Effects of serial carotid atherosclerosis quantification to prevent cardiovascular disease

Corresponding Author:

Michel Romanens, MD

Vascular Risk Foundation

Spitalstr. 9

CH-4600 Olten, Switzerland

Fax: +41 62 212 44 30

michel.romanens@hin.ch

Word count: 6’258.
Version: 15.10.2024

Abstract

Background

Atherosclerosis detected by imaging is associated with very high cardiovascular risk. Monitoring plaque burden over time in an outpatient cardiology setting with regular visits can help identify patients who need more intensive preventive care.

Methods

A population of 1,224 patients (mean age 57 years, 38% women) underwent repeated vascular ultrasound examinations to quantify carotid plaque burden (cTPA) every 1.3 years on average, with a median cardiovascular outcome follow-up of 6.5 years. Patients who did not achieve treatment goals or who had plaque progression were counseled to intensify preventive treatment. Expected cardiovascular events were calculated and compared with observed events. Hazard ratios were calculated for plaque progression and regression.

Results

During follow-up, the following 52 ASCVD were recorded in the progression and regression groups, respectively MI 7 vs. 1, stroke/TIA 7 vs. 4, CABG 7 vs. 1, PTCA 14 vs. 4, death 1 vs. 0, CAD/PAD 5 vs 1 and total events 41 vs 11 or 6.7% vs 1.8% ($p<0.0001$). The mean SCORE2DMFINAL was lower in the regressors ($p=0.0009$) and the HR of PR was 3.54 (95%CI: 1.80 -7.00, $p=0.0003$). Using multiple regression analysis, SCORE2DMFINAL was significantly associated with TPADIFF (F-ratio 25.69, $p<0.0001$).

Conclusions

In middle-aged cardiology patients, regular visits for cardiovascular risk factor adjustment and more intensive treatment, especially in patients with cTPA progression, resulted in more frequent cTPA regression, and plaque regression was associated with lower ASCVD event rates. The high HR for PR should prompt external validation. Serial measurements of carotid plaque burden is simple, reproducible, low-cost and cost-effective for the management of atherosclerosis and associated cardiovascular events.

List of Abbreviations

1	code for baseline values
2	code for final value
ACS	acute coronary syndrome
AGE1	patient age at baseline
AGLA	Working group on lipids and atherosclerosis of the Swiss Society of Cardiology
ARCO	Atherosclerosis Risk on cardiovascular Outcomes Cohort study
ASCVD	atherosclerotic cardiovascular disease
AUC	area under the curve, derived from receiver operating curves (ROC)
CABG	coronary artery bypass grafting
CAC	coronary artery calcifications, quantified by Agatston Scores (does not require contrast media injection)
CAD	coronary artery disease
CT	computed tomography
cTPA	carotid total plaque area
CV	cardiovascular
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiogram
ESC	European Society of Cardiology
GDP	gross domestic product
GP	general practitioner
HR	hazard ratio derived from Cox proportional Hazard regression
IMT	intima-media-thickness
MEDI	MEDI is coded with 0 for no medication; 1= therapy with statins, 2=therapy with antihypertensive drugs, 3=therapy with statins and antihypertensive drugs
MI	myocardial infarction
MRI	magnetic resonance imaging
NNT	Numbers needed to treat. Calculation: 100 divided by absolute risk reduction. NNT decreases linearly over time, when the relative risk reduction remains constant over

	time.
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PR	group of patients with cTPA progression or regression
QUART	quartile
ROC	receiver operating curves
ROI	return on investment (cost-effectiveness analysis)
PROCAM	Prospective Cardiovascular Munster Study
PTCA	percutaneous transluminal coronary angioplasty
PTP	posttest probability
SPECT	single photon emission computed tomography
SCORE2DM	risk prediction algorithm: new models to estimate 10-year risk of cardiovascular disease in Europe that includes risk for patients with diabetes mellitus Type II.
TIA	transient ischemic attack
TIME	observation time, follow-up time
TPA	total plaque area
TPADIFF	difference of TPA between maximum amount and amount at final visit, or between minimal amount and maximum amount occurring at the final visit
VSL	Value of a statistical life
VSLY	Value of a statistical life per year (according to WHO and referenced, VLSY is calculated by multiplying the gross domestic product (BIP) of a Swiss person by 3. Example for Switzerland: 88 209 CHF in 2022 x 3 = 264 627 CHF.

Introduction

Since we cannot treat what we do not measure [1], the idea of quantifying and monitoring carotid plaque to more accurately and favourably manage cardiovascular risk was born in 2002. Since then, we have been quantifying plaque circumference to calculate carotid total plaque area (cTPA), as described by Spence in 2002[2]. With time, experience, accessibility, rapidity of quantification, low-cost and global ease of bedside management, cTPA has remained the most feasible tool to guide atherosclerosis management beyond major cardiovascular risk factors or other imaging techniques like carotid intima-media thickness[3] and coronary calcifications[4] in our daily clinical practice and has been measured at every patient visit in both primary and secondary prevention for the past 20 years[2].

Atherosclerotic plaque is a well-described hallmark of cardiovascular risk, and the development of carotid atherosclerosis over time may be a preferred risk indicator for future cardiovascular events[4]. Atherosclerosis is a common cause of atherosclerotic cardiovascular disease (ASCVD) worldwide [5] and can be diagnosed and quantified using atherosclerosis imaging [4,6]. Higher levels of atherosclerosis are associated with higher rates of ASCVD event [7–12].

Atherosclerosis imaging modalities are increasingly available and include a variety of anatomical and functional imaging techniques such as computed tomography, magnetic resonance, ultrasound, positron emission tomography, near-infrared fluorescence, nanoparticle imaging, molecular imaging, optical coherence tomography, and functional imaging[13]. Despite the plethora of atherosclerosis imaging modalities, a complete assessment of plaque vulnerability has not been achieved[14]. This is consistent with the concept of global atherosclerotic disease burden for cardiovascular risk assessment, which moves away from individual vulnerable plaque lesions [15]. For the clinician in daily primary care practice, fancy and experimental radiology is usually not available for personalized cardiovascular risk assessment, and reliance on readily available imaging modalities is preferred, e.g., ultrasound of the carotid and femoral arteries or a simple coronary computed tomography (CT) scan without contrast media for assessment of coronary calcifications and their quantification (Agatston score, calcified coronary plaque volume). Atherosclerosis Imaging of carotid plaque using the total plaque area (cTPA) is cost-effective [16] and coronary calcium (CAC) as well as carotid plaque quantification using cTPA can be imaged with high reliability and reproducibility [3,17]. Furthermore, Atherosclerosis Imaging is well suited to observe changes in atherosclerotic burden over time [18–27] and patients with carotid plaque regression or stabilisation incur about 50% less ASCVD events [2], while

CAC is not suited to observe plaque regression over time, because statins increase – due to the healing process of inflamed atherosclerotic leasons - the amount of CAC [28,29]. Imaging may also be used to observe effects of medical intervention over time as a surrogate marker for cardiovascular events [30]. Others have found a linkage between changes in plaque amount over time and ASCVD events [2,18,31–33]. As stated by [32]: “Plaque progression precedes cardiovascular events [32]; If outcome data linking plaque regression to reduce cardiovascular (CV) events emerge, monitoring the response to coronary plaque treatment may ultimately supersede surrogate markers like risk scores and lipoprotein levels”. Therefore, the new paradigm of treating arteries instead of risk factors [34] receives more scientific evidence and serial imaging of the global plaque burden, e.g. in the carotid arteries appears most suitable for atherosclerosis management using cTPA [35–37].

The importance of integrating cTPA in the outpatient setting for the clinical management of the risk of fatal and nonfatal cardiovascular events over this long period has not been well studied. One problem in considering how such a benefit might be adequately demonstrated is that routine clinical interventions affect cardiovascular risk, which is confounded by the individual's exposure to the cardiovascular risk factors being treated. Thus, established risk factors would be rendered irrelevant or of secondary importance by the intervention. The solution to this problem was to design the trial to observe the effect of medical interventions on plaque progression or regression, as measured by global risk expectations calculated by the SCORE2DM calculator, and on cardiovascular events. Indeed, up to 20 years of clinical cardiovascular risk management is a long time. If carotid plaque area initially decreases with consistent preventive medical therapy but increases again with age or due to unrecognised risk factors (J-curve of atherosclerotic area over time), different scenarios are possible to define the effect of medical intervention. For this study, we decided to define plaque progression as the maximum amount of plaque on the last day of the consultation, whereas plaque regression was defined as a lower amount of plaque on the last day of the consultation than the maximum amount of plaque ever measured in that patient. This approach may also avoid randomized trials in which patients with established atherosclerosis are left without optimal medical care to test the hypothesis that such patients have more cardiovascular events.

The objectives of our cohort study were twofold: 1) to determine the effect of atherosclerosis management on observed versus expected cardiovascular events; 2) to examine the effect of aggregated (SCORE2DM) and individual cardiovascular risk factors on progression and regression of cTPA and cardiovascular events.

Methods

Patient selection

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 Diagnostic Center, both located in Olten, between 2003 and 2024. Individuals were referred either for a cardiological work-up by general practitioners or for a cardioradiological examination (cardiac MRI, CT, nuclear SPECT imaging). Individuals with cardioradiological visits, single visits, without follow-up information or with a follow-up of less than 1 year and without cTPA measurements were excluded. For the remaining individuals, information on sex and age at baseline and last visit and number of visits was known.

Definition of a complete data set

A complete data set was defined as the availability of the following variables in patients with at least 1 year of follow-up: maximum and final cTPA, date of birth, sex, diabetes mellitus, smoking, sex, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, and event. Missing values were defined as being recorded as normal, but without a numerical record. Such missing values were allowed for only 1 of the following variables: systolic blood pressure, total cholesterol, HDL cholesterol, or LDL cholesterol. Missing blood pressure values were calculated as normal (120 mm Hg systolic blood pressure), and lipid values were replaced by the mean of the group with a complete data set or by calculation of the Friedewald formula[38].

Subgroup definition

We recorded a complete data set in a subset of individuals and divided them into two groups: Group 1 were cTPA progressors, defined as an increase in cTPA>0 at the last visit compared with the maximum cTPA at previous visits, and Group 2 were cTPA regressors, defined as cTPA ≤0 at the last visit compared with the maximum cTPA at previous visits.

Collection and definition of outcome variables

Outcome was defined as the occurrence of fatal or nonfatal myocardial infarction or stroke, TIA, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), death from any cause, diagnosis of peripheral artery disease (PAD), or coronary artery disease on invasive angiogram with at least 50% stenosis of an epicardial vessel (CAD). Outcome information was collected at the final visit, by mail, or from hospital or physician records.

Carotid plaque measurements

As described elsewhere[4], 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 sum of all plaques (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[3].

Clinical Intervention and patient management

Patients were referred by their general practitioners, with a median follow-up per patient of 1.3 years (interquartile range 0.9-1.8 years). Whenever possible, cardiovascular risk factors were collected from patient history and laboratory values. Blood pressure was measured in the office with a sphygmomanometer in the sitting position. Medication use was recorded and verified when information appeared unreliable. During the cardiological visit, cTPA was measured in each patient. After the evaluation, patients and their physicians received a detailed report on the appropriate recommendations for the achievement of risk factor goals. During the follow-up visits, the achievement of the goals was checked and corrected if necessary.

This study did not require formal approval by an ethics committee, as all medical interventions were performed as part of routine medical management, which was the same for all patients.

