Low risk factor based detection rates of old arteries in middle-aged women. An observation from a derivation and a confirmation group in Switzerland and Germany.

Prelimary communication / Paper in preparation for submission

December 10th, 2016

Germany: Ansgar Adams, MD
adams-praevention-herzinfarkt
www.adams-praevention-herzinfarkt.de

Switzerland: Michel Romanens, MD
Vascular Risk Foundation
www.varifo.ch

Database and Statistics
Laurent Estoppey
www.varifo.ch

Abstract

Background

Intensity of preventive therapy in primary prevention is guided by predicted absolute risk of future cardiovascular disease. The clinical performance with the underlying sensitivity and specificity of risk calculators depends primarily on the recommended treatment decision threshold and is poorly validated.

Methods

We assess the prevalence and the detection rate of old arteries (70 years or more) in healthy primary care subjects in Switzerland (derivation group) and in Germany (independent observation, confirmation group). We compared sensitivity, specificity, and discriminatory performance of SCORE, PROCAM and AGLA coronary risk calculators to detect arterial age ≥ 70 years ("old arteries") in 3'248 healthy subjects without preventive medication in Switzerland and Germany.

Results

In patients age 40 – 65 years, 12% of Swiss women had old arteries (11% in men), similar to Germany (11% and 17%). We found a sensitivity of 6% at the 10% AGLA-threshold in women and 30% in men in Switzerland, confirmed for PROCAM with a sensitivity of 8% in women and 56% in men in Germany. At the SCORE threshold of 5%, sensitivity ranged between 0% (Germany) to 5% (Switzerland) in women and between 16% and 18% in men, respectively. Subjects with old arteries were 5 years older (56 versus 51 years) and showed higher rates of smoking, higher systolic blood pressure and higher LDL cholesterol.

Conclusions

In women aged 40-65 years, the prevalence of old arteries is one out of seven and the detection rate of AGLA and SCORE is 6% and 5% respectively, validated by a large German group. Low risk factor based detection rates at current decision thresholds of old arteries was clearly evidenced in middle-aged women. Further research is needed to validate the prognostic impact of current risk assessment tools, especially in women.

[word count:]

Abbreviations and Acronyms

TPA, Total plaque area; risk charts, women, carotid plaque imaging, arterial age

Introduction

The detection rate of primary care subjects at a high cardiovascular risk is low in intermediate age groups (1,2). A clinician's preventive efficacy is dependent on meaningful sensitivity thresholds of cardiovascular risk equations. A "present time" confirmation to assesses the accuracy of coronary risk calculators can be derived from patients admitted for a first myocardial infarction (2,3). A low detection rate for cardiovascular events was e.g. confirmed by the Copenhagen General Population Study, where 68 fatal and 767 fatal and non-fatal cardiovascular events occurred over an observation time of 7 years. Sensitivity at the 5% SCORE level was 42% and 26% respectively (3).

Instead of waiting until a myocardial infarction occurs, atherosclerosis imaging offers a second "present time" confirmation to evaluate coronary risk calculators, e.g. by measuring arterial age derived from the total carotid plaque burden as published by our group previously (4). Such information can therefore be used to test risk calculators for their performance to detect old arteries. For the purpose of this study, we defined old arteries as an arterial age of 70 years or more. We assessed the detection rates of old arteries in a group of healthy in Swiss women and men (derivation group, age range 40-65 years) and hypothesized, that women are discriminated in comparison to men due to lower detection rates of old arteries at current decision thresholds in Switzerland for PROCAM / AGLA and SCORE. We tried to confirm our results independently in a German group of primary care subjects (confirmation group, equal age range of 40-65 years).

Materials and methods

Subject selection

Subjects were assessed at the practice based level as described elsewhere (4). In the Swiss Imaging Center in Olten, subjects were referred by their primary care physician (58%) or self-referred to the vascular risk foundation (42%,(5)). In the German Center in Koblenz, all subjects were referred within a working medicine setting (6). Subjects had to be free of cardiovascular symptoms or disease and not currently being treated against high blood pressure or cholesterol. Laboratory values, blood pressure and medical history were measured locally and entered into a data spread-sheet (Excel, Microsoft, Richmond, USA).

Ethical aspects

Subjects with self-referral to the Vascular Risk Foundation gave written consent. The study protocol was approved by the local ethical committee of Solothurn, Switzerland. Practice based subjects were entered into an anonymized study registry, for which current legislation in Switzerland and Germany does not require formal ethical committee consent.

