shown that carotid atherosclerosis is as good as, if not better than, calcium score [4]. The noninvasive and radiation-free test makes it especially suitable for longitudinal monitoring and preventive interventions. Direct imaging of carotid atherosclerosis - particularly quantifying carotid total plaque area - provides an accurate, reproducible, and clinically meaningful measure of vascular disease burden. Its use is increasingly acknowledged in cardiovascular risk assessment and disease monitoring. For further risk stratification, the accuracy of direct imaging of atherosclerosis has been demonstrated [5].

In this study, we compare atherosclerosis imaging using cTPA- and coronary calcium testing with the following two questions 1. Is carotid atherosclerosis more common than coronary calcium, especially in women? 2. What are the therapeutic implications of LDL-lowering therapies?

Methods

We reviewed 21,224 patient records of a total of 9,747 individuals who visited the Kardiolab, an independent cardiology practice with additional affiliation to the Rodiag Radiology Center, both located in Olten, Switzerland, between 2003 and 2024. Individuals with a cTPA and a calcium score measured within 3 months were identified.

Carotid plaque measurements

As described elsewhere [6], the presence of carotid plaque defined as IMT thickening of at least 1 mm, was imaged longitudinally, the plaque surface was traced on the screen, and the total plaque area (cTPA) was calculated from all plaques in both carotid arteries imaged from the clavicle to the jaw (common, internal, external, and bulb). The reproducibility of cTPA has been published elsewhere [7].

Coronary Calcium Measurements

We used the Agatston method to quantify coronary calcifications based on plaque area and plaque density. Between 2003 and 2006, coronary calcifications were visualized for further processing by using a single-breath hold, multislice (Aquilion, Toshiba, Japan) ECG-gated, non-contrast enhanced, low-radiation scan sequence and image data were processed by using the NetraMD software (ScImage Palo Alto, California, USA), which provides reproducible data on total Agatston calcium scores, percentile of Agatston scores, and plaque volumes for all coronary arteries and total plaque volume. The cut-off point to define that a plaque as calcified was set at 130 Hounsfield units. From 2018 to 2024 we used a vendor-specific quantification tool provided by General Electric.

SCORE2/-OP risk and posttest risk calculation (subgroup analysis)

In 607 patients our database allowed for the calculation of SCORE2/-OP [1]. We used the BAYES formula to calculate posterior probabilities [8]. For accurate comparisons between cTPA and CAC posterior risk prediction, three conditions must be met: 1. Test sensitivity and specificity at predefined result cutoffs from cohort studies must be available; 2. Result cutoffs for different tests must be associated with comparable risk; 3. The outcome endpoints should be the same. We used cTPA results <22 mm^2, 22-62 mm^2, and >62 mm^2 from our ARCO outcome study for the occurrence of MACE (fatal or non-fatal myocardial infarction or stroke). Based on our literature review, CAC is often reported for the outcome of coronary heart disease (CHD) or death, but not for MACE. An important exception was presented by the MESA investigators [9]. In this study, event rates for CAC and CHD or MACE were reported separately and for CAC levels of 0, 1-99 and ≥100. Comparing the cTPA cutoffs with the CAC cutoffs, we found similar event rates and were able to extract the sensitivities, specificities, and AUC results from these data (Appendix Table 1).

We then calculated the risk-based indication for LDL lowering as follows:

1. Calculation of post-test risk of SCORE2/-OP using the sensitivities for MACE of cTPA and CAC.
2. Grouping patients into low to intermediate (group 1), high (group 2), very high (group 3) according to SCORE2/-OP posttest risk (SCORE2PTPcode 1, 2, 3) using the SCORE2/-OP risk category criteria.
3. Grouping patients into sex groups
4. Indication for LDL lowering, if SCORE2TPTPcode 1: LDL > 5.0 mmol/l, code 2: LDL > 1.8 mmol/l, code 3: LDL > 1.4 mmol/l.
5. Repeated algorithm for SCORE2/-OP without post-test risk calculations.

We then compare the number of sex-specific individuals with an indication for intensified / more intensive lipid lowering based on cTPA posttest risk and CAC posttest risk.

To validate the prognostic significance of this risk-based LDL-lowering indication, we used our previous outcome study [2] and applied these calculations (Appendix Table 2): the indication for LDL-lowering treatments was reduced by 7% from 56% for SCORE2/-OP versus 49% for SCORE2TPA and with SCORE2/-OP 88% with ASCVD events would have been treated, but with SCORE2TPA 95% with ASCVD events would have been treated with LDL-lowering drugs. Accordingly, the Cox hazard regression was 2.9 for SCORE2/-OP and was 13.6 for SCORE2TPA ($p<0.0001$).

Statistical analysis

Statistical analysis was performed using MedCalc (MedCalc® Statistical Software version 23.0.2 MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024), and data were entered into an Excel spreadsheet. The Mann-Whitney test for independent samples or CHI^2 analysis, as appropriate, was used to compare between groups with non-normally distributed data. The effect of explanatory independent variables was assessed by regression analysis (logistic regression, multiple regression, and probit regression).

The Bayes theorem [8] calculates the posttest risk probability (PTP) using pretest probability = SCORE2-/OP (equal to prevalence PV) in case the imaging test is positive (PTP pos: e.g. Agatston Score >0, carotid Total Plaque Area > 21 mm2), otherwise PTP neg formula is used and from the four-field table, sensitivity (SE) and specificity (SP) of a test can be derived as follows: PTP pos: (PV x SE)/[PV x SE + (1 – PV) x (1 – SP)] and PTP neg: [PV x (1 – SE)]/[PV x (1 – SE) + SP x (1 – PV)]. Statistical significance was set at <0.05.

Results

Baseline clinical variables are described in Table 1: There were 907 patients, 35% female, mean age 60 ± 9 years, 16% with a history of atherosclerotic cardiovascular disease (ASCVD). In patients with available SCORE2/-OP data (N=608, no missing values), the baseline characteristics did not differ significantly. While 35% of patients had no CAC, only 9% had zero cTPA, and only 6% of patients had neither CAC nor cTPA. Diabetes mellitus was present in 12% of patients and 28% were active smokers.