Cost effectiveness model

We calculated cost-effectiveness in 1’000 patients treated by calculating cost of treatment minus the costs per event averted in the first year. We created a model of cost-effectiveness in the first year based on expected and observed events, a nonfatal to fatal event rate of 9:2 [39], estimate of productivity loss and indirect cost in the first year of an acute coronary event [40], we estimated that a fatal event is associated with 10 years of life lost [41] at a cost per annum of 3 times the Swiss gross domestic product (GDP) per person [41,42], we estimated the cost of the cardiology services based on our average cost per patient per year, and we estimated the cost of internal medicine services based on the average cost per patient per year from a national Swiss national data set of 5’112 medical practices that treated 4’873’153 patients in 2016. Finally, we estimated that cardiologists and general practitioners spent 1:10 of the total cost per patient for cardiovascular prevention (counselling, medication, visits, laboratory, ECG, stress tests, echocardiography, cTPA, if indicated and appropriate).

Statistical analysis

Statistical analysis was performed with 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 variables predicting outcome was assessed by Cox proportional hazards regression using univariate and stepwise models. The effect of explanatory independent variables on plaque progression or regression was assessed with regression analysis (logistic regression, multiple regression, and probit regression) and the Variance Inflation Factor (VIF) was calculated: a high Variance Inflation Factor is an indicator of multicollinearity of the independent variables. Multicollinearity refers to a situation in which two or more explanatory variables in a multiple regression model are highly linearly related. If necessary, confounding variables were adjusted by propensity matching. If indicated, non-normally distributed variables were LOG transformed for multiple regression analysis. Statistical significance was set at <0.05.

Results

Patients

Patients with cardio-radiological visits, single visits, without follow-up information or with a follow-up of less than 1 year or without cTPA measurements were excluded (N=7'764). The remaining patients were N=1'983, for whom follow-up information, sex and age at baseline and last visit, and number of visits were known. We recorded a complete data set in 1,224 individuals (group PR) and divided PR into two groups: Group 1 were cTPA progressors (N=611) and Group 2 were cTPA regressors (N=613).

Baseline and follow-up data

Baseline and follow-up data in the full dataset group were as follows (Table 1). At baseline, the median age was 57 years in both progressors and regressors, and there were no statistical differences in age, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, number of current smokers, and SCORE2DM. In the regressor group, there were more women (43% vs 32%, p=0.009), more patients with diabetes mellitus (12.4% vs 8.8%, p=0.01) and a higher median cTPA (64 vs 45 mm2, p<0.0001). The following events were recorded in the progression and regression groups: myocardial infarction 7 vs 1, stroke/TIA 7 vs 4, CABG 7 vs 1, PTCA 14 vs 4, death 1 vs 0, CAD/PAD 5 vs 1 and total events 41 vs 11 or 6.7% vs 1.8% (p<0.0001). A total of 52 events (4.2%) were recorded. The median follow-up was 7.4 years for progressors and 5.7 years for regressors. The extrapolated 10-year event rates were 9.1% and 3.1% (p=0.001), and the expected event rates based on SCORE2DMTPA were 11.8% and 13.6%, resulting in an absolute risk reduction of 2.7% and 10.5% (NNT 37 vs 10), respectively. During follow-up, the age of progressors and regressors increased from 57 to 65 and from 57 to 64 years, respectively (p=0.0045), LDL decreased from 3.4 mmol/l to 2.5 mmol/l and from 3.4 mmol/l to 2.4 mmol/l (p=NS) and median cTPA increased from 45 mm^2 to 81 mm^2 and decreased from 64 mm^2 to 40 mm^2 (p<0.0001), SCORE2DM increased from 5.4% to 7.8% and from 5.3% to 6.9% (p=0.0.0009), SCORE2DMTPA increased from 11.8% to 19.6% and from 13.6% to 13.7% (p<0.0001).

Independent variables predicting outcome (Cox proportional-hazards regression)

Univariate predictors of outcome are listed in Table 2. Significant baseline predictors were sex (HR

for female sex 0.34, p=0.0082), older age (p=0.0132), higher systolic blood pressure (p=0.0014), lower LDL (p=0.0331), DM2 (HR 2.7, p=0.0051), higher TPA (p<0.0001), higher SCORE2DM (p<0.0001), higher SCORE2DMTPA (p<0.0001), cTPA progression (HR 2.6, p=0.0063) and patients in secondary prevention (HR 3.4, p<0.0001). Significant predictors at the final visit were lower HDL (p=0.0041), higher triglycerides (p=0.0239), DM2 (HR 2.0, p=0.0306), higher SCORE2DMTPAFINAL (p<0.0001). Significant univariate predictors of outcome were entered into a **multivariate stepwise Cox proportional hazards regression** (SEXCODE, AGE1, BDS1, DIAB1, TPA1, SCORE2DM, TPADIFF, TPA2, SCORE2DMTPA, and PR. Only SCORE2DMTPA (hazard ratio 1.0664, 95%CI: 1.0424-1.0910, p<0.0001) and PR (hazard ratio 3.1, 95%CI: 1.6-6.0, p=0.0012) remained significant predictors of ASCVD events regarding single cardiovascular risk factors and their aggregation in SCORE2DM.
In a multivariate model, we used the following **multivariate predictors** of outcome (Table 3a): SCORE2DM (clinical), cTPA1 (cTPA at baseline), SCORE2DMTPA (combination of clinical and imaging) and TPADIFF (cTPA difference from last visit to the maximum cTPA ever recorded). Only SCORE2DMTPA and TPADIFF remained significant (HR 1.06 [1.04 - 1.09], p<0.0001 and HR 1.01 [1.00 -1.01], p=0.0318). The Hazard Ratio per quartile increase of SCORE2DMTPAQUART was 1.71 (95%CI: 1.32-2.22, p=0.0001) and per TPADIFFQUART increase was 1.478 (1.14-1.92, p=0.0033). In a multivariate model, we used the following **multivariate predictors** of outcome (Table 3b): SCORE2DM (clinical), SCORE2DMTPA (combination of clinical and imaging) and PR (PR=1 is the progressor group, PR=0 is the regressor group). Only SCORE2DMTPA and PR remained significant (HR 1.12 [1.08 - 1.12], p<0.0001 and HR 3.54 [1.80 -7.00], p=0.0003, Figure 1), while SCORE2DM was excluded from the model. **Kaplan Meier** survival curve for PR illustrates the effect of PR on ASCVD survival (Hazard ratio 2.3, p=0.0047; Figure 2)

Independent variables diagnosing cTPA progression or regression and events

Using ROC analysis for PR Group, SCORE2DM was not significant (AUC 0.51, 95%CI: 0.48-0.54, p=NS, Table 4a), but SOCRE2DMFINAL was (AUC 0.56, 95%CI: 0.54-0.59, p<0.0001 for the AUC difference). The PR group was also evaluated by regression analysis. Using logistic regression with PR coded as 0 for regressors and 1 for progressors, SCORE2DM did not explain PR, but SCORE2DMFINAL did (p=0.0011), and the odds ratio increased by quartiles of SCORE2DMFINAL: 2. Quartile 1.61 (95%CI: 1.17-2.21, p=0.0037), 3. Quartile 1.73 (95%CI: 1.26-2.37, p=0.0007), 4. Quartile 1.83 (95%CI: 1.33-2.52, p=0.0004). Using probit regression (dose-response analysis), increasing values of SCORE2DMFINAL increased the probability of being in the progressor group (PR=1,

p=0.0010, Figure 3).

Using simple regression analysis, SCORE2DM was not correlated with the difference in cTPA (final minus peak, TPADIFF, p=0.4579), but SCORE2DMFINAL was significantly associated with TPADIFF (F-ratio 25.69, p<0.0001, Figure 4). Because AGE2 was significantly higher in progressors, we performed propensity matching for age, resulting in 1,124 subjects with a mean age of 64.3 years in progressors and regressors (p=0.9380), and repeated the simple regression analysis with SCORE2DMFINAL and TPADIFF: F-Ratio 15.07, p=0.0001.

SCORE2DMFINAL was also predictive for cardiovascular events based on logistic regression (Wald 4.2258, p=0.0398; after propensity matching: p=0.0453) and ROC analysis (AUC 0.60, 95%CI: 0.57-0.63, p=0.0086, Table 4a, after propensity matching p=0.0181).

Using a stepwise forward multiple regression to adjust for confounders of TPADIFF, we entered TIME, BP2, CHOL2, LDL2, NIK2, DIAB1 and SCORE2DMFINAL into the model (Table 4b). Significant predictors of TPADIFF were TIME (p<0.0001), lower BDS2 (p=0.0042), higher LDL2 (p= 0.0005) and SCORE2DMFINAL (p<0.0001). No relevant collinearity among explaining variables was present.

Because CHOL2, LDL2, and SCORE2DMFINAL were not normally distributed, we performed a LOG transformation and recalculated the results from Table 4b. Agan by using a stepwise forward multiple regression to adjust for confounders of TPADIFF, we entered TIME, BP2, LOGCHOL2, LOGLDL2, NIK2, DIAB1 and LOGSCORE2DMFINAL into the model (Table 4c). Significant predictors of TPADIFF were TIME (p<0.0001), younger AGE2 (p=0.045), lower BDS2 (p=0.002), higher LOGLDL2 (p= 0.0029) and LOGSCORE2DMFINAL (p<0.0001). No relevant collinearity among explaining variables was present. An overview of the distribution plots is displayed in Figure 7.

The summary statistics of the continuous variables explaining TPADIFF are listed in Table 4d. Despite LOG transformations, some skewness and kurtosis persisted. However, by visual inspection, the distribution of these variables appears acceptable. An overview of the distribution plots is displayed in Figure 7.

Comparison of expected and observed outcome

A total of 1,983 patients (mean and median age 57 years, 41% women, mean cTPA 63 mm^2, median cTPA 47 mm^2) with outcome data were available. There were 83 (4.2%) ASCVD events during a mean follow-up of 7.3 (95% CI: 7.1-7.5) years and an expected 10-year event rate (by linear extrapolation) of 5.8%. Female sex was associated with a hazard ratio for ASCVD events of 0.40 (95%CI: 0.23-0.47, p=0.0007, Figure 5), patients with a median cTPA of 47 mm^2 or greater had a hazard ratio of 3.3

(95%CI: 2.0-5.4, p<0.0001), and PR was associated with a hazard ratio of 1.8 (95%CI: 1.1-3.0, p=0.0320). Using Probit Regression, TPADIFF was related to 82 ASCVD event probability in 1’960 patients (Wald 21.70, p<0.0001, Figure 6) and area under the curve was 0.67 (95%CI: 0.65 to 0.69, p<0.0001).

For the entire group, the expected SCORE2DMTPA was 12.7% (Figure 2), and the observed 10-year ASCVD event rate was 5.2%, for an absolute risk reduction of 7.5% (NNT 13.3). The expected SCORE2DMTPA was 14.8% in men and 9.3% in women (estimated from the patients with a complete data set) and the observed 10-year event rate was 6.8% in men and 2.3% in women for all patients with outcome information, therefore the absolute risk reduction was estimated to be 8% in men and 7% in women (NNT of 12.5 in men and 14.3 in women).

In patients with a complete data set (N=1,224), the expected 10-year ASCVD risk was 11.8% and the observed risk was 6.7% at 7.4 years in cTPA progressors (extrapolated 10-year risk 9.1%, absolute risk reduction 2.7%, NNT 36.6); the expected 10-year ASCVD risk was 13.6% and the observed risk was 1.8% at 5.7 years in cTPA regressors (extrapolated 10-year risk 3.1%, absolute risk reduction 10.5%, NNT 9.6).

Cost-effectiveness results

For 1,000 patients, the number of cardiology visits was 0.75/year at a cost of CHF 577 per year, and we estimated the average cost of specific preventive cardiology services to be 1:10, resulting in CHF 42.8 per patient-year. Global treatment costs, including medications, laboratory, physiotherapy, physician visits, and other external costs provided or ordered by internal medicine (GP) facilities, were CHF 1,129 per patient-year, and specific preventive services were CHF 112.90 per patient-year (specific cardiovascular prevention costs assumed at 1:10 of total costs). The treatment costs were therefore CHF 42.80+112.90=155.65 per patient or CHF 155’650 in 1’000 patients per year.