Carotid imaging

Burden of longitudinal carotid plaque surface was imaged with a high resolution ultrasound linear transducer probe (7.5–12.0 MHz), which identified plaques with intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed up to the total plaque area (TPA) in mm^2. All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. Arterial age was calculated as previously published (4).

Computation of cardiovascular risk

Cardiovascular risk was computed using the published risk formulae in an Excel spread sheet. We used the European Society of Cardiology risk calculators for low risk populations (SCORE (7)) and the German PROCAM risk (8). For Switzerland, PROCAM risk was multiplied by the factor 0.7 (according to the Swiss AGLA guidelines 2014 (9)) in order to calculate the AGLA risk score.

Statistics

We used MedCalc software (Version 16.8.4) to calculate ROC curves and their comparisons (10). Level of statistical significance was set at $p < 0.05$.

Results

Patient characteristics

We assessed 5'383 healthy German and Swiss subjects from the Arteris Group aged 20-80 years. We excluded 1'265 subjects who were outside the pre-specified age range of 40 to 65 years, and we further excluded 870 subjects with statin or antihypertensive treatment (Fig. 1). Therefore, 3'248 subjects remained for further evaluation. Clinical and ultrasound information from carotid plaques for Swiss (CH) subjects (N=1'429, derivation group) was collected and compared to 1'819 German (DE) subjects (confirmation group). CH subjects were older (54±7 versus 50±6 years) with comparable results for the number of females and current smokers in each group, for systolic blood pressure, lipids, and global risk scores (Table 1). Average 10-year risk among groups was low. Swiss prevalence of arterial age ≥ 70 (AA70) was 12% in women and 11% in men (11% and 17% respectively in Germany). AA70 was found for a TPA of 58 mm^2 in women and for a TPA of 105 mm^2 in men, corresponding to the 93^{th} and 96^{th} percentile in the Tromsø cohort (N= 6'226, personal communication) and corresponding to the 80^{th} and 86^{th} percentile in the Arteris cohort (N=5'383, Table 2).

Sensitivity and Specificity of high risk coronary risk thresholds for the detection AA70

At current intervention thresholds (AGLA / PROCAM ≥ 10% 10 year risk, SCORE ≥ 5% 10 year risk), the sensitivity to detect AA70 was 6% (95%CI: 2%-14%) in Swiss women (significantly higher in men with 30%, 95%CI 21%-41%) and was 8% (95%CI 3%-15%) in German women (significantly higher in men with 56%, 95%CI 48%-64%); similarly, for SCORE, sensitivity for Swiss women was 5% (18% in men) and was 0% for German women (16% in men, Table 3). For lower risk decision thresholds, as expected, sensitivity increased and specificity decreased: for AGLA 2%, sensitivity was 54% in women (90% in men) and for PROCAM 2% was 47% in women and 96% in men.

Comparison of subjects with and without AA70

Subjects with AA70 (N=394) were significantly older (average and SD 5±6 years) and were more frequently current smokers (39% versus 22%) and highly significant differences ($p<0.0001$) for total cholesterol, LDL cholesterol, blood pressure, and SCORE and PROCAM respectively were found (Table 4). The average arterial age in women was 79 years and 76 years in men.

C-Statistics of coronary risk calculators

We assessed the diagnostic accuracy of PROCAM and SCORE to detect women and men with AA70 (Table 5, Figure 2). In men, SCORE performed significantly better than PROCAM ($p=0.0066$), whilst no difference was found in women. Further AUC was satisfactory with ranges between 0.73 to 0.77.

Discussion

In a middle age group of 3'238 practice based subjects aged 40-65 years, we found a prevalence of old arteries (AA70) in about 1 of 7 in women living in Switzerland, with similar rates for Swiss men and confirmed for women and men living in Germany. The prevalence of old arteries is substantial in middle age and detecting it may improve cardiovascular risk.

In Swiss women with old arteries, average arterial age was 79 years in 82 women, average chronological age was 57 years, resulting in a difference of 22 years. The detection rate of old arteries was only 6% (5 of 82 women) for the AGLA cutoff of 10% and was only 5% the SCORE cutoff of 5%. These results were confirmed by independent observations in Germany (confirmation group) with detection rates 8% and 0% respectively (Table 3).