Results from the whole group (N=907):

In Table 2, detectable cTPA>21mm^2 or CAC>10 was compared between age groups and the prevalence and results from the 4-field table, using CAC as the golden standard. The sensitivity of cTPA for CAC increased with age from 13% to 80%, while the specificity remained low between 15% and 56% across all age groups. The percentage of false negatives, e.g. cTPA<22mm^2 in patients with CAC>10, was similar in all age groups and ranged from 8% to 13%. The difference in the prevalence of cTPA>21mm^2 minus CAC>10 was greatest in the younger age groups (30-45 and 50-55 years, 23% and 26%, respectively).

In Table 3, higher risk cTPA>61 mm^2 or CAC≥100 was compared between age groups and the prevalence and results from the 4-field table using CAC as the golden standard. The sensitivity of cTPA for CAC increased from 0% to 71% with increasing age, while the specificity decreased from 92% to 61% with decreasing age. The percentage of false negatives, e.g. cTPA<62 mm^2 in patients with CAC>100, was similar in all age groups and ranged from 8% to 17%. The difference in the prevalence of cTPA≥62 mm^2 minus CAC≥100 was <11% for all age groups.

Regarding sex differences (Table 4), we compared the frequency of the presence of cTPA>21 mm^2 or >61 mm^2 with the frequency of CAC≥10 or CAC≥100 with no plaque for both imaging tests. While 75 women (23%) had cTPA>21 mm^2 with CAC=0, cTPA=0 mm^2 with CAC≥10 was detected in only 8 (3%) women (p<0.0001), comparable to men (p<0.0001), but more frequently in women (23.4% vs. 17.2%, p=0.02). When comparing higher risk plaques (TPA62 mm^2 + CAC=0 or CAC100 + TPA=0 mm^2), similar distributions were found with 7.2% versus 0.6% in women and 5.6% versus 1.0% in men (both p<0.0001), and for the gender difference p was 0.35.

Using logistic regression analysis for the dependent variables cTPA62 and CAC100, significant predictors were identified in 907 patients in univariate analysis (Table 5), namely age, male sex, diabetes mellitus, nicotine, systolic blood pressure and imaging parameters, but not family history of premature ASCVD.

Results from the SCORE2/-OP subgroup (N=608):

The baseline characteristics of the SCORE2/-OP subgroup are described in Table 1 and were not statistically different from the overall group. The distribution among the SCORE2/-OP risk categories and the indication for LDL-lowering treatments are shown in Table 6 and Figure 1. Both imaging modalities shifted patients from high to very high risk, e.g. the probability of SCORE2/-OP was 50% for high risk and 12% for very high risk patients, whereas for SCORE2TPA the posttest probability was high in only 20% but very high in 50% of patients (for SCORE2CAC the posttest probabilities were 17% and 45%, respectively). The difference in frequency and LDL treatment is mainly driven by about 50 patients in the SCORE2/-OP LOW-INTERM segment who were moved into a higher risk category by SCORE2TPA, whereas SCORE2CAC would only see an indication for LDL treatment in 11 additional patients compared to SCORE2/-OP. However, there were significant differences in the number of patients treated to targets (LDL < 1.8 mmol/l in high risk, LDL < 1.4 mmol/l in very high risk patients): with SCORE2/-OP, the number of patients with a treatment target of < 1.8 mmol/l was 274 out of 305 patients and patients with a treatment target of < 1.4 mmol/l was 69 out of 74 patients, while the number of patients with a treatment target of < 1.8 mmol/l was 279 out of 302 patients with SCORE2TPA and 257 out of 276 patients with SCORE2CAC.

Using linear logistic regression for the detection of TPA62 or CAC100, no significant odds ratios emerged for CAC100 and 2 variables with borderline results emerged for patients in secondary prevention and lower blood pressure regarding the prediction of TPA62 (Table 7). Using ROC analysis, none of the variables showed a significant AUC (data not shown).

Regarding sex differences in LDL treatment indication according to the risk stratification algorithm (SCORE2/-OP versus SCORE2TPA versus SCORE2CAC) by age group (Table 8): In 209 women, the percentage with an LDL-lowering indication was highest with SCORE2TPA, while the numbers were comparable in men. We calculated Chi^2 by age group and sex to test for significant differences, which were set at $p<0.05$ for a Chi^2 value >3.86 (Table 9, Figure 2): In women, SCORE2TPA added significantly more indications for LDL therapy across all combined age classes compared with SCORE2/-OP, while SCORE2CAC did not. In men, there were also significantly more indications for LDL-lowering therapy with SCORE2TPA up to age 35-60 years.

Of the 608 patients, 57 (9.4%) and 50 (8.2%) had very discrepant posttest risk differences, defined as low to intermediate posttest imaging risk versus very high posttest imaging risk (Tables 10a and 10b for posttest risk discrepancy). When stratified by SCORE2/OP risk (Table 10b), there were no mismatch cases in patients with risk < 2.5%, 1.2% mismatch cases with risk < 5.0, and 5.9% and 4.9% mismatch cases with risk < 7.5%. The difference for risk mismatch was not statistically significant, but was highest in the high-risk SCORE2/-OP group for cTPA (16.4%) versus CAC (11.8%, Table 10a). In those with risk mismatch, logistic regression identified current smoking, lower HDL, and higher TG as explanatory variables for cTPA and higher SCORE2/-OP risk for CAC (Table 11, Figure 3).

Discussion

The key findings of this observational study are a higher prevalence of carotid atherosclerosis than CAC and an underestimation of LDL lowering indication in women, when using SCORE2/-OP or CAC.