Event costs were estimated to be CHF 90’794.40. Expected events were 12.7 in usual care and 5.8 in cTPA assisted care in 1’000 patients treated per one year.

The return on investment was CHF 471 per patient using the preventive strategy. Including the value of a life lost over 10 years, the return on investment was CHF 3,318, and the total return on invested preventive care was CHF 3,789 per patient (Table 5).

Discussion

This retrospective cohort study of 1,224 patients treated in a cardiology practice primarily for primary prevention showed that the incidence of cardiovascular events was significantly lower than expected with the information on amount of plaque and plaque progression in cardiovascular risk management, and that this effect led to significantly fewer cardiovascular events, particularly in patients with plaque regression. However, given the lack of a control group, the validity of this is discussed as follows.

Effect of cardiovascular risk factors management on cTPA progression and regression

An important question concerns the association and possible causal role of the treated risk factors, aggregated in the SCORE2DM calculator, on its effect in predicting plaque progression or regression. We used several statistical tests for this purpose. The ROC analysis was not statistically significant at baseline (AUC 0.51, p=0.5544) to discriminate between plaque progression and regression, but showed a significant result regarding the detection of the plaque progression group at the final visit (SCORE2DMFINAL AUC 0.56, p=0.0001). Logistic regression showed no significant diagnostic information (SCORE2DM odds ratio 1.0033, 95%CI 0.9719-1.0357 p=0.8400), but a significant result at the final visit (SCORE2DMFINAL odds ratio 1.0399, 95%CI 1.0158 to 1.0645, p=0.011). At the individual level, we performed a simple linear regression analysis for SCORE2DM and SCORE2DMFINAL to predict TPADIFF. We found that SCORE2DM was not significantly correlated with TPADIFF (p=0.4579), but SCORE2DMFINAL was (F-ratio 25.6861, p<0.0001). Significant predictors of TPADIFF before and after LOG transformation of TIME, LDL2, and SCORE2DMFINAL were lower AGE2, lower BDP2, higher LDL2 and higher LOGSCORE2DMFINAL.

According to our interpretation of these results, the preventive medical intervention leads to a detectable influence on the SCORE2DMFINAL risk at the last clinical examination, and this influence is statistically significantly correlated with plaque progression or regression over time, even after adjustment for multiple risk factors and observation time. This implies that the favorable influence of cardiovascular risk factors is likely to reduce the amount of carotid plaque over time, that this result is not confounded by the difference of age (AGE2) at the final visit or to other variables used in the regression model. This observation suggests that the beneficial effect of preventive medical intervention on cardiovascular outcomes is due to the medical intervention itself. This finding underscores the importance of assessing SCORE2DMFINAL in individual patients, but because of the

small differences in risk factors, cTPA and its progression provide a more reliable and direct tool for atherosclerosis management beyond traditional cardiovascular risk factors as measured in this study.

Observed versus expected cardiovascular events

In public health cohort studies, natural history is usually associated with risk factors, as in the Framingham Heart Study[43]. As all our patients were being assessed and treated for their cardiovascular risk guided by the information of cTPA amounts or progression to prevent a cardiovascular event, the effect size of this approach to manage cardiovascular risk should be derived from the difference between expected and observed cardiovascular events. While observed events have occurred, expected events are subject to inaccuracies in calibration and discrimination. For our cohort, it is largely unknown whether the SCORE2DM calculator would have correctly calculated the risk for our patients assessed at baseline. The correct assignment of expected risk in a cohort undergoing preventive medical intervention therefore requires validation. For our cohort, we used an earlier cohort that was largely untreated and calibrated the risk as accurately as possible based on risk factors or their combination. According to our previous publication[44], calibration for cardiovascular events, as defined for this study, is best achieved by using the posttest probability (as calculated from the Bayes theorem) from SCORE2DMTPA[45]. In fact, we were able to show that the Bayes posttest risk in this cohort of 2,842 middle-aged (50 years) individuals and observing 154 cardiovascular events over a period of 5.6 years, improved the Hosmer-Lemeshow test of Pearson's CHI^2 for goodness of fit between expected and observed probabilities (according to a logistic regression model) increased the global CHI^2 from 203 to 306 compared to SCORE2DM alone, leading to a statistically significant improvement in discrimination (based on ROC analysis) from 0.82 (95%CI: 0.81-0.84) to 0.87 (95%CI: 0.86-0.89).

In absolute numbers, we found an observed event rate extrapolated over 10 years of 9.2% and an expected event rate based on SCORE2TPA of 7.0%. SCORE2DM alone predicted an event rate of only 5.0%, significantly underestimating the observed cardiovascular risk. Thus, SCORE2DMTPA improved not only the discrimination of cardiovascular events but also the calibration, although the absolute risk was still underestimated by approximately 24% with SCORE2DMTPA. Thus, the use of SCORE2DMTPA provides a conservative estimate of the expected cardiovascular risk.

Based on these assumptions, a relatively accurate determination of the expected 10-year event rate can be made. The effect of preventive measures was then calculated separately for plaque progression and regression. The results showed an absolute risk reduction of 2.7% for plaque

progression and 10.5% for plaque regression.

Prediction of cardiovascular events

Carotid plaque progression and regression, as measured by total carotid plaque area (PR), was an independent predictor of cardiovascular events (HR 3.1, 95%CI: 1.6-6.0, p=0.0012 in a model including individual cardiovascular risk factors and hazard ratio of 3.5, 95%CI: 1.8 -7.0, p=0.0003, Figure 1, in a model including SCORE2DM and SCORE2DMTPA). The risk factor status of cTPA progression for cardiovascular events had a HR of 1.48 per quartile change (p=0.0033). In contrast, individual traditional risk factors, their aggregation in SCORE2DM or TPA1 alone became predictive for cardiovascular events only when the global information of cardiovascular risk factors was calculated in combination with the Bayes posttest information of baseline cTPA (TPA1) (SCORE2DMTPA, HR per quartile increase 1.71, p=0.0001), highlighting the improved predictive power of combining clinical and imaging data.

Carotid plaque progression and regression, comparison with other studies

A notable finding of this study is the observation of carotid plaque regression in approximately 50% of our cohort of 1,224 patients. According to current knowledge, negative plaque remodelling, at least in the coronary arteries, is rarely achieved, but progression can be abolished by high-dose statins with substantial LDL cholesterol lowering[46]. On the other hand, Spence et al. showed in 4’378 patients observed over 10 years that intensified medical preventive therapy was able to reduce cTPA with plaque regression in up to 50% of patients and plaque stabilization, defined as cTPA progression or regression of less than 5 mm^2 per year, was achieved in up to 31% of patients, whereas patients receiving usual care without the new paradigm of treating arteries rather than cardiovascular risk factors had plaque progression in up to 62% of patients[34]. Mendieta et al measured global carotid plaque volume in 3’471 patients over 6 years and found plaque regression in only 8% of patients, but the amount of regression had to be 100% in global plaque volume over time and the type of medical intervention in those with plaque progression at 3 years was not specified[47]. Fuster et al. found a significantly lower all-cause mortality in 732 patients aged 68 years over a median follow-up time of 8.9 years, if any plaque regression was observed (log-rank p=0.04)[48]. In plaque progressors (78%), mortality was about 5% in 3 years. Only 8.6% showed plaque regression and 13.4% remained free of carotid plaques. There was no report about an intensified medical intervention in those with plaque progression. These observational data imply a relevant impact of plaque progression and regression

on the occurrence of cardiovascular events and death. Serial imaging of plaque burden is likely to enhance the management of atherosclerosis and patients with plaque progression should receive intensified preventive therapy.

Should Atherosclerosis Imaging guide clinical decision?

As most cardiovascular events occur in patients at low cardiovascular risk [11], risk modification using emerging cardiovascular risk factors such as Atherosclerosis Imaging are recommended by the ESC and by AGLA [49]: “Assessment of arterial (carotid and/or femoral) plaque burden by arterial ultrasound should be considered as a risk modifier in individuals at low or moderate risk”. The ESC key message regarding risk modifying cardiovascular risk factors was: “Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and all risk factors require immediate attention. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium score >100, or extreme Lp(a)elevation”. ESC defined the following findings as categorizing patients to very high risk as follows: “Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.” Regarding the predictive value of imaging, the ESC stated: “Assessment of carotid or femoral plaque burden with ultrasound has also been demonstrated to be predictive of CV events, comparable to CAC [7,50], while the measurement of the carotid intima-media thickness is inferior to CAC score and carotid plaque detection [51–53]. Arterial (carotid and/or femoral) plaque burden on arterial ultrasound should be considered as a risk modifier in individuals at low or moderate risk: **Class IIa** recommendation, level of evidence B. CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk: **Class IIa** recommendation, level of evidence B.”

Atherosclerotic plaque as a guide for preventive medicine: ethical aspects

Numerous studies have documented that treatment of cardiovascular risk factors reduces both cardiovascular risk and the burden of non-calcified atherosclerotic plaque even in advanced stages of

atherosclerosis [54–56]. Animal studies have shown that aggressive lowering of LDL cholesterol to 0.3-0.9 mmol/l significantly reduces plaque lesion area even in advanced atherosclerotic plaques [57]. The reversibility of atherosclerosis with preventive intervention is a clinically relevant aspect, as has been shown extensively for lipid lowering drugs [18,20,23,25] and the improved prognosis with regression of coronary [21] and carotid [2,58] atherosclerosis. Tracking carotid atherosclerosis over time using a test that includes cTPA has been shown to reduce cTPA in more than 10'000 intensively statin-treated patients by Hackam in Canada [58], by Herder in Norway [59] and by Sturlaugsdottir in Iceland [37]. Because statins reduce cardiovascular risk, and because cTPA regression or progression is slower with statins or more intensive statin use, current evidence supports the idea that regression or stabilisation of carotid plaque is most likely to improve cardiovascular outcomes. This is further supported by Spence et al, in whom no progression or reduction of carotid plaque over time was a statistically significant predictor of cardiovascular events during follow-up [2].

To our knowledge, there is no formal proof of concept from controlled randomised and placebo-controlled interventional trials in humans that treatment of cardiovascular risk factors simultaneously reduces cardiovascular events and atherosclerotic plaque burden. The only available evidence comes from observational studies, which show a reduction in cardiovascular events in patients with stable or regressing plaque burden [2,58].

The question of whether it is ethical to wait for randomised clinical trials to treat cardiovascular risk factors is a complex one. Randomised clinical trials are considered the gold standard for evaluating the effectiveness of treatments. Current evidence suggests that it may not be ethical to wait for such trials with the inclusion of an untreated control group. For example, there is already strong evidence that treatment of cardiovascular risk factors reduces cardiovascular risk and reduces non-calcified atherosclerotic plaque. There is overwhelming evidence to support this association and no evidence of an opposite effect, such as an excess of non-calcified atherosclerotic plaque growth in those treated for cardiovascular risk factors compared with patients not treated for these cardiovascular risk factors (PubMed search 25.07.2023). There is evidence that noncalcified atherosclerotic plaque growth is associated with an increased risk of cardiovascular events, and death[48]. This association has been found in a variety of populations, including those with and without traditional risk factors for cardiovascular disease. In contrast, there is no evidence that treatment of cardiovascular risk factors, such as statins, leads to growth of non-calcified atherosclerotic plaque. Significant amounts of atherosclerotic plaque detected by cardiovascular imaging automatically place primary care patients in

the very high-risk category, as defined by the European Society of Cardiology [49]. According to the recommendations of these guidelines, patients with relevant amounts of atherosclerosis detected by imaging must be treated with known cardiovascular preventive therapies to achieve the predefined treatment goals of very high-risk patients. In our previous observational study, a significant protective effect was observed in patients with advanced carotid atherosclerosis and statin treatment [60]. Withholding preventive cardiovascular therapy is neither recommended nor ethical in individuals with significant amounts of atherosclerotic plaque on imaging, including older men and women [61]. In our opinion, it is unethical to conduct a controlled, randomised, placebo-controlled interventional trial in humans with atherosclerotic plaque. Such a trial can only be limited to early stages of atherosclerosis, when the risk of cardiovascular events in the placebo-treated group is very likely to remain low. Such a trial was proposed by Jennifer Robinson in 2018 in the "Proposed CURE ATHERO Trial"[62].