In Swiss men with old arteries, average arterial age was 77 years in 83 men, average chronological age was 56 years resulting in a difference of 21 years. The detection rates of old arteries in men were higher than in women (30% for PROCAM and 18% for SCORE, respectively) and even higher in German men (56% and 16%, respectively, Table 3).

Our results indicate that women with extensive carotid plaque formation (above the 80th percentile, average age 79 years in women and 77 years in men) in mid-life remain frequently undetected. This may cause unnecessary delays for an intensified primary prevention of cardiovascular events. The conundrum of risk prediction is not resolved by the current methods especially in women (11). From a clinical point of view, sensitivities of coronary risk calculators should to be as high as possible in order to create a situation, where high cardiovascular risk is detected, since sensitivity (detection rate) is a composite of those with disease (true positives = those with disease) and is low, when positives (those with disease) are missed frequently (false negatives).

Further, we found a lower diagnostic performance using ROC analysis for PROCAM to detect old arteries in men (Table 5). This calls for a population based prospective study about the prognostic accuracy of the PROCAM algorithm when compared to SCORE in men in Germany and Switzerland.

Although ROC analysis show generally good discriminatory performance of coronary risk calculators externally (12) and in our study, reliance on recalibration based on predicted-to-observed (P/O) event ratio in cohorts where true negatives (the non-diseased) by far outweigh numerically true positives (the diseased) usually creates a calibration in favor of true negatives [1,2,18]. Such a down-calibration was performed with the Swiss AGLA coronary risk calculator, which is the German PROCAM coronary

risk calculator multiplied by 0.7 (13), therefore reducing coronary risk as compared to Germany by 30%. As outlined in Table 3, an AGLA risk of 4% is better suited for the definition of intermediate or higher risk in Swiss women (sensitivity 33%, specificity 92%) and current Swiss guidelines may therefore need revision in favor of women. To obtain acceptable sensitivities, decision thresholds should also be lowered in women for SCORE to 1%-2% and in men to 3%-4%.

We assessed the prognostic impact of our arterial age function derived from TPA in 1500 men and women (4) by substituting chronological age for arterial age in the PROCAM function to detect 13 myocardial infarction having occurred in 684 Canadian subjects over a time period of 2.6 years (4,14). AUC was improved by 0.13 from 0.65 to 0.78 (p=0.02). Therefore, our arterial age function is validated externally and has proven prognostic impact. Old arteries are an accepted surrogate marker for cardiovascular risk, it is acknowledged, that the presence of carotid plaque has to be interpreted as a high risk cardiovascular finding (15,16) and the integration of subclinical markers in cardiovascular risk prediction improves the performance of SCORE (17). Recommendations from US and European guidelines call to treat atherosclerosis evidenced by imaging medically (18–20). Use of total plaque burden is accurate to predict cardiovascular risk [6,21,22]. Further, atherosclerosis imaging gave support to the new 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for cholesterol management defined new eligibility criteria for statin therapy (24) and cost-efficiency analysis found acceptable costs for an PCE risk down to 3% (25). Confirmation by plaque imaging as a tool to test the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk has also led to a better acceptance of the PCE calculator (15,26).

Earlier detection of old arteries is clinically useful, since early preventive therapy protects better against harms due to atherosclerosis later in life, which has been shown both for arterial hypertension (27) and hypercholesterolemia (28); further, statin treatment is still highly effective even in the fittest groups (29). The five year treatment of 1000 healthy men aged between 45 to 54 years with pravastatin (40 mg/day) saved the British Health Care System £710 000 over a 15-year period and savings were even higher (£840’000) in those at low risk (7.5% in 10 years risk) (30), a strong indication for substantial numbers of non-low risk subjects stratified as low-risk in primary prevention.

Total plaque area was found to have a higher risk ratio for future myocardial infarction in women than in men (31), underscoring the possible higher importance of carotid imaging in women than in men. The myocardial infarction event rate was 22.6% per 1000 patient years in men for those above the 3rd tertile with a multivariate adjusted risk ratio of 1.6 (p=0.02) and was 15.6% per 1000 patients years in women above the 3rd tertile with a multivariate adjusted risk ratio of 4.0 (p<0.001). Therefore, AA70 (corresponding to > 90th percentile in the Tromsø cohort, and to > 80th percentile in our cohort, Table

2) represents a high risk finding in men and a intermediate to high risk finding in women, for which intensified primary prevention is warranted.