Prevalence of cTPA and CAC stratified by age group and sex

Absence of carotid plaque (cTPA=0 mm^2) was present in 9% of 907 patients aged 59.9 ± 9.4 years, and absence of coronary calcifications (CAC=0) was present in 35% of these patients (Table 1). The prevalence of cTPA21 was higher than CAC10 across all age groups and was highest in the 30-45 year age group (23% higher) (Table 2). The prevalence difference for higher risk atherosclerosis (cTPA62, CAC 100) was small across age groups, ranging between 10% (cTPA 30%, CAC 20%) in patients aged 46-50 years, while the prevalence was similar in all other age groups (Table 3).
In women, cTPA21 and CAC0 was found in 23% of women and in 17% of men (p=0.02), while the opposite, e.g. cTPA0 and CAC10, was found in only 2.5% of women and 2.9% of men (p=NS); similarly, cTPA61 and CAC0 was found in 7% of women and 6% of men (p=NS), while the opposite, e.g. cTPA0 and CAC100, was found in only 0.6% of women and 1% of men (Table 4). Therefore, CAC substantially underestimated intermediate and high-risk carotid plaque in more patients than cTPA underestimated intermediate-to-higher-risk CAC.

Associations of variables with cTPA and CAC

Patient variables were predictive for cTPA62 and CAC100 in logistic regression, namely age, sex, diabetes mellitus, nicotine, blood pressure, family history of ASCVD, cTPA or CAC, respectively, with the expectation of nicotine not being predictive for CAC100.

Earlier appearance of carotid plaque, current evidence

Similar to our study, Gudmundsson stratified female and male subjects according to CAC and cTPA levels. In the absence of CAC, the presence of any carotid plaque was found in 36% of women and 19% of men (Chi2 = 5.01, p= 0.024 for the sex difference), whereas the absence of carotid plaque with the presence of CAC>0 was found in 5.5% of women and 4.6% of men (p NS for the sex difference). A significant amount of CAC (e.g., CAC ≥100) without carotid plaque was present in 1.4% of women and 1.6% of men [4], and the results using area under the curve (AUC) and net reclassification improvement for events were comparable for cTPA and CAC in 3 models adjusting for covariates.
In the PESA study, in which 4,066 patients were examined for the presence of carotid plaque and coronary calcium, stratified by sex and with a mean age of 45.8±4.3 years, the presence of carotid plaque was found in 36% of men (24% of women), but CAC was found in only 25% of men and 5% of

women [10]. In patients with familial hypercholesterolemia, authors calculated the average age for the appearance of carotid plaque, coronary plaques and coronary calcifications, respectively, and found ages 17, 26, and 31 years for male and 30, 36, and 40 years for female patients [11]. Therefore, in familial hypercholesterolemia, coronary calcifications appeared 14 years later in men and 10 years later in women than carotid plaques. Carotid plaque are also associated with a higher incidence of developing coronary calcium in the future [12].

We and others clearly show, that CAC is less prevalent than carotid atherosclerosis and our study adds more information regarding sex and age classes, where the difference in prevalence with underdiagnosed significant atherosclerosis by CAC is higher at younger ages and in women.

Risk estimates and LDL targets using SCORE2/-OP, SCORE2TPA and SCORE2CAC

Imaging shifted patients from a high to a very high risk category, and the indication to lower LDL treatment targets from 1.8 mmol/l to 1.4 mmol/l occurred in 69 of 74 patients with SCORE2/-OP, but in 279 of 302 patients with SCORE2TPA and in 257 of 276 patients with SCORE2CAC (Table 6). The mean SCORE2/-OP risk was 6.6±4.2% and 11.9%±10.4% for SCORE2TPA ($p<0.0001$) and 11.0%±10.0% for SCORE2CAC ($p<0.0001$), showing a consistent near doubling of risk with both imaging modalities. Therefore, the value of imaging was to better identify very high risk patients who need maximum preventive therapies.

Explaining Clinical variables for TPA62 and CAC100

Patients at increased risk due to relevant atherosclerosis defined by TPA62 and CAC100 were not identified by traditional risk factors or SCORE2/-OP using logistic regression analysis (Table 7). Only patients in secondary prevention had an odds ratio of 1.6 (95%CI: 1.1-2.4) for TPA62 ($p=0.0179$).

Sex differences for more intensive LDL treatment indications by age group using SCORE2TPA and SCORE2CAC compared to SCORE2/-OP

Using cumulative frequencies for 5-year aggregated age groups in women, the Chi^2 analysis for differences showed highly significant results for the age group 35-80 years with SCORE2TPA but not with SCORE2CAC compared to SCORE2/-OP. In men, the same situation was found for the age group 35-60 years (all $p<0.05$). Therefore, SCORE2/-OP underestimates the need for aggressive LDL lowering especially in women (Table 9, Figure 2).

Risk discrepancy between imaging modalities

If one test (SCORE2TPA) shows a very high risk and the other test (SCORE2CAC) shows a low to intermediate risk ("HL") and vice versa ("LH"), the therapeutic measures may differ significantly. It is therefore important to know how often such discrepancies in risk estimates occur. We identified 57 HL and 50 LH patients out of 608 patients, which is less than 10%. Regression analysis for HL was significant for smokers, low HDL and high triglycerides, while LH was significant for SCORE2/-OP. When SCORE2/-OP exceeds 7.5%, about 5% of patients show this type of discrepancy (Figure 3). Therefore, severe underestimation of risk by either imaging test was not a common finding, but the risk of missing very high SCORE2CAC risk with SCORE2TPA increases in very high risk categories defined by SCORE2/-OP.

The earlier the better

In accordance with the prevailing paradigm that advocates for the initiation of preventive treatments at the earliest possible opportunity [13], the presence of carotid plaque in the absence of coronary calcium (CAC) provides a valuable opportunity to initiate treatment earlier. With respect to cardiovascular outcomes, the long-term Hazard Ratio (HR) for patients with carotid plaque but no CAC is 1.66 (95% CI: 1.04–2.66), as determined by a model that adjusts for age, sex, and cardiovascular risk factors. Following an average observation period of 16 years, those with carotid plaque exhibited a higher incidence of developing coronary calcium during follow-up visits. [14]. In the long-term follow-up of the Nixforf recall study, women exhibited a 21% incidence of cardiovascular events among those with a baseline CAC=0 (men: 9%) [15].