There is overwhelming evidence that plaque regression is an important clinical and therapeutic goal. In subjects with plaque progression, intensified preventive therapy is mandatory. cTPA appears to be a particularly attractive test for serial testing over time to observe the effects of prevention on subclinical atherosclerosis (Table 4), helping patients to improve their cardiovascular risk.

Cost-effectiveness of cTPA guided clinical atherosclerosis management

Furthermore, we attempted to relate these preventive medical effects to cost-effectiveness. Unfortunately, there is a lack of data in Switzerland to reliably compare clinical events with direct and indirect costs. However, our preliminary estimates suggest that practice-based, interdisciplinary, specific preventive treatment of cardiovascular risk costs approximately CHF 155.70 per patient per year. These costs lead to a return on investment of CHF 471 per patient-year in terms of direct and indirect costs of fatal and non-fatal cardiovascular events. Using the value of a statistical life-year lost, the return on investment was found to be CHF 3,318 per patient, so the total return on investment per patient for a treatment cost of CHF 155.70 per year was CHF 3,789. Obviously, we need better data on the relationship between avoided diseases and prevention costs in Switzerland. Overall, however, we assume that interdisciplinary prevention of cardiovascular disease is cost-effective, which is consistent with an analysis of the cost-effectiveness of cTPA in our previous publication [63].

Study limitations

Finally, several important limitations of this study must be acknowledged: **a)** the **linear extrapolation** of expected event rates increases the uncertainty in the long-term projections. The extrapolated

results might not accurately reflect real-world outcomes over the full 10-year period; **b) limited generalizability** due to a single cardiology center, limiting its applicability to other populations or healthcare settings. Differences in patient demographics, healthcare systems, and treatment plans could affect the reproducibility of results. The findings may not be generalizable to broader populations or different clinical environments; **c)** measurement of plaque progression and regression may vary based on imaging techniques and **operator skill**. Variability in measurement could lead to inconsistent assessments of atherosclerosis progression or regression, however, cTPA measurements are reliable, reproducible, and rapidly obtained [3]; **d) potential for overestimation of cost-effectiveness**, we acknowledge a lack of robust data in Switzerland to link clinical events with direct and indirect costs. The calculated cost per avoided event and the return on investment may be overestimated or underestimated due to incomplete or uncertain cost data; a recent report of the Swiss government about cost-effects of traffic [41] and associated costs of lives lost over an average time of about 10 years with an VSLY of about 240'000 lend important support to our assumptions; **e) the external validation** of risk models (e.g., SCORE2DMTPA) are not fully validated for the cohort in the study, and the calibration of these models for patients undergoing preventive interventions is uncertain. This raises questions about the accuracy of the models' risk predictions and the reliability of the calculated absolute risk reduction; **f)** Despite **LOG transformation of the variables** explaining plaque progression and regression, normality of the continuous data distribution was not achieved. Although more data are clearly needed, the effects of the explanatory variables (particularly SCORE2DMFINAL) on event-free survival and COX proportional hazards regression, which do not require a normal distribution of the explanatory variables, are consistent with the results from multiple regression. According to MedCalc, "Multiple linear regression analysis assumes that the residuals (the differences between the observations and the estimated values) follow a Normal distribution. This assumption can be evaluated with a formal test, or by means of graphical methods. The different formal Tests for Normal distribution may not have enough power to detect deviation from the Normal distribution when sample size is small. On the other hand, when sample size is large, the requirement of a Normal distribution is less stringent because of the central limit theorem. Therefore, it is often preferred to visually evaluate the symmetry and peakedness of the distribution of the residuals using the Histogram, Box-and-whisker plot, or Normal plot" (See Histogram for TPADIFF residuals in Figure 8). It can be concluded, that the multiple linear regression analysis is feasible, since, by visual inspection, the residuals of TPADIFF follow a near Normal distribution.

Conclusion

This is the first real-world study to monitor the long-term effects of intensified medical intervention to prevent cardiovascular events, particularly in individuals with carotid plaque progression as assessed by serial measurement of cTPA in an outpatient cardiology practice. Our data suggest that as cTPA increases over time, more intensive preventive medical evaluation and intervention may be warranted because plaque progression-an independent marker of cardiovascular risk-indicates increased risk even when traditional cardiovascular risk factors are well controlled, and this may also trigger intensified preventive medical measures or further diagnostic testing, such as measurement of Lp(a) or homocysteine.

Carotid TPA is a reliable and reproducible tool for the detection, quantification, and treatment of atherosclerosis. It is a cost-effective, low-cost, radiation-free, software-free, easy-to-learn, bedside imaging modality that is widely available using linear ultrasound probes and can be integrated into cardiovascular risk calculators using the BAYES theorem. The test has been validated and could be included in the detection and management of ASCVD risk in Switzerland. In contrast to coronary artery calcium (CAC), the cost-effectiveness of which is unknown, at least in Switzerland, is radiation- and software-dependent, and is not performed at the bedside, cTPA undoubtedly offers significant advantages over CAC, especially for the follow-up and monitoring of atherosclerosis.

Intensified preventive treatment of cardiovascular risk factors appears to lead to regression of carotid atherosclerosis, to a significantly lower event rate than in patients with plaque progression, the absence of fatal events from any cause suggests a preventive effect of preventive medical therapy on all-cause mortality, and this approach of treating arteries rather than risk factors may be cost-effective.

Tables

Table 1: Baseline and final visit characteristics, risk estimations and expected outcome, observed outcome

Kardiolab 2002-2024	Baseline	Baseline			Follow Up		
VARIABLES	**ALL**	**Progressors**	**Regressors**	**P**	**Progressors**	**Regressors**	**P**
Number (N, % primary prevention)	1224 (87%)	611	613		611	613	
ASCVD N (%) Baseline	149 (13)	86 (14)	70 (11)	NS			
AGE YEARS median (IQR)	57 (54-64)	57 (50-64)	57 (57-64)	NS	65 (58-73)	64 (56-71)	**0.0045**
BP SYSTOLIC (mmHg) median (IQR)	125 (119-137)	125 (120-135)	125 (118-139)	NS	127 (120-139)	127 (120-140)	NS
CHOLESTEROL (mmol/l) median (IQR)	5.6 (4.7-6.4)	5.5 (4.7-6.3)	5.6 (4.7-6.4)	NS	4.6 (3.8-5.6)	4.4 (3.7-5.3)	NS
HDL-C (mmol/l) median (IQR)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.4 (1.1-1.6)	NS	1.4 (1.1-1.7)	1.4 (1.1-1.7)	NS
LDL-C (mmol/l) median (IQR)	3.4 (2.7-4.1)	3.4 (2.7-4.1)	3.4 (2.7-4.2)	NS	2.5 (1.8-3.5)	2.4 (1.8-3.3)	NS
cTPA median (IQR)		45 (20-86)	64 (34-103)	**<0.001**	81 (43-140)	40 (20-75	**<0.0001**
SEX FEMALE N (%)	464 (38)	198 (32)	266 (43)	**0.009**			
DIABETES MELLITUS N (%)	130 (11)	54 (8.8)	76 (12.4)	**0.01**			
CURRENT SMOKER N (%)	278 (22.7)	146 (23.9)	132 (21.5)	NS	104 (17.0)	98 (16.0)	NS
SCORE2DM mean ± SD	5.3 (3.5)	5.4 (3.5)	5.3 (3.6)	NS	7.8 (5.1)	6.9 (4.8)	**0.0009**
SCORE2DMTPA mean ± SD	12.7 (10.7)	11.8 (10.7)	13.6 (10.6)	**0.003**	19.6 (13.1)	13.7 (12.5)	**<0.0001**
EVENT (ASCVD) N (%)	52 (4.2)				41 (6.7)	11 (1.8)	**<0.0001**
Extrapolated 10-Y event rate ASCVD %					9.1	3.1	**0.0001**
Expected EVENT 10 YEARS (ASCVD)	12.7				11.8	13.6	
FOLLOW UP TIME median	6.5				7.4	5.7	
Observed absolute risk reduktion					2.7	10.5	
Number needed to treat					36.6	9.6	

Table 2: univariate predictors of outcome (ASCVD events)

		HAZARD RATIO		
		Exp(b)	95% CI of Exp(b)	P
SEXCODE	SEX FEMALE	0.3395	0.1523 to 0.7566	**0.0082**
AGE1	AGE BASELINE	1.0366	1.0070 to 1.0672	**0.0132**
AGE2	AGE LAST VISIT	0.9958	0.9695 to 1.0228	0.758
BDS1	BP BASELINE	1.0191	1.0038 to 1.0346	**0.0014**
BDS2	BP LAST VISIT	0.9833	0.9653 to 1.0016	0.0735
CHOL1	CHOLESTEROL BASELINE	0.8055	0.6349 to 1.0218	**0.00748**
CHOL2	CHOLESTEROL FINAL VISIT	0.8278	0.6586 to 1.0404	0.1051
HDL1	HDL BASELINE	0.5515	0.2722 to 1.1176	0.55.15
HDL2	HDL LAST VISIT	0.502	0.2511 to 1.0036	**0.0413**
LDL1	LDL BASELINE	0.7549	0.5829 to 0.9777	**0.0331**
LDL2	LDL FINAL VISIT	0.8453	0.6478 to 1.1031	0.8435
TG1	TRIGLYCERIDES BASELINE	1.1334	0.9382 to 1.3693	0.1941
TG2	TRIGLYCERIDES FINAL VISIT	1.2556	1.0306 to 1.5297	**0.0239**
NIK1	NICOTIN USE BASELINE	1.1469	0.6121 to 2.1487	0.6688
NIK2	NICOTIN USE FINAL VISIT	1.584	0.8134 to 3.0843	0.1761
DIAB1	DIABETES BASELINE	2.6941	1.3469 to 5.3887	**0.0051**
DIAB2	DIABETES FINAL VISIT	1.9672	1.0655 to 3.6320	**0.0306**
VISITS	NUMBER OF VISITS	0.1932	0.1035 to 0.3604	**<0.0001**
TPA1	TPA BASELINE	1.009	1.0049 to 1.0130	**<0.0001**
MEDI1	MEDICATION CODE BASELINE	1.4376	1.1521 to 1.7938	**0.0013**
MEDI2	MEDICATION CODE FINAL VISIT	1.3257	1.0262 to 1.7127	**0.0310**
SCORE2DM	SCORE2 BASELINE	1.1580	1.0901 to 1.2303	**<0.0001**
SCORE2DMTPA	SCORE2 + TPA BASELINE	1.0612	1.0373 to 1.0856	**<0.0001**
SCORE2DMFINAL	SCORE2 FINAL	1.0182	0.9670 to 1.0720	0.4935
SCORE2DMFINALTPA	TPA FOLLOW UP	1.0076	1.0045 to 1.0107	**<0.0001**
SCORE2FINALTPAQUART	TPA FOLLOW UP QUARTILE	1.4399	1.0998 to 1.8851	**0.0058**
PR	CTPA PROGRESSSION / REGRESSI	2.5528	1.3033 to 5.0002	**0.0063**
TPADIFF	CTPA DIFFERENCE	1.0054	1.0002 to 1.0106	**0.0487**
TPADIFFQUART	CTPA DIFFERENCE QUARTILE	1.4561	1.1059 to 1.9171	**0.0074**
TPA1QUART	TPA QUARTILES BASELINE	1.6864	1.2992 to 2.1890	**0.0001**
TPA2	TPA BASELINE QUARTILE	1.6864	1.2992 to 2.1890	**0.0001**
TPA2QUART	TPA QUARTILES FINAL VISIIT	1.9306	1.4411 to 2.5863	**<0.0001**
PREV1	SECONDARY PREVENTION	3.3788	1.9084 to 5.9823	**<0.0001**