As confirmed by the 15 years observational Tromsø study (32), extensive plaque presence derived from the total plaque area – a rapid and cheap test that does not need expensive radiology, radiation exposure and software – is a high risk finding for incident myocardial infarction (32): 6,257 subjects with 894 incident cases of myocardial infarction were observed over a median follow-up time of 15.4 years. TPA of 40±22 mm^2 derived from the right carotid artery was associated with an unadjusted coronary risk of 23.9% (95%CI: 21.2–27.1) in 10 years. The Hazard Ratio per 1-SD increase in TPA (2.43 mm^2) was 1.23 (95%CI: 1.15–1.32) using age as time scale and adjustments for sex, body mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and hypertension.

Our work has some limitations: it examines practice based groups of subjects that cannot be generalized to the whole population. This may also be viewed as a strength of the study, since practice based subjects may serve as an external confirmation for coronary risk calculators.
Second, images were obtained within a clinical setting as part of routine measurements by two different observers. However, the remarkable congruence of the findings from Koblenz and Olten may be viewed as a mutual confirmation. Further, the total plaque area, a measure of the total carotid plaque burden anticipated the results from the IMPROVE-IT study, thus confirming the high prognostic validity of such measurements (33–36).

Conclusion

In our practice based middle-aged and on average low-risk group of 3'248 subjects without cardiovascular disease and without preventive use of statins and antihypertensive drugs, we analyzed current decision thresholds derived from cardiovascular risk calculators (PROCAM, SCORE) to explore an intensified primary prevention, e.g. regarding the prescription of statins, in subjects with old arteries. We observed and validated externally a very low sensitivity of such decision thresholds in women, which may create a disadvantage for a similar efficiency of the primary prevention of cardiovascular events.

Further we show that high ROC values of coronary risk calculators do not necessarily reflect a high clinical performance; we expect that down-calibration based on predicted-to-observed (P/O) event ratios, as performed with the AGLA calculator in Switzerland and others, further reduces the detection rate of subjects with advanced atherosclerosis by calibrating excessively in favor of the majority: those without future cardiovascular events within the next 10 years. The down-calibration of AGLA by 30% when compared to PROCAM is not justified according to our data. The lower diagnostic accuracy of PROCAM when compared to SCORE to detect old arteries in men calls for a validation of PROCAM in Switzerland and Germany and its widespread use may be questioned.

Decision thresholds may be lowered in women, e.g. to PROCAM 4% instead of 10% and SCORE to 1%-2% in women and to 3%-4% in men instead of 5%, in order to obtain a detection rate of at least 30% in those affected from advanced atherosclerosis, defined by an arterial age of at least 70 years in those aged 40-65.

The addition of arterial age offers a solution to the risk stratification conundrum, in that a more individualized diagnostic strategy may allow for a more tailored preventive therapy to be delivered especially in women. Further studies would be helpful to assess the return on investment of our imaging approach assuming costs of 70 € per carotid exam.

Conflict of interest

None declared

References

1. Navar-Boggan AM., Peterson ED., D'Agostino RB., Pencina MJ., Sniderman AD. One Size May Not Fit All: Using Age- and Sex-Specific Risk Thresholds to Guide Statin Therapy. J Am Coll Cardiol 2015;65:1633–9.
2. Mortensen MB., Falk E. Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction. BMJ Open 2014;4:1–8.
3. Mortensen MB., Afzal S., Nordestgaard BG., Falk E. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30 824 Europeans: the Copenhagen General Population Study. Eur Heart J 2015;ahead of p.
4. Romanens M., Ackermann F., Sudano I., Szucs T., Spence JD. Arterial age as a substitute for chronological age in the AGLA risk function could improve coronary risk prediction. Swiss Med Wkly 2014:1–7.
5. Romanens M. Vascular risk foundation (Varifo).
6. Adams A., Bojara W. Vorhersage einer stenosierenden KHK durch Bestimmung von Plaque-Fläche und -Dicke vs. IMT an der A. carotis. Herz 2015:1–5.
7. Descamps OS., Cooney MT., De Backer G., Graham I. A simple multiplier to calculate the impact of HDL cholesterol on cardiovascular risk estimation using SCORE. Atherosclerosis 2012;222(2):564–6.
8. Assmann G., Schulte H., Cullen P., Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Münster (PROCAM) study. Eur J Clin Invest 2007;37:925–32.
9. Eckardstein A. AGLA Guidelines. Available at: www.agla.ch. Accessed August 1, 2016.
10. MedCalc Software bvba, Ostend B. MedCalc Statistical Software version 2013.
11. McEvoy JW., Diamond G a., Detrano RC., et al. Risk and the physics of clinical prediction. Am J Cardiol 2014;113:1429–35.