Carotid plaques allow to find LDL treatment indications earlier than CAC

The present findings support the hypothesis that carotid atherosclerosis and, consequently, cardiovascular risk amenable to intensified preventive therapy are frequently overlooked in patients, especially women of all ages, when a CAC is still zero. Since CAC is the result of a healing process [16], many patients with CAC=0 but carotid atherosclerosis are likely to have non-calcified coronary atherosclerosis. Consequently, reliance on CAC0 to guide preventive therapy is misleading especially in younger women.

Potential for clinical use of cTPA

The results of this study suggest several potential implications for clinical practice. The ease of acquiring cTPA images at the bedside, the absence of radiation, and the minimal environmental impact of carotid scans, along with the ability to monitor the effects of medical preventive therapy with cTPA [5], [17], indicate a need for a paradigm shift in the management of patients aged 30-65 in men and patients aged 35-80 years in women to first perform cTPA, and to use CAC only in those cases where cTPA<21 is likely to underestimate CAC, e.g., in red flag situations with long-duration of diabetes mellitus, elevated Lp(a), LDL>5.0 mmol/l, smoking, or the combination of such situations.

The results of our logistic regression analysis further reveal that, in general, cardiovascular risk factors do not predict high-risk plaques in our study patients. Therefore, imaging appears as an independent cardiovascular risk stratification tool with additive and independent effects on atherosclerosis risk management.

Limitations

Notwithstanding its valuable findings, this study has several important limitations that should be considered when interpreting the results. First, there is potential selection bias, as the study examined patients from a cardiology practice and not the population found in the general population. These patients likely exhibited clinical indications for imaging, suggesting a higher prevalence of atherosclerosis compared to the general population. Secondly, the single-center design, where all measurements were conducted at a single cardiology practice with an affiliated radiology center, may limit the generalizability of findings to other clinical settings and populations. Thirdly, the cross-sectional analysis provides a comparison of cTPA and CAC without longitudinal follow-up data in the main analysis, which limits causal inferences about the temporal relationship between carotid and coronary atherosclerosis progression. Fourthly, technical considerations must be taken into account. The imaging protocols evolved over the study period (2003-2024), with different equipment used for CAC assessment between 2003-2006 and 2018-2024. Although standardized procedures were applied, technological advances may have influenced measurement consistency. Fifthly, a comparison of the chosen cutoff values for cTPA and CAC in terms of cardiovascular risk prediction is warranted. The present study endeavored to address this by comparing thresholds with similar event rates from prior studies; however, optimal cutoff values may still require further validation. Sixth, It is noteworthy that approximately 10% of patients exhibit substantial post-test risk discrepancies, underscoring the need for further investigation into the underlying causes of these variations. Notwithstanding these limitations, the study provides valuable insights into the comparative performance of cTPA and CAC for cardiovascular risk assessment and highlights the potential advantages of carotid ultrasound, particularly for women and younger individuals at risk for cardiovascular disease.

Conclusion

cTPA should be regarded as the primary imaging modality for evaluating cardiovascular risk in male patients aged 30 to 65 years and female patients up to age 80, in whom SCORE2 may result in an underestimation or overestimation of ASCVD risk. This strategy reduces radiation exposure, enables straightforward measurement of atherosclerosis progression and, due to its cost-effectiveness and potential for point-of-care testing, is a compelling option for primary care physicians. cTPA has the potential to serve as a management test, analogous to blood pressure or cholesterol assessments. Given the high prevalence of cTPA in patients referred for cardiological evaluation, it is essential to assess carotid plaque burden using cTPA to better guide or correct preventive strategies in these patients. Furthermore, cTPA has the potential to reduce the gender gap in cardiovascular imaging, as CAC frequently underestimates the presence of atherosclerosis, especially in female patients.

Tables:

Table 1: baseline characteristics of patients (N=907) and with SCORE2/-OP data (N=608)

Patient groups	ALL	SCORE2/-OP
All Patients	907	608
Age (mean ± SD)	59.9 ± 9.4	59.4 ± 9.1
Female (N, %)	321 (35)	209 (34)
Active smokers (N, %)	254 (28)	177 (29)
Diabetes mellitus Type II (N, %)	110 (12)	72 (12)
History of ASCVD (N, %)	142 (16)	88 (14)
Systolic Blood pressure in mm Hg (mean ± SD)	132 ± 19	131± 19
CHOL mmol/l (mean ± SD)		5.4 ± 1.3
HDL mmol/l (mean ± SD)		1.4 ± 0.5
LDL mmol/l (mean ± SD)		3.3 ± 1.3
TG mmol/l (mean ± SD)		1.8 ± 1.2
cTPA mm^2 (mean ± SD)	57 ± 55	57 ± 54
cTPA = 0 (N, %)	82 (9)	48 (8)
CAC Agatston score (mean ± SD)	224 ± 595	197 ± 512
CAC = 0	314 (35)	214 (35)
cTPA and CAC = 0	52 (6)	30 (5)

Table 2: Comparison for presence of detectable cTPA or CAC (N=907) by age groups

4 Field Table (Definition)							
true positive (TP)	TPA +	CAC +					
false positive (FP)	TPA+	CAC -					
true negative (TN)	TPA -	CAC -					
false negative (FN)	TPA -	CAC +					
Definition of test positivity: CAC>10 = CAC+ / cTPA >21 mm^2 =cTPA+							
Age Class	30-45	46-50	51-55	56-60	61-65	66-70	75-99
TP	2	26	40	63	92	79	111
FP	14	33	35	49	46	26	28
TN	18	21	36	50	20	14	5
FN	5	10	13	24	23	11	13
Sensitivity	29	72	75	72	80	88	90
Specificity	56	39	51	51	30	35	15
Positive predictive value	13	44	53	56	67	75	80
Negative predictive value	78	68	73	68	47	56	28
Accuracy	51	52	61	61	62	72	74
Number of patients per age group	39	90	124	186	181	130	157
positive likelihood ratio	0.7	1.2	1.5	1.5	1.1	1.4	1.1
negative likelihood ratio	1.3	0.7	0.5	0.5	0.7	0.3	0.7
false negatives (%)	13	11	10	13	13	8	8
Prevalence cTPA+ (%)	41	66	60	60	76	81	89
Prevalence CAC+ (%)	18	40	43	47	64	69	79
Prevalence difference (%)	23	26	18	13	13	12	10