Table 3a: SCORE2DM, TPA1, SCORE2DMTPA and TPADIFF as predictors of 52 ASCVD events in forward COX proportional hazards regression

Coefficients and Standard Errors

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
SCORE2DMTPA	0.06035	0.01169	26.6283	<0.0001	1.0622	1.0381 to 1.0868
TPADIFF	0.005378	0.002505	4.6087	0.0318	1.0054	1.0005 to 1.0103

Variables not included in the model

SCORE2DM

TPA1

Table 3b: SCORE2DM, SCORE2DMTPA, SCORE2DMFINAL, SCORE2DMTPAFINAL, AND PR as predictors of 52 ASCVD events in forward COX proportional hazards regression

Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
SCORE2DMTPA	0.115	0.01711	45.1336	<0.0001	1.1218	1.0848 to 1.1601
PR=1	1.2641	0.3459	13.3558	0.0003	3.54	1.7971 to 6.9732

Variables not included in the model

SCORE2DM

Table 4a: Effect of SCORE2DM and SCORE2DMFINAL on PR, TPADIFF and EVENT using ROC analysis, logistic regression, and least square analysis

Prediction of plaque progression für PR Groups				
ROC analysis				
Variable	AUC	SE a	95% CI b	
SCORE2DM	0.51	0.0165	0.481 to 0.538	
SCORE2DMFINAL	0.563	0.0163	0.535 to 0.591	
p for difference	<0.0001			
Logistic regression analysis: PR groups				
Coefficients and Standard Errors				
Variable	Coefficient	Std. Error	Wald	P
SCORE2DM	0.0032763	0.016229	0.04076	0.84
SCORE2DMFINAL	0.039123	0.011947	10.7242	0.0011
Variable		Odds ratio	95% CI	
SCORE2DMFINALQUART=2		1.6064	1.1659 to 2.2133	0.0037
SCORE2DMFINALQUART=3		1.7276	1.2602 to 2.3683	0.0007
SCORE2DMFINALQUART=4		1.8333	1.3326 to 2.5222	0.0002
Least squares regression: TPADIFF			F-ratio	p
SCORE2DM			0.5514	0.4579
SCORE2DMFINAL			25.6861	<0.0001
Logistic regression analysis: EVENT				
Coefficients and Standard Errors				
Variable	Coefficient	Std. Error	Wald	P
SCORE2DMFINAL	0.049164	0.023916	4.2258	0.0398
Prediction of EVENTS				
ROC analysis				
Variable	AUC	SE a	95% CI b	P
SCORE2DMFINAL	0.601	0.0384	0.573 to 0.628	0.0086

Table 4b: Multiple forward regression to explain the effects of clinical, laboratory, and SCORE2DMFINAL on TPADIFF

Least squares multiple regression, N=1224, Method: Forward

Independent variables	Coefficient	Std. Error	95% CI	t	P	VIF
(Constant)	-1.59	10.53	-22.2604 to 19.0733	-0.1513	0.8798	
TIME	2.82	0.28	2.2683 to 3.3823	9.9519	<0.0001	1.058
BDS2	-0.22	0.07	-0.3832 to -0.07182	-2.8669	0.0042	1.112
LDL2	3.65	1.04	1.6106 to 5.6937	3.5097	0.0005	1.027
SCORE2DMFINAL	1.07	0.25	0.5817 to 1.5762	4.2573	<0.0001	1.155

Variables not included in the model: AGE2, CHOL2, DIAB2, NIK2

Table 4c: Multiple forward regression to explain the effects of clinical, laboratory, and SCORE2DMFINAL on TPADIFF, with LOG transformed data, where appropriate

Least squares multiple regression, N=1224, Method: Forward

Independent variables	Coefficient	Std. Error	95% CI	t	P	VIF
(Constant)	6.1308	15.3512	-23.9870 to 36.2486	0.3994	0.6897	
LOGTIME	35.5584	4.4698	26.7891 to 44.3278	7.9553	<0.0001	1.076
AGE2	-0.3997	0.1992	-0.7905 to -0.00880	-2.0061	0.0451	3.304
BDS2	-0.2594	0.08363	-0.4235 to -0.09536	-3.1023	0.002	1.203
LOGLDL2	19.4464	6.5114	6.6715 to 32.2213	2.9865	0.0029	1.078
LOGSCORE2DMFINAL	32.216	7.5605	17.3828 to 47.0491	4.2611	<0.0001	3.492

Variables not included in the model: DIAB1, LOGCHOL2

Table 4d: Summary statistics of continuous explaining variables

Summary statistics						
Variable	**TPADIFF**	**AGE2**	**BDS2**	**LOGCHOL2**	**LOGLDL2**	**LOGSCORE2DMFINAL**
Sample size	1224	1224	1224	1224	1224	1224
Lowest value	-264	27.6521	90	0.1139	-0.3979	-0.3768
Highest value	192.4	90.2027	186	1.0453	0.8808	1.5966
Arithmetic mean	7.0569	64.2219	129.5392	0.6543	0.3873	0.773
95% CI for the Arithmetic mean	4.6529 to 9.4610	63.6187 to 64.8251	128.6723 to 130.4061	0.6475 to 0.6610	0.3768 to 0.3979	0.7567 to 0.7894
Median	0	64.5589	127	0.6532	0.3979	0.7814
95% CI for the median	0.0000 to 2.0000	63.9507 to 65.0706	126.0000 to 128.0000	0.6435 to 0.6628	0.3802 to 0.3979	0.7642 to 0.8013
Variance	1837.8814	115.6907	238.9944	0.0143	0.03535	0.08492
Standard deviation	42.8705	10.756	15.4594	0.1196	0.188	0.2914
Relative standard deviation	6.0749 (607.49%)	0.1675 (16.75%)	0.1193 (11.93%)	0.1828 (18.28%)	0.4854 (48.54%)	0.3770 (37.70%)
Standard error of the mean	1.2254	0.3074	0.4419	0.003418	0.005374	0.008329
Coefficient of Skewness	0.6204 (P<0.0001)	-0.3203 (P<0.0001)	0.5031 (P<0.0001)	-0.1096 (P=0.1169)	-0.2557 (P=0.0003)	-0.2790 (P=0.0001)
Coefficient of Kurtosis	3.4995 (P<0.0001)	0.07883 (P=0.5384)	0.08324 (P=0.5192)	0.2366 (P=0.1099)	0.02704 (P=0.7945)	0.1109 (P=0.4085)
Shapiro-Wilk test	W=0.9348	W=0.9914	W=0.9754	W=0.9956	W=0.9929	W=0.9951
Reject normality	<0.0001	<0.0001	<0.0001	0.0014	<0.0001	0.0005

Table 5: Suggested cost-effectiveness model

Annualized Model in 1'000 Patients		
Direct and indirect cost model	**No Prevention**	**Prevention**
Medical Cost	0	155 650
Expected and observed events	12.7	5.8
Cost per event	90 794	90 794
Cost for all events	1 153 084	526 605
Cost for all events plus medical cost	1 153 084	682 255
Cost Saving (no prevention minus prevention		470 829
Cost Saving per Patient (Return on Investment)		471
Value of a statistical life (VSL) model	**No Prevention**	**Prevention**
Ratio of fatal to non-fatal event 2:9		
Number of Deaths	2.30909	1.05455
Number of avoided deaths		1.25455
Cost per death (VSLY)	270 000	270 000
Cost of 10-year life lost	2 700 000	2 700 000
Cost of deaths to society	6 234 545	3 387 273
Total Costs + VSL	7 387 629	4 069 528
Cost saving (no prevention minus prevention)		3 318 101
Total Costs + VSL / Patient (Return on investment)		3 318
Return on investment (costs + VSL) per patient		**3 789**

Figures

Figure 1: Forward Cox proportion hazards regression for cTPA progressors and regressors (PR) and aggregated clinical (SCORE2DM) and aggregated clinical and imaging information (SCOREDMTPA) in 1’224 patients

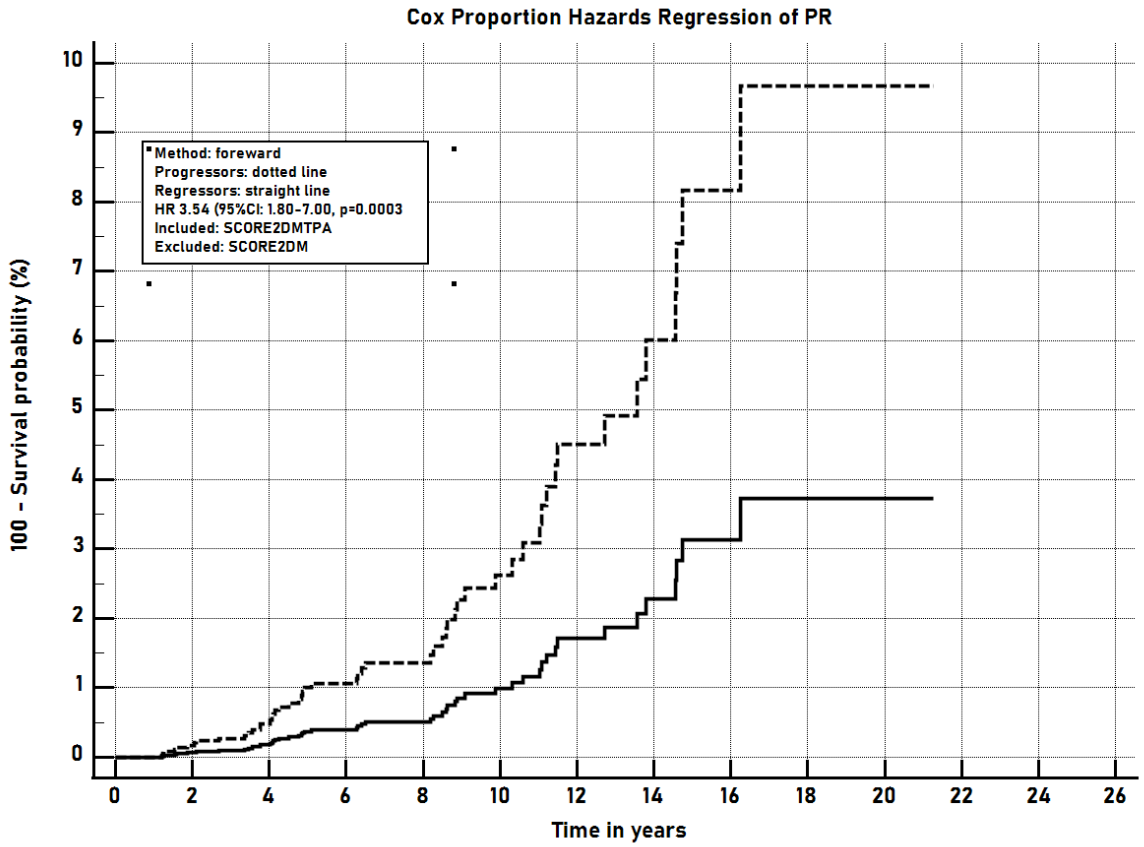


Figure 2: Kaplan Meier survival curves in cTPA progressors (dotted line) and regressors (straight line). Also displayed is the estimated 10-year ASCVD risk derived from SCORE2DMTPA.