12. DeFilippis AP., Young R., Carrubba CJ., et al. An Analysis of Calibration and Discrimination Among Multiple Cardiovascular Risk Scores in a Modern Multiethnic Cohort. Ann Intern Med 2015;162:266–75.

13. Romanens M., Berger D., Battegay E. Predictive value of clinical risk assessment tools and guidelines for 10-year coronary heart disease risk in practice-based primary care. Kardiovaskuläre Medizin 2005;8:180–6.

14. Romanens M., Ackermann F., Schwenkglenks M., Szucs T., Spence JD. Posterior probabilities in sequential testing improve cardiovascular risk prediction using carotid total plaque area. Kardiovaskuläre Medizin 2011;14:53–7.

15. Robinson JG., Stone NJ. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence. Eur Heart J 2015:2110–8.

16. Piepoli M., Hoes A., Agewall S., et al. European guidelines on cardiovascular disease prevention in clinical practice, update 2016. Eur Heart J 2016;28:2375–414. Doi: 10.1093/eurheartj/ehm316.

17. Sehestedt T., Jeppesen J., Hansen TW., et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J 2010;31(7):883–91. Doi: 10.1093/eurheartj/ehp546.

18. Mansia G., De Backer G., Dominiczak A., et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16(3):135–232.

19. De Backer G., Ambrosioni E., Borch-Johnsen K., et al. European guidelines on cardiovascular disease prevention in clinical practice - Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. Eur J Cardiov Prev R 2003;10:1–10.

20. Stone NJ., Robinson JG., Lichtenstein AH., et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the

American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol 2014;63:2889–934.

21. 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.

22. Spence JD., Eliasziw M., DiCicco M., Hackam DG., Galil R., Lohmann T. Carotid Plaque Area: A Tool for Targeting and Evaluating Vascular Preventive Therapy. Stroke 2002;33:2916–22.

23. Spence D., Hackam D. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. Stroke 2010;41:1193–9.

24. Pursnani A., Massaro J., D'Agostino R., O'Donnel C., Hoffmann U. Guideline-Based Statin Eligibility, Coronary Artery Calcification, and Cardiovascular Events. JAMA 2015;314:134–41.

25. Pandya A., Sy S., Weinstein M., Gaziano T. Cost-effectiveness of 10-Year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. JAMA 2015;314:142–50.

26. Johnson KM., Dowe D a. Accuracy of Statin Assignment Using the 2013 AHA/ACC Cholesterol Guideline Versus the 2001 NCEP ATP III Guideline. J Am Coll Cardiol 2014;64:910–9.

27. Gottesman RF., Schneider ALC., Albert M., et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol 2014;71:1218–27.

28. Navar-Boggan a. M., Peterson ED., D'Agostino RB., Neely B., Sniderman a. D., Pencina MJ. Hyperlipidemia in Early Adulthood Increases Long-Term Risk of Coronary Heart Disease. Circulation 2015;131:451–8.

29. Kokkinos PF., Faselis C., Myers J., Panagiotakos D., Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study 2012;6736:10–5.

30. Mc Connachie A., Walker A., Robertson M., et al. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: A record linkage study. Eur Heart J 2014;35:290–8.

31. Johnsen SH., Mathiesen EB., Joakimsen O., et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. Stroke 2007;38:2873–80.

32. Hald EM., Lijfering WM., Mathiesen EB., et al. Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism: The Tromso Study. Arterioscler Thromb Vasc Biol 2013;34:226–30.

33. Cannon CP., Blazing M a., Giugliano RP., et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387–97.

34. Spence JD. Is Carotid Intima-Media Thickness a Reliable Clinical Predictor? Mayo Clin Proc 2008;83:1299–300.

35. Spence JD. Carotid plaque measurement is superior to IMT. Atherosclerosis 2012;220:34–5.

36. Bogiatzi C., Spence JD. Ezetimibe and regression of carotid atherosclerosis: importance of measuring plaque burden. Stroke 2012;43:1153–5.