Table 3: Comparison for presence of higher risk cTPA or CAC (N=907) by age groups

4 Field Table							
true positive (TP)			TPA +	CAC +			
false positive (FP)			TPA+	CAC -			
true negative (TN)			TPA -	CAC -			
false negative (FN)			TPA -	CAC +			
Definition of test positivity: CAC≥100 = CAC+ / cTPA ≥62 mm² =cTPA+							
Age Class	30-45	46-50	51-55	56-60	61-65	66-70	75-99
TP	0	8	14	20	34	26	65
FP	3	19	12	38	30	32	24
TN	33	53	84	108	89	50	42
FN	3	10	14	20	28	22	26
Sensitivity	0	44	50	50	55	54	71
Specificity	92	74	88	74	75	61	64
Positive predictive value	0	30	54	34	53	45	73
Negative predictive value	92	84	86	84	76	69	62
Accuracy	85	68	79	69	68	58	68
Number of patients per age group	39	90	124	186	181	130	157
positive likelihood ratio	0.0	1.7	4.0	1.9	2.2	1.4	2.0
negative likelihood ratio	1.09	0.75	0.57	0.68	0.60	0.75	0.45
Prevalence CAC+ (%)	8	20	23	22	34	37	58
false negatives (%)	8	11	11	11	15	17	17
Prevalence cTPA+ (%)	8	30	21	31	35	45	57
Prevalence CAC+ (%)	8	20	23	22	34	37	58
Prevalence difference (%)	0	10	-2	10	1	8	-1

TABLE 4: Direct comparison of TPA0 TO CAC10/100 AND CAC=O TO TPA21/61 in men and women

		cTPA>21, CAC=0	cTPA=0, CAC>10	%	%	
F	321	75	8	23.4	2.5	<0.0001
M	586	101	17	17.2	2.9	<0.0001
ALL	907	176	25	19.4	2.8	
				p=0.02		
		cTPA>61, CAC=0	cTPA=0, CAC≥100	%	%	
F	321	23	2	7.2	0.6	<0.0001
M	586	33	6	5.6	1.0	<0.0001
ALL	907	56	8	6.2	0.9	
				p=0.35		

Table 5: Odds Ratios and 95%CI derived from univariate logistic regression for the dependent variables cTPA62 and CAC100 using age, sex, blood pressure, cTPA, CAC, DIAB, NIC and SECPREV as the explaining variables.

Variables	Univariate Predictors of TPA62			Univariate Predictors of CAC100		
	Odds ratio	95%-CI	P	Odds ratio	95%-CI	P
AGE	1.0594	1.0427 to 1.0764	<0.0001	1.0740	1.0559 to 1.0924	<0.0001
FEMALE	0.5341	0.3966 to 0.7195	<0.0001	0.5170	0.3794 to 0.7044	<0.0001
DIAB	1.6872	1.1282 to 2.5231	<0.0001	1.8643	1.2430 to 2.7960	<0.0001
NIC	1.4591	1.0830 to 1.9657	0.013	1.1070	0.8130 to 1.5074	0.5187
BP	1.0171	1.0096 to 1.0246	<0.0001	1.0158	1.0082 to 1.0234	<0.0001
SECPREV	1.8121	1.3186 to 2.4904	0.0002	3.3757	2.4422 to 4.6660	<0.0001
FAM	0.5478	0.3640 to 0.8245	0.0039	0.4985	0.3228 to 0.7698	0.0017
CAC	1.0010	1.0007 to 1.0014	<0.0001			
CAC100	4.0314	2.9993 to 5.4186	<0.0001			
TPA				1.0146	1.0116 to 1.0177	<0.0001
TPA62				4.0314	2.9993 to 5.4186	<0.0001

TABLE 6: Distribution of MACE risk categories and the indication for LDL therapy for SCORE2/-OP, SCORE2TPA AND

	RISK CATEGORY			
	LOW-INTERM	**HIGH**	**VERY HIGH**	**ALL**
SCORE2/-OP RISK	229	305	74	608
SCORE2/-OP %	38	50	12	100
LDL TREAT	15	274	69	358
LDL TREAT %	7	90	93	59
SCORE2TPA RISK	182	124	302	608
SCORE2TPA RISK %	30	20	50	100
TPA62	51	117	46	214
TPA62%	24	55	21	100
LDL TREAT	16	113	279	408
LDL TREAT %	9	91	92	67
SCORE2CAC RISK	227	105	276	608
SCORE2CAC RISK %	37	17	45	100
CAC100	40	106	41	187
CAC100 %	21	57	22	100
LDL TREAT	18	94	257	369
LDL TREAT %	8	90	93	61

Table 7: Logistic Regression analysis of cardiovascular risk factors to detect higher risk plaques (cTPA62, CAC100)