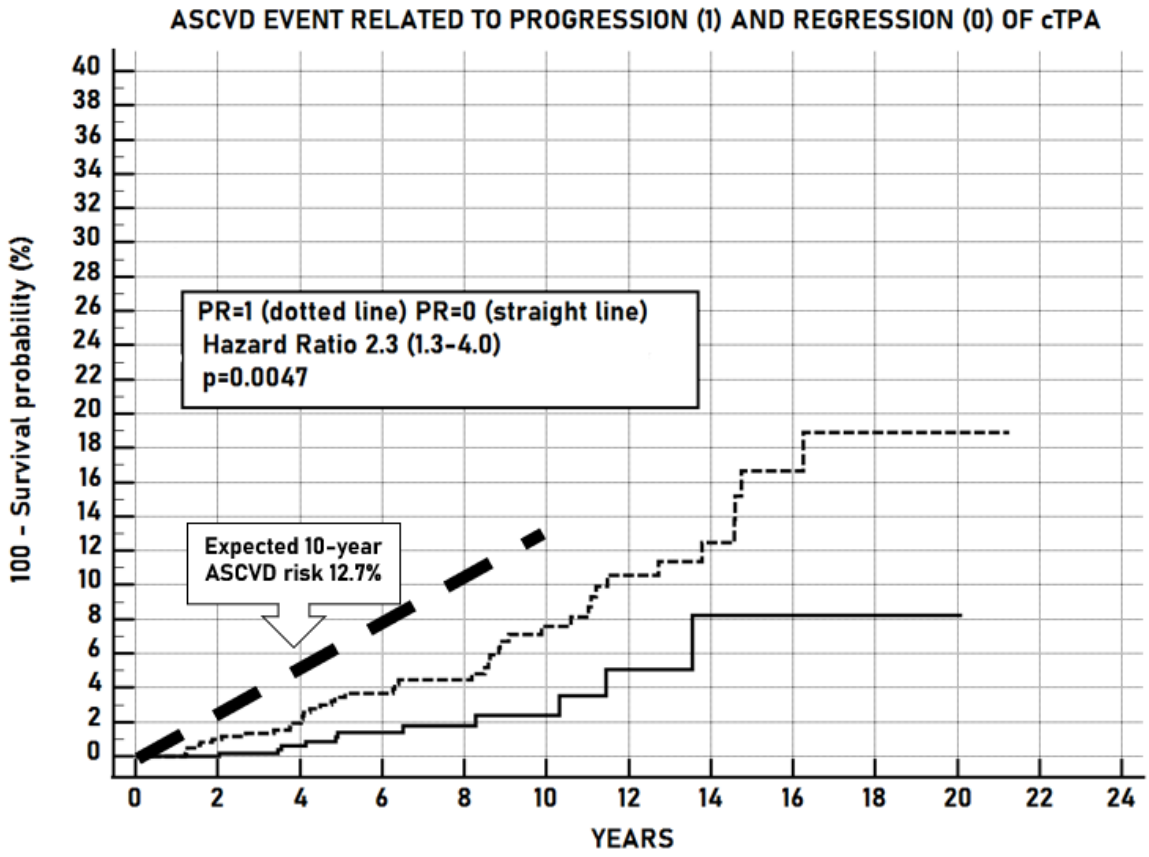


Figure 3: Probit regression dose-response plot of the probability of an individual being a cTPA progressor with the explaining variable SCORE2DMFINAL

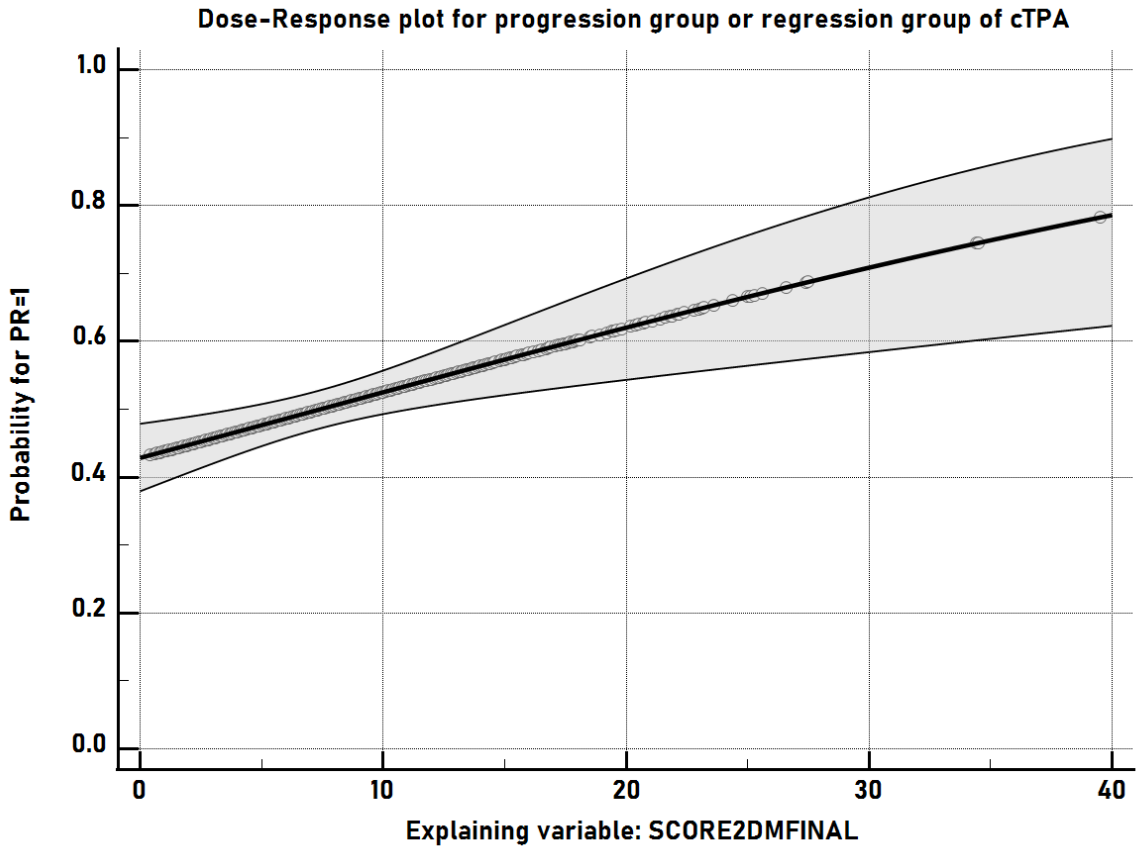


Figure 4: Simple least square linear regression plotted for the difference of cTPA and SCORE2DMFINAL.

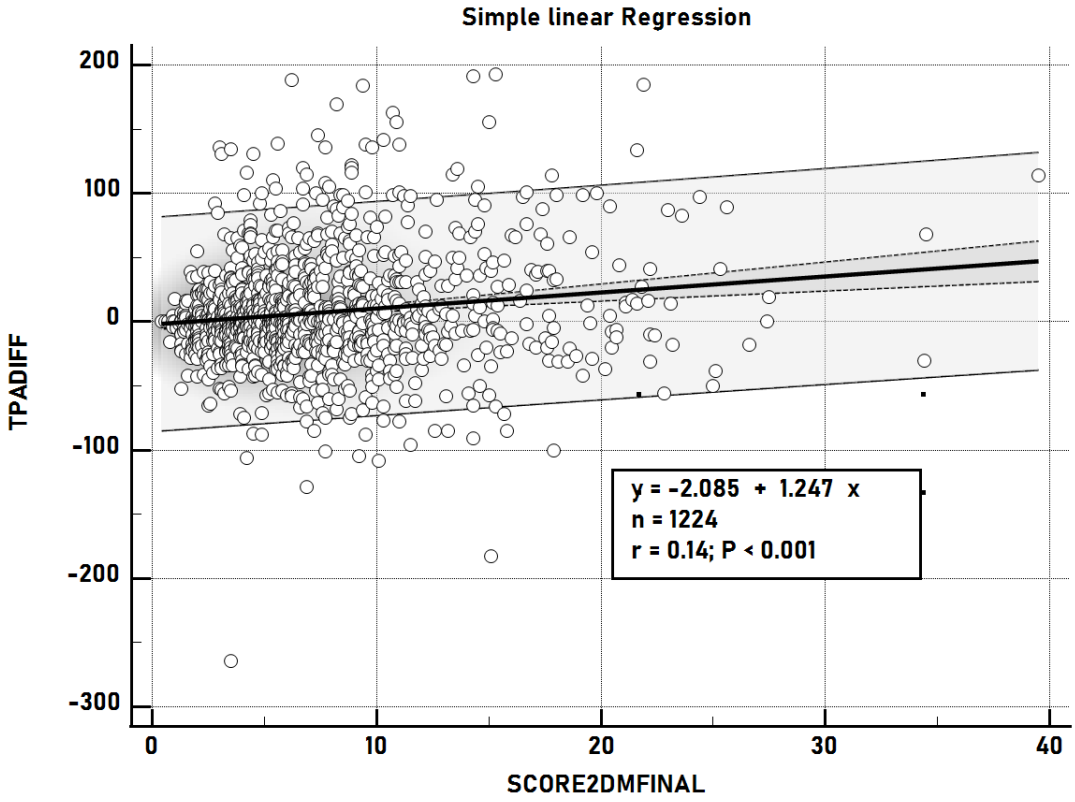


Figure 5: Cox proportional hazard regression for ASCVD events and sex in the total group with recorded events (N=1'983)

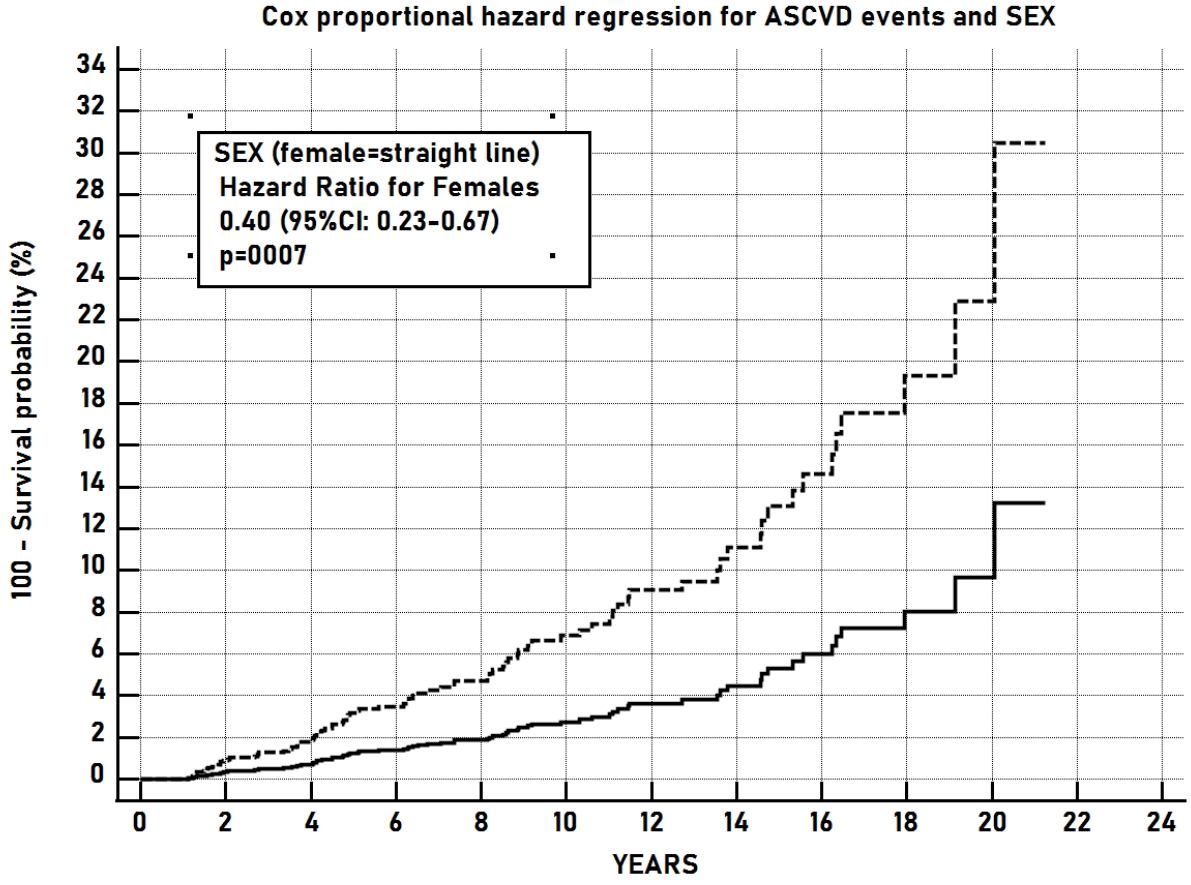


Figure 6: Probit regression dose-response plot of the probability of an individual having an ASCVD event with the explaining variable TPADIFF