Tables

Table 1: Clinical characteristics of the Swiss and the German Arteris Group subjects

Country	CH	DE
Number of subjects (N)	1'429	1'819
Female, N, %	679, 48%	640, 35%
Mean age (N ± SD)	53.9±6.7	49.8±6.1
Family history for CAD (N, %)	273, 19%	408, 22%
Current smoker (N, %)	332, 23%	435, 24%
Blood pressure systolic, mm Hg mean ± SD	127±15	123±15
TPA mm^2 mean ± SD	42±41	39±49
Individuals with arterial age ≥ 70	165, 12%	229, 13%
Total cholesterol, mmol/l, mean ± SD	6.0±1.2	6.0±1.1
HDL cholesterol, mmol/l, mean ± SD	1.5±0.5	1.5±0.4
LDL cholesterol, mmol/l, mean ± SD	3.8±1.0	3.9±0.9
Triglycerides, mmol/l, mean ± SD	1.5±0.9	1.7±1.2
SCORE	1.6±1.6	1.2±1.2
PROCAM	5.2±6.3	5.0±6.5
AGLA	3.7±4.4	

Table 2: Percentile value of AA70 in the Arteris and in the Tromsø cohorts

	TPA (mm^2)	Arteris	Tromsø
Female	58	80^{th}	93^{th}
Male	105	86^{th}	96^{th}

Table 3: sensitivity and specificity of AGLA, PROCAM, and SCORE to detect AA70 at various decision cutoffs and for female and male subjects in Switzerland and Germany (Note: AGLA=PROCAM x 0.7)

Switzerland	AGLA 2%		AGLA 4%		AGLA 6%		AGLA 8%		AGLA 10%	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
SENS	54 (42 - 65)	90 (82 - 96)	33 (23 - 44)	72 (61 - 82)	16 (9 - 26)	53 (42 - 64)	11 (5 - 20)	40 (29 - 51)	6 (2 - 14)	30 (21 - 41)
SPEC	77 (73 - 80)	30 (26 - 33)	92 (90 - 94)	57 (53 - 61)	96 (95 - 98)	73 (70 - 77)	98 (96 - 99)	81 (78 - 84)	99 (97 - 99)	87 (84 - 89)
	SCORE 1%		**SCORE 2%**		**SCORE 3%**		**SCORE 4%**		**SCORE 5%**	
SENS	73 (62 - 82)	95 (88 - 99)	33 (23 - 44)	76 (65 - 85)	15 (8 - 24)	52 (41 - 63)	10 (4 - 18)	31 (22 - 42)	5 (1 - 12)	18 (11 - 28)
SPEC	67 (63 - 71)	31 (28 - 35)	89 (86 - 92)	59 (56 - 63)	97 (96 - 98)	79 (76 - 82)	99 (98 - 100)	90 (87 - 92)	99 (98 - 100)	94 (92 - 96)

Germany	PROCAM 2%		PROCAM 4%		PROCAM 6%		PROCAM 8%		PROCAM 10%	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
SENS	47 (34 - 60)	96 (92 - 98)	21 (12 - 33)	86 (80 - 91)	11 (5 - 22)	75 (68 - 82)	8 (3 - 18)	63 (68 - 82)	8 (3 - 18)	56 (48 - 64)
SPEC	84 (81 - 87)	24 (22 - 27)	94 (92 - 96)	50 (47 - 53)	97 (95 - 98)	66 (63 - 69)	98 (97 - 99)	78 (75 - 80)	99 (98 - 100)	83 (81 - 86)
	SCORE 1%		**SCORE 2%**		**SCORE 3%**		**SCORE 4%**		**SCORE 5%**	
SENS	35 (24 - 49)	92 (87 - 96)	10 (4 - 20)	65 (58 - 73)	2 (0 - 9)	40 (32 - 47)	0 (0 - 6)	26 (19 - 33)	0 (0 - 6)	16 (10 - 22)
SPEC	90 (88 - 93)	52 (49 - 56)	97 (95 - 98)	79 (77 - 82)	99 (98 - 100)	91 (89 - 93)	100 (99 - 100)	96 (95 - 97)	100 (99 - 100)	98 (97 - 99)

Table 4: Comparison of Group 1 (AA70 present) and Group 2 (AA70 absent)