	cTPA62			CAC100		
	Odds Ratio	**Odds Ratio 95%-CI**	**P value**	**Odds Ratio**	**Odds Ratio 95%-CI**	**P value**
AGE	0.9926	0.9748 to 1.0107	N.S.	0.9933	0.9745 to 1.0124	N.S.
MALE SEX	1.3106	0.9316 to 1.8436	N.S.	1.1737	0.8191 to 1.6817	N.S.
NIC	1.1541	0.8076 to 1.6493	N.S.	1.2275	0.8447 to 1.7840	N.S.
DIABETES MELL	1.4794	0.9022 to 2.4259	N.S.	1.41	0.8452 to 2.3521	N.S.
SECPREV	1.6292	1.0891 to 2.4371	0.0179	1.3341	0.8758 to 2.0320	N.S.
BPS	0.9908	0.9820 to 0.9997	0.0422	0.9997	0.9905 to 1.0090	N.S.
CHOL	1.0836	0.9589 to 1.2245	N.S.	1.0952	0.9630 to 1.2454	N.S.
HDL	1.1447	0.8002 to 1.6375	N.S.	1.0898	0.7473 to 1.5893	N.S.
LDL	1.0699	0.9408 to 1.2167	N.S.	1.0526	0.9197 to 1.2047	N.S.
TG	0.9938	0.8630 to 1.1444	N.S.	1.1265	0.9760 to 1.3002	N.S.
SCORE2/-OP	0.9898	0.9518 to 1.0294	N.S.	1.0009	0.9608 to 1.0427	N.S.
CAC	1.0000	0.9997 to 1.0004	N.S.			
CAC100	0.8325	0.5827 to 1.1895	N.S.			
SCORE2CAC	0.9945	0.9783 to 1.0109	N.S.			
TPA				0.9995	0.9963 to 1.0028	N.S.
TPA62				1.0299	0.7188 to 1.4757	N.S.
SCORE2TPA				1.0059	0.9895 to 1.0226	N.S.

Table 8: Sex differences for LDL treatment indications by age groups.

		ALL	35-55	35-60	35-65	35-70	35-75	35-80
	Female	%	%	%	%	%	%	%
SCORE2/-OP	96	46	29	26	32	43	43	45
SCORE2TPA	136	65	47	43	55	60	63	65
SCORE2CAC	109	52	33	31	41	47	49	52
ALL WOMEN	209							

		ALL	35-55	35-60	35-65	35-70	35-75	35-80
	Male	%	%	%	%	%	%	%
SCORE2/-OP	269	67	59	56	62	65	67	67
SCORE2TPA	284	71	64	66	67	69	71	71
SCORE2CAC	271	68	52	57	63	65	67	68
ALL MEN	399							

Table 9: Chi^2 values of Table 8 results by sex and differences for LDL treatment indications by age groups ($p<0.05$ for Chi^2 > 3.85).

Age Group	**35-55**	**35-60**	**35-65**	**35-70**	**35-75**	**35-80**
SCORE2TPA female	2.99	***6.709****	***14.91****	***10.036****	***14.752****	***15.582****
SCORE2CAC female	0.205	0.635	2.619	0.552	1.473	1.63
Age Group	**35-55**	**35-60**	**35-65**	**35-70**	**35-75**	**35-80**
SCORE2TPA male	0.783	***4.609****	2.117	1.492	1.768	1.714
SCORE2CAC male	1.527	0.0831	0.0642	0.0000	0.0237	0.023

*** = p<0.05**

Table 10a: Number and percent of patients with very high posttest risk by SCORE2TPA versus low-intermediate risk by SCORE2CAC and very high posttest risk by SCORE2CAC and low-intermediate risk by SCORE2TPA stratified by SCORE2/-OP risk categories

Numbers	HL	LH	ALL
ALL	57	50	608
SCORE2/-OP LM	3	5	229
SCORE2/-OP H	50	36	305
SCORE2/-OP VH	4	9	74

Percent Table	HL	LH	Difference
ALL	9.4	8.2	1.2
SCORE2/-OP LM	1.3	2.2	-0.9
SCORE2/-OP H	16.4	11.8	4.6
SCORE2/-OP VH	5.4	12.2	-6.8

Legend: LM=low to intermediate SCORE2/-OP risk, H=high risk, VH=very high risk, HL=very high cTPA posttest risk with low to intermediate CAC posttest risk and vice versa (=LH).

Table 10b: Number and percent of patients with very high posttest risk by SCORE2TPA versus low-intermediate risk by SCORE2CAC and very high posttest risk by SCORE2CAC and low-intermediate risk by SCORE2TPA stratified by SCORE2/-OP absolute 10-year risk

	CUMULATIVE FREQUENCY			
SCORE2/-OP	**cTPA HL**	**%**	**CAC HL**	**%**
<2.5	0	0.0	0	0.0
<3.0	1	0.2	1	0.2
<4.0	2	0.3	3	0.5
<5.0	7	1.2	7	1.2
<6.0	17	2.8	13	2.1
<7.0	28	4.6	23	3.8
<7.5	36	5.9	30	4.9
ALL	**57**	**9.4**	**50**	**8.2**

Table 11: Number of patients with very high posttest risk by SCORE2TPA versus low-intermediate risk by SCORE2CAC and very high posttest risk by SCORE2CAC and low-intermediate risk by SCORE2TPA: logistic regression of predicting variables in 608 patients.

	SCORE2TPA				SCORE2CAC			
Variable	**HL**	**NOT HL**	**OR (95%-CI)**	**p=**	**HL**	**NOT HL**	**OR (95%-CI)**	**p=**
N=	57	551			50	558		
AGE	59	59		0.8659	62	59		0.0838
SEX	41	358		0.2932	39	360		0.0546
NIC	**26**	**151**	**2.2 (1.3-3.9)**	**0.0039**	17	160		0.4279
FAM	5	83		0.1993	5	83		0.3488
DIAB	10	62		0.1622	9	63		0.2401
BPS	131	131		0.9822	134	131		0.2933
CHOL	5.5	5.4		0.5719	5.5	5.4		0.5758
HDL	**1.2**	**1.4**	**0.4 (0.2-0.8)**	**0.0061**	1.3	1.4		0.0596
LDL	3.4	3.3		0.5352	3.4	3.3		0.5058
TG	**2.2**	**1.8**	**1.3 (1.1-1.6)**	**0.0037**	1.9	1.8		0.7426
SCORE2-OP	7.1	6.5		0.3421	**8.2**	**6.4**	**1.08 (1.02-1.14)**	**0.0036**
SECPREV	51	443		0.0666	43	445		0.2881

Figure 1: Distribution of MACE risk categories indication for LDL therapy for SCORE2/-OP, SCORE2TPA AND SCORE2CAC.