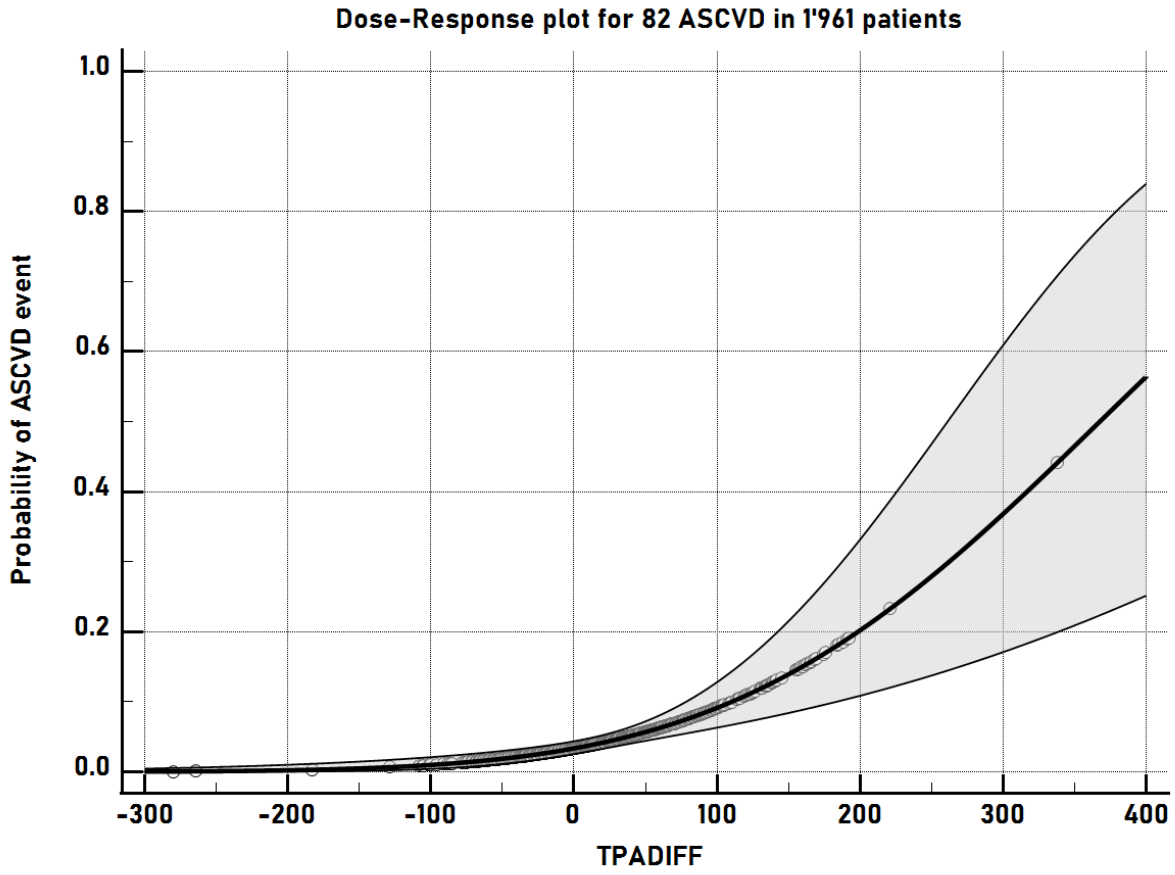


Figure 7: Distribution plot of variables explaining TPADIFF, in part after LOG transformation (further details in Table 4c)

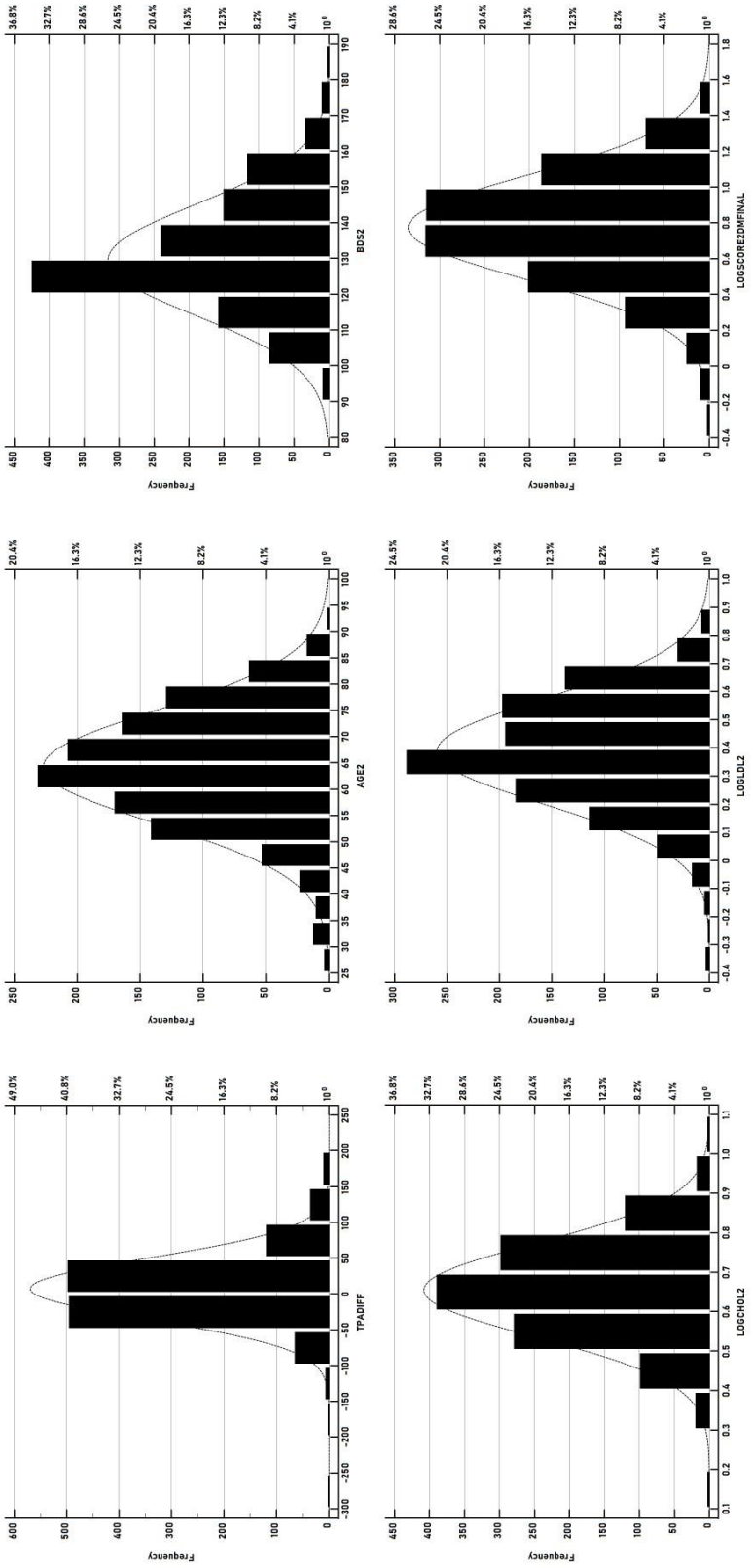
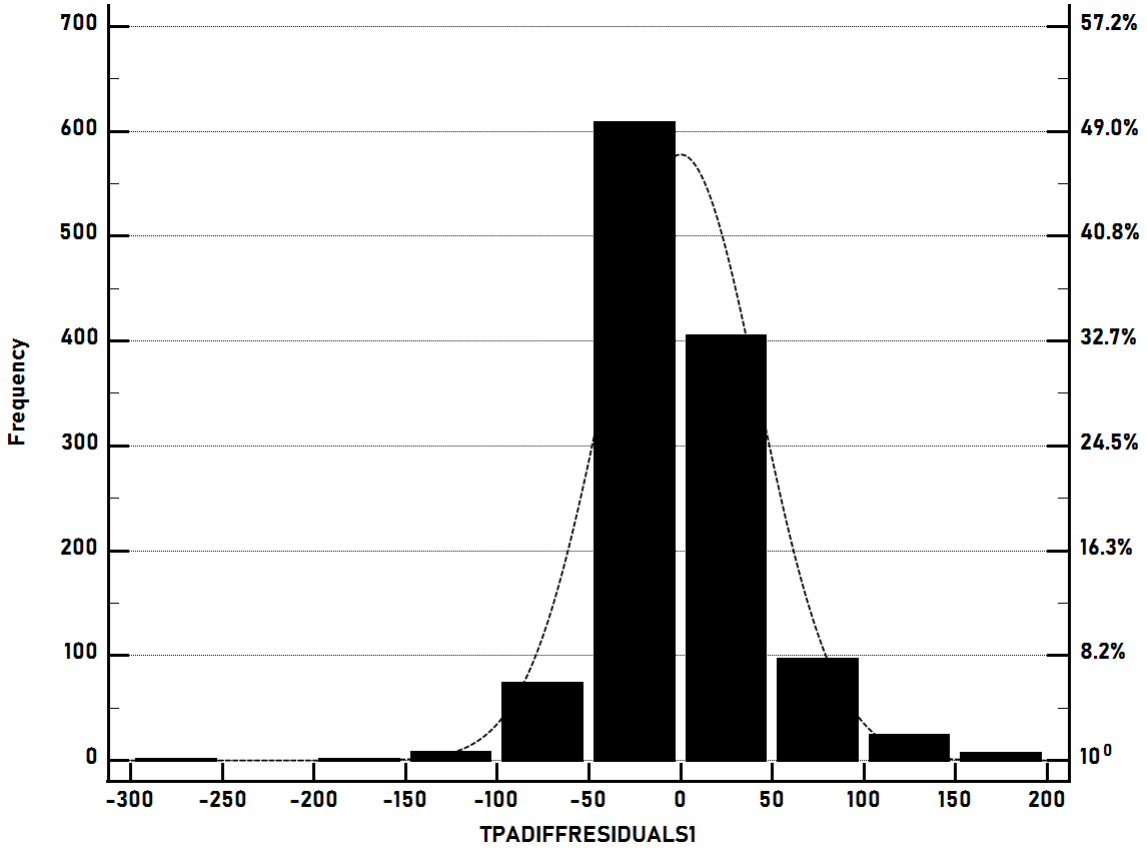


Figure 8: Distribution plot of TPADIFF residuals in the multivariate regression model variables described in Figure 7 and Table 4d.