	Group 1	**Group 2**	
Number of subjects (N)	394	2854	p=
Female, N, %	144, 37%	1175, 41%	0.0800
Age women (mean ± SD)	57.0±5.8	51.6±6.7	< 0.0001
Age men (mean ± SD)	55.5±5.6	50.5±6.4	< 0.0001
Arterial age women (mean ± SD)	79.2±7.9	35.8±16.4	< 0.0001
Arterial age men (mean ± SD)	76.9±6.4	39.5±16.6	< 0.0001
Family history for CAD (N, %)	93, 24%	588, 21%	< 0.0001
Current smoker (N, %)	153, 39%	614, 22%	< 0.0001
Blood pressure, mm Hg mean ± SD	132±18	124±15	< 0.0001
TPA mm2 mean ± SD	131±51	28±26	< 0.0001
Total cholesterol, mmol/l, mean ± SD	6.4±1.6	6.0±1.1	< 0.0001
HDL cholesterol, mmol/l, mean ± SD	1.4±0.4	1.5±0.4	= 0.0001
LDL cholesterol, mmol/l, mean ± SD	4.2±1.1	3.8±0.9	< 0.0001
Triglycerides, mmol/l, mean ± SD	1.7±1.1	1.6±1.1	= 0.0043
SCORE	9.9±9.6	4.4±5.5	< 0.0001
PROCAM	2.6±2.1	1.2±1.3	< 0.0001

Table 5: Results of ROC analysis to detect AA70 in women and in men

ROC results	PROCAM	SCORE	P =
Female (95%CI)	0.751 (0.727 to 0.774)	0.769 (0.746 to 0.792)	0.2072
Male (95%CI)	0.747 (0.727 to 0.766)	0.785 (0.766 to 0.803)	0.0066

Figure 1: Flowchart regarding patient selection in the Arteris Group

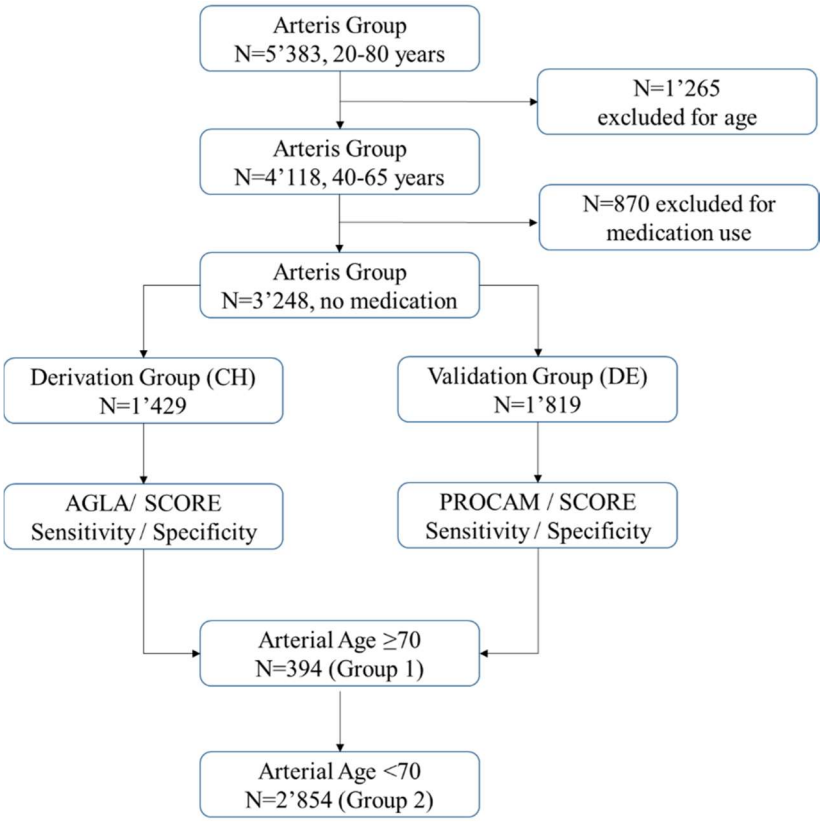

Figure 2: Comparison of ROC curves (detection of AA70 with SCORE and PROCAM) in 1'929 male subjects (combined DE and CH groups). Results for SCORE were 0.78 (95%CI: 0.76-0.81) and for PROCAM were 0.75 (95%CI: 0.72-0.78, p= 0.0066)