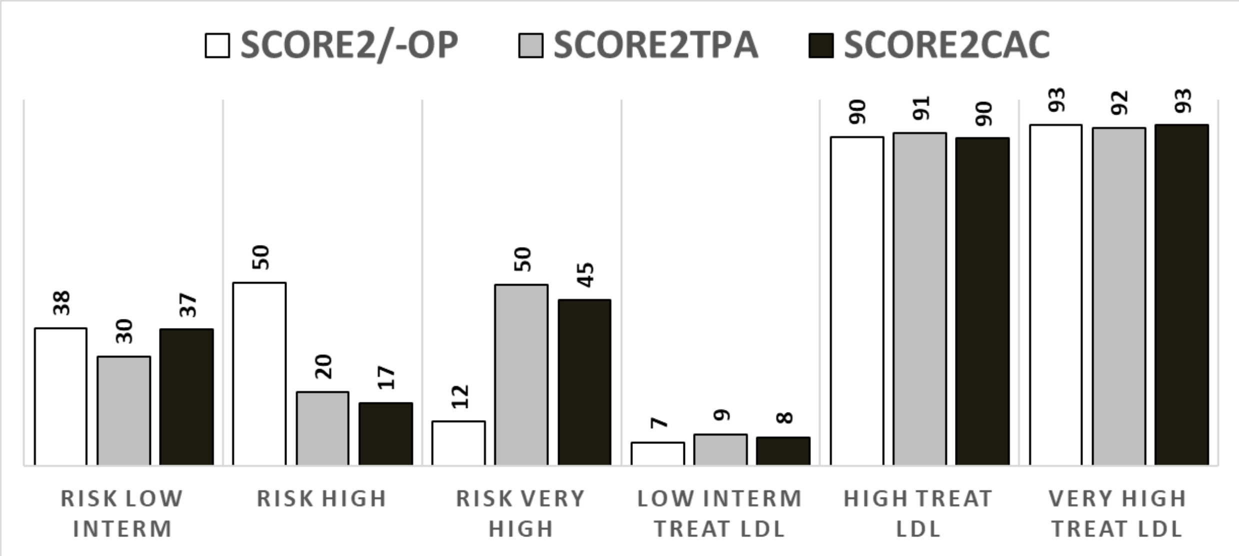


Figure 2: Chi^2 differences from results of Table 8 for LDL treatment indications by sex and age groups (p<0.05 for Chi2 > 3.85, vertical axis).

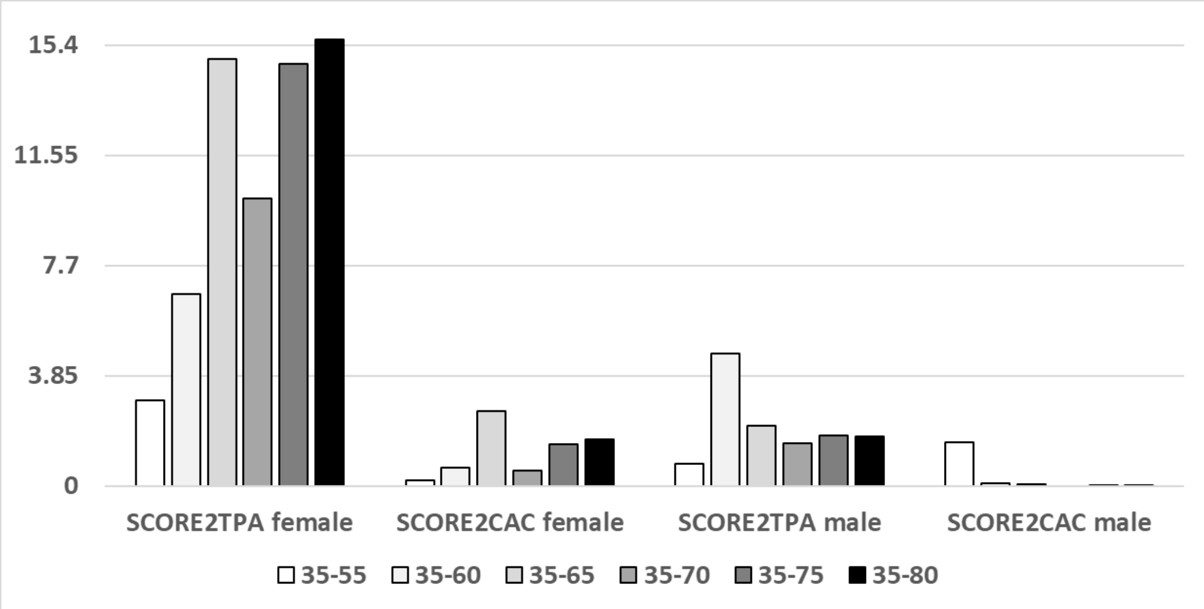
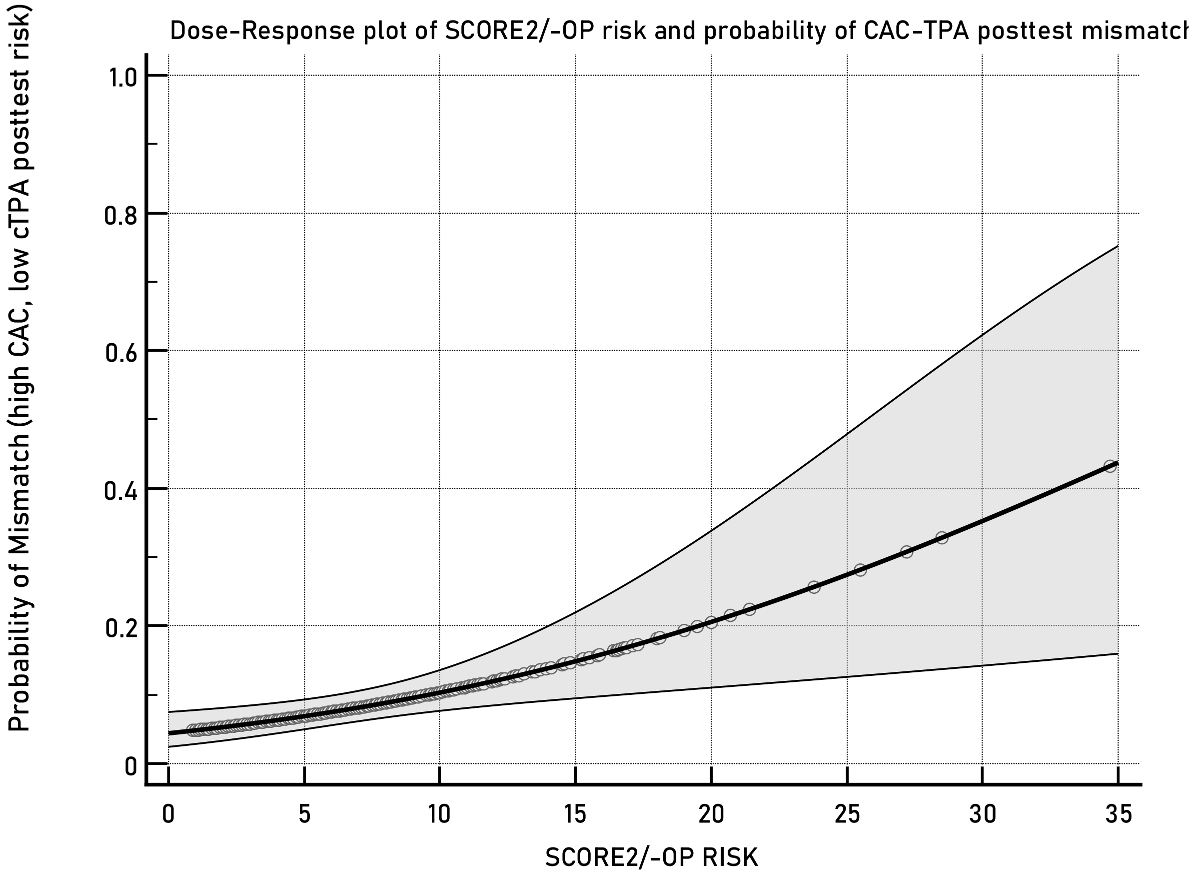