References

1. Liuzzo G, Ridker PM. Universal Screening for hsCRP in Patients with Atherosclerotic Disease: A Major Therapeutic Opportunity. *Eur Heart J*. Epub ahead of print 30 August 2024. DOI: 10.1093/EURHEARTJ/EHAE565.
2. Spence JD, Eliasziw M, Dicicco M, et al. Carotid Plaque Area: a tool for targeting and evaluating vascular preventive therapy. *Stroke* 2002; 33: 2916–2922.
3. Azarpazhooh MR, Mathiesen E, Rundek T, et al. Reliability, reproducibility and advantages of measuring carotid total plaque area. *Journal of the American Society of Echocardiography*. Epub ahead of print 2022. DOI: 10.1016/j.echo.2021.12.016.
4. Romanens M, Sudano I, Adams A, et al. Sonographic assessment of carotid atherosclerosis: preferred risk indicator for future cardiovascular events? *Swiss Med Wkly* 2019; 149: w20142.
5. Herrington W, Lacey B, Sherliker P, et al. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circ Res* 2016; 118: 535–546.
6. Tarkin JM, Dweck MR, Evans NR, et al. Imaging Atherosclerosis. *Circ Res* 2016; 118: 750.
7. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: The bioimage study. *J Am Coll Cardiol* 2015; 65: 1065–1074.
8. Sillesen H, Muntendam P, Adourian A, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: Comparison with other tests for subclinical arterial disease in the high risk plaque bioimage study. *JACC Cardiovasc Imaging* 2012; 5: 681–689.
9. Östgren CJ, Söderberg S, Festin K, et al. Systematic Coronary Risk Evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: A population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study. *Eur J Prev Cardiol*. Epub ahead of print 2020. DOI: 10.1177/2047487320909300.
10. Baber U, Mehran R, Sartori S, et al. 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* 2014; 63: A998.
11. Romanens M, Adams A, Sudano I, et al. Prediction of cardiovascular events with traditional risk equations and total plaque area of carotid atherosclerosis: The Arteris Cardiovascular Outcome (ARCO) cohort study. *Prev Med (Baltim)*; 147. Epub ahead of print 1 June 2021. DOI: 10.1016/j.ypmed.2021.106525.
12. Lo-Kioeng-Shioe MS, Rijlaarsdam-Hermsen D, van Domburg RT, et al. Prognostic value of coronary artery calcium score in symptomatic individuals: A meta-analysis of 34,000 subjects. *Int J Cardiol* 2020; 299: 56–62.
13. Tarkin JM, Dweck MR, Evans NR, et al. Atherosclerosis Compendium Imaging Atherosclerosis. Epub ahead of print 2016. DOI: 10.1161/CIRCRESAHA.115.306247.
14. Poznyak A V., Sukhorukov VN, Eremin II, et al. Diagnostics of atherosclerosis: Overview of the existing methods. *Frontiers in Cardiovascular Medicine*; 10. Epub ahead of print 2023. DOI: 10.3389/fcvm.2023.1134097.
15. Arbab-Zadeh A, Fuster V. The myth of the ‘vulnerable plaque’: transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015; 65: 846–855.
16. Romanens M, Sudano I, Adams A, et al. 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.
17. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study. *Radiology* 2005; 236: 477–484.

18. Kalanuria AA, Nyquist P, Ling G. The prevention and regression of atherosclerotic plaques: emerging treatments. *Vasc Health Risk Manag* 2012; 8: 549–561.
19. Dave T, Ezhilan J, Vasnawala H, et al. Plaque regression and plaque stabilisation in cardiovascular diseases. *Indian J Endocrinol Metab* 2013; 17: 983–9.
20. Bogiatzi C, Spence JD. Ezetimibe and regression of carotid atherosclerosis: importance of measuring plaque burden. *Stroke* 2012; 43: 1153–1155.
21. Dohi T, Miyauchi K, Okazaki S, et al. Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. *J Atheroscler Thromb* 2011; 18: 231–9.
22. Sato Y, Inoue F, Yoshimura A, et al. Regression of an atherosclerotic coronary artery plaque demonstrated by multislice spiral computed tomography in a patient with stable angina pectoris. *Heart Vessels* 2003; 18: 224-226 ST-Regression of an atherosclerotic cor.
23. Migrino RQ, Bowers M, Harmann L, et al. Carotid plaque regression following 6-month statin therapy assessed by 3T cardiovascular magnetic resonance: Comparison with ultrasound intima media thickness. *Journal of Cardiovascular Magnetic Resonance*; 13. Epub ahead of print 2011. DOI: 10.1186/1532-429X-13-37.
24. Rusconi C, Raddino R. Atherosclerotic Plaque Regression and Arterial Reverse Remodelling in Carotid and Femoral Arteries by Statin Use in Primary Prevention Setting : Ultrasound Findings. In: *Ultrasound Imaging - Medical Applications*. 2011.
25. Rollefstad S, Ikdahl E, Hisdal J, et al. Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study. *Arthritis & Rheumatology* 2015; 67: 1718–1728.
26. E Kadoglou NP, Sailer N, Moumtzouoglou A, et al. From the Society for Vascular Surgery Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization. DOI: 10.1016/j.jvs.2009.07.119.
27. Di Giovanni G, Nicholls SJ. Intensive lipid lowering agents and coronary atherosclerosis: Insights from intravascular imaging. *Am J Prev Cardiol* 2022; 11: 100366.
28. Rishi Trivedi MMJBMMRSBMFMC-AM. The Agatston Coronary Artery Calcium Score in Statin Users: Recent Insights from the CAC Consortium and Pathways Forward - American College of Cardiology, https://www.acc.org/latest-in-cardiology/articles/2021/01/19/14/27/the-agatston-coronary-artery-calcium-score-in-statin-users (accessed 20 August 2022).
29. Puri R, Nicholls SJ, Shao M, et al. Impact of Statins on Serial Coronary Calcification During Atheroma Progression and Regression. *J Am Coll Cardiol* 2015; 65: 1273–1282.
30. Tarkin JM, Dweck MR, Rudd JHF. Imaging as a surrogate marker of drug efficacy in cardiovascular disease. *Heart* 2019; 105: 567–578.
31. Dave T, Ezhilan J, Vasnawala H, et al. Plaque regression and plaque stabilisation in cardiovascular diseases. *Indian J Endocrinol Metab* 2013; 17: 983.
32. Dawson LP, Lum M, Nerleker N, et al. Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2022; 79: 66–82.
33. Páramo JA, Civeira F. Is regression of atherosclerotic plaque possible? *Clínica e Investigación en Arteriosclerosis (English Edition)* 2017; 29: 46–50.
34. Spence JD, Hackam DG, Spence D, et al. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. *Stroke* 2010; 41: 1193–1199.
35. Sturlaugsdottir R, Aspelund T, Sigurdsson S, et al. Cardiovascular risk factors association with total plaque area and progression in a general population: The refine-reykjavik study. *Atherosclerosis* 2015; 241: e49.
36. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, et al. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. *BMJ Open* 2016; 6: e012457.
37. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, et al. Predictors of carotid plaque progression over a 4-year follow-up in the Reykjavik REFINE-study. *Atherosclerosis* 2018; 269: 57–62.
38. Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. *J Am Coll Cardiol* 2013; 62: 732–739.

39. Felder S, Jüni P, Meier CA, et al. *SMB Statin Recommendation*, https://www.swissmedicalboard.ch/fileadmin/public/news/2013/bericht_smb_statine_primaerpraevention_lang_2013.pdf (2014).
40. Mach F, Lyrer P, Hullin R, et al. Productivity loss and indirect costs in the year following acute coronary events in Switzerland. *Cardiovasc Med*. Epub ahead of print 23 November 2022. DOI: 10.4414/CVM.2021.02143.
41. Externe Effekte des Verkehrs 2021. Epub ahead of print 2024. DOI: https://www.are.admin.ch/dam/are/de/dokumente/verkehr/dokumente/bericht/GKV21_SB_final.pdf.download.pdf/GKV21_SB_final.pdf.
42. Schwappach DLB. Resource allocation, social values and the QALY: a review of the debate and empirical evidence. *Health Expect* 2002; 5: 210.
43. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117: 743–753.
44. Romanens M, Adams A, Wenger M, et al. Prognostic impact of carotid plaque imaging using total plaque area added to SCORE2 in middle-aged subjects: the ARteris Cardiovascular Outcome (ARCO) cohort study. *Swiss Med Wkly* 2024; 154: 3735.
45. Romanens M, Ackermann F, Spence JDJD, et al. Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics. *Eur J Cardiovasc Prev Rehab* 2010; 17: 18–23.
46. Sarraju A, Nissen SE. Atherosclerotic plaque stabilization and regression: a review of clinical evidence. *Nat Rev Cardiol*. Epub ahead of print 2024. DOI: 10.1038/S41569-023-00979-8.
47. Mendieta G, Pocock S, Mass V, et al. Determinants of Progression and Regression of Subclinical Atherosclerosis Over 6 Years. *J Am Coll Cardiol* 2023; 82: 2069–2083.
48. Fuster V, García-Álvarez A, Devesa A, et al. Influence of Subclinical Atherosclerosis Burden and Progression on Mortality. *J Am Coll Cardiol* 2024; 84: 1391–1403.
49. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111–188.
50. Perrone-Filardi P, Achenbach S, Mohlenkamp S, et al. Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Soci. *Eur Heart J* 2011; 32: 1986–1993.
51. Yeboah J, Mcclelland RL, Polonsky TS, et al. Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals. *JAMA* 2012; 308: 788–797.
52. Den Ruijter HM, Peters S a E, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. *JAMA* 2012; 308: 796–803.
53. Lorenz M, Schaefer C, Steinmetz H, et al. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J* 2010; 31: 2041–2048.
54. Wilkins JT, Gidding SS, Robinson JG. Can Atherosclerosis Be Cured? *Curr Opin Lipidol* 2019; 30: 477.
55. Robinson JG, Williams KJ, Gidding S, et al. Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein b lipoproteins earlier in life. *J Am Heart Assoc*; 7. Epub ahead of print 1 October 2018. DOI: 10.1161/JAHA.118.009778.
56. Williams KJ, Tabas I. Lipoprotein retention- and clues for atheroma regression. *Arterioscler Thromb Vasc Biol* 2005; 25: 1536–1540.
57. Björkegren JLM, Hägg S, Talukdar HA, et al. Plasma cholesterol-induced lesion networks activated before regression of early, mature, and advanced atherosclerosis. *PLoS Genet*; 10. Epub ahead of print February 2014. DOI: 10.1371/JOURNAL.PGEN.1004201.
58. Hackam DG, Spence JD. Decline in the Severity of Carotid Atherosclerosis and Associated Risk Factors From 2002 to 2014. *Stroke* 2018; 49: 6–8.
59. Herder M, Arntzen KA, Johnsen SH, et al. Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008. *Arterioscler Thromb Vasc Biol* 2013; 33: 858–62.

60. Adams A, Bojara W, Romanens M. Ultraschalluntersuchung der A. carotis zur verbesserten Vorhersage kardiovaskulärer Ereignisse und der Wirkung einer Statinbehandlung bei fortgeschrittener Atherosklerose. *Herz*. Epub ahead of print 5 July 2023. DOI: 10.1007/s00059-023-05197-z.
61. Raggi P, Gongora MC, Gopal A, et al. Coronary Artery Calcium to Predict All-Cause Mortality in Elderly Men and Women. Epub ahead of print 2008. DOI: 10.1016/j.jacc.2008.04.004.
62. Robinson JG, Williams KJ, Gidding S, et al. Eradicating the Burden of Atherosclerotic Cardiovascular Disease by Lowering Apolipoprotein B Lipoproteins Earlier in Life. *J Am Heart Assoc* 2018; 7: 1–12.
63. Romanens M, Adams A, Bojara W, et al. Cost-effectiveness analysis of statins in primary care: results from the Arteris cohort study. *Swiss Med Wkly*; 151. Epub ahead of print 2021. DOI: 10.4414/smw.2021.20498.