Figure 3: Risk mismatch for very high risk defined by SCORE2CAC with simultaneous low-intermediate risk for SCORE2TPA using probit logistic regression analysis



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Supplemental Material

Suppl. Table 1a: comparison of different cTPA and CAC cutoff-points for diagnostic values (Area under curve) and associated 5 year outcomes from the ARCO [18] and the MESA study [19].

DIAGNOSTIC ACCURACY OF IMAGING (MESA CAC, ARCO cTPA)								
	MESA Coronary Heart Disease							
	CHD	No CHD	ALL	Sens	Spec	AUC1	STANDARD ERROR	5 YEAR RISK
CAC 0	31	2330	2361	0.8072	0.5733	0.738	0.0189	0.7
CAC 1-99	44	1049	1093	0.8072	0.5733			2.1
CAC 100+	90	685	775	0.5422	0.8314			5.8
ALL	165	4064	4229					
	MESA MACE					AUC2	STANDARD ERROR	5 YEAR RISK
CAC 0	54	2307	2361	0.7787	0.5788	0.715	0.0161	1.2
CAC 1-99	73	1020	1093	0.7787	0.5788			3.3
CAC 100+	116	659	775	0.54	0.86			7.5
ALL	243	3986	4229					
	ARCO MACE					AUC3	STANDARD ERROR	5 YEAR RISK
TPA<22	3	1413	1416	0.9474	0.5074	0.798	0.0214	0.3
TPA 22-61	12	707	719	0.9474	0.5074			1.2
TPA 62+	42	665	707	0.7368	0.7612			6.4
ALL	57	2785	2842					

Suppl. Table 1b: Example of posttest risk for a SCORE2/-OP risk of 0.05 (=5%).

POST TEST RESULTS FOR POSITIVE AND NEGATIVE TESTS (BAYES THEOREM)					
	IMAGING TEST NEGATIVE				
	Risk	Sens	Spec	Bayes neg	Risk change
MESA CHD	0.05	0.807	0.5733	0.017	0.033
MESA MACE	0.05	0.779	0.5788	0.020	0.030
ARCO MACE	0.05	0.9474	0.5074	0.005	0.045
	IMAGING TEST POSITIVE LOW RISK				
	Risk	Sens	Spec	Bayes pos	
MESA CHD	0.05	0.807	0.5733	0.091	0.041
MESA MACE	0.05	0.779	0.579	0.089	0.039
ARCO MACE	0.05	0.947	0.507	0.092	0.042
	IMAGING TEST POSITIVE RELEVANT RISK				
	Risk	Sens	Spec	Bayes pos	
MESA CHD	0.05	0.542	0.8314	0.145	0.095
MESA MACE	0.05	0.540	0.86	0.169	0.119
ARCO MACE	0.05	0.737	0.761	0.140	0.090

Legend: RISK=SCORE2/-OP chosen at 0.05 (=5%). For each cutoff (Table 1a) posttest risk is calculated using the Bayes theorem. Example: with the imaging test being negative (Bayes neg), post test risk dicreases vom 5% to 2% (Risk change 3%) with MESA MACE sensitivities and specificities; with ARCO MACE, risk decreases to 0.5% (Risk change 4.5%), which is due to the higher sensitivity of cTPA when compared to MESA MACE, where 54 (2.3%) of MACE occurred with CAC0, while only 3 (0.2%) MACE occurred with ARCO.

Suppl. Table 2: LDL treatment indication using the algorithm SCORE2/-OP and SCORE2TPA

	SCORE2/-OP	SCORE2TPA	DIFFERENCE
LDL TREAT	1586	1398	-188
LDL TREAT %	56	49	-7
EVENTS	135	146	11
EVENTS %	88	95	7
COX Hazard regression	2.9	13.6	10.7
95%-CI	1.8-4.7	6.6-28.2	4.8-23.5