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Extensive carotid atherosclerosis and the diagnostic accuracy of coronary risk calculators

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ABSTRACT

Preventive therapy in primary care is guided by risk thresholds for future cardiovascular events. We aimed to assess whether the sensitivity of various risk calculators for the detection of subclinical carotid atherosclerosis (TPA80) could be improved by lowering risk thresholds in younger age groups. We compared sensitivity, specificity, and discriminatory performance of SCORE, SCORE-HDL, PROCAM, AGLA, FRAM and PCE coronary risk calculators to detect total plaque area > 80 mm2 (TPA80), a coronary risk equivalent, in age groups 40–55, 56–65, 66–75 from Germany (DE, $N = 2942$) and Switzerland (CH, $N = 2202$) during the years 2002 to 2016. All calculators showed good to moderate discriminatory performance to detect TPA80 with AUC ranging from 0.74 (CH-AGLA) to 0.87 (DE- SCORE), but the sensitivity of high risk risk thresholds varied widely from 39% for DE-FRAM-CVD to 5% for CH-AGLA. Lowering of the risk threshold increased sensitivity substantially at the expense of minor losses in specificity, but the sensitivity generally remained <45% at the 90% specificity threshold.
Current risk thresholds of American and European coronary risk calculators have a low sensitivity to detect TPA80 in younger individuals.

1. Introduction

Tests used in clinical and preventive medicine have a certain sensitivity (disease detection rate in those with disease) and specificity (rate of exclusion of a disease in those without the disease). In preventive medicine, 10-year risk estimates are calculated and in general lower treatment thresholds are associated with a higher sensitivity and a lower specificity. In the Framingham Offspring Study coronary risk prediction was improved by reducing risk thresholds in younger subjects (Navar-Boggan et al., 2015a).

While a clinician's preventive efficacy is dependent on meaningful sensitivity thresholds, tests need proof with regards to their discriminatory value. By taking the whole range of test results, a plot of sensitivity and specificity is created by receiver operating curves (ROC) to detect those with a future event. Acceptable area under the curve (AUC) is usually larger than 0.80.

Such calculations are based on cardiovascular events occurring over time. By definition, such an approach translates observations from the past into the present. A "present time" validation to assesses the accuracy of coronary risk calculators can be derived from patients admitted for a first myocardial infarction, where a very low sensitivity was revealed for the European calculator (SCORE-CVD (Conroy et al., 2003)) risk threshold of 5% (Mortensen et al., 2015; Mortensen & Falk, 2014). Instead of waiting until a myocardial infarction occurs, atherosclerosis imaging also offers a "present time" validation for coronary risk calculators by measuring the total carotid plaque burden. Such information can therefore be used to test risk calculators for their performance before the occurrence of an acute coronary event and may help to define sensitivity cutoffs in those populations, where atherosclerosis burden information is available (Arbab-Zadeh & Fuster, 2015).

For the purpose of this study, we used a total plaque area of greater than or equal to 80 mm^2 (TPA80), for which a coronary risk of >20% was

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found in a long-term observational study (median observation time 15.4 years) in 6257 subjects from the Norwegian Tromsø area (Hald et al., 2013) in order to test the performance of various risk calculators for their sensitivity and specificity in three different age.

2. Materials and methods

2.1. Subject selection

Subjects were assessed at the practice based level as described elsewhere (Romanens et al., 2014; Romanens et al., 2011). In the Swiss (CH) Imaging Center in Olten, subjects were referred by their primary care physician (57%) or self-referred to the vascular risk foundation (43%; www.varifo.ch). In the German (DE) Center in Koblenz, all subjects were referred within a workplace medicine setting (Adams & Bojara, 2015). Subjects had to be free of cardiovascular symptoms or diseases. The medical history was assessed, laboratory values, blood pressure determined locally and entered into a data spread-sheet (Excel, Microsoft, Richmond, USA).

2.2. 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.

2.3. 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. A TPA ≥ 80 mm^2 (TPA80) defined a coronary risk equivalent (risk >20% for fatal and non-fatal myocardial infarction in 10 years) (Hald et al., 2013). Intraobserver reproducibility (MR) was tested for the right carotid artery in 57 patients with a correlation coefficient of r^2 0.964 (left carotid artery: r^2 0.944, both arteries r^2 0.986). For the cutoffs of TPA 0–9 mm^2, 10–49 mm^2, 50–99 mm^2 and >100 mm^2 Kappa value was 0.69 (0.54–0.84 95% CI).

2.4. Computation of 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 and SCORE-HDL (Descamps et al., 2012)), the pooled cohort equation (PCE (Robinson & Stone, 2015)) and the Framingham risk calculator for major cardiac (FRAM-CHD (D'Agostino et al., 2008)) and major cardiovascular events (FRAM-CVD (D'Agostino et al., 2008)). The German PROCAM risk (Assmann et al., 2007) was calculated manually online, since the algorithm is not published. For Switzerland, PROCAM risk was multiplied by the factor 0.7 (CH-AGLA, according to the Swiss AGLA guidelines 2014 (Eckardstein, 2014)). SCORE risk was calculated using the algorithm published by Conroy (Conroy et al., 2003) and the SCORE-HDL (Cooney et al., 2009) risks were calculated as previously described by Descamps (Descamps et al., 2012).

2.5. Statistics

We used MedCalc software (Version 13.3.3.0) to calculate ROC curves and their comparisons (MedCalc Software bvba, 2013). For comparison of risk calculators, equivalent SCORE risk was set to be four times lower than in the remainder, therefore, a PROCAM or FRAM risk of 20% would correspond to an SCORE risk of 5%. Level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

We assessed 2202 healthy Swiss and 2942 healthy German subjects. The characteristics of the study subjects are shown in Table 1. The Swiss group was older than the German group (57 ± 9 versus 46 ± 10 years) with more women (49% versus 34%). Average 10-year risk among groups was low. Prevalence of TPA80 was 22% in Switzerland and 15% in Germany. Lipid profiles were comparable.

3.2. Prevalence of TPA80

The prevalence of TPA80 was low in Swiss women aged 40–55 years (4%), but increased to 14% and 36% in the two remaining age groups. For men, TPA80 was prevalent in all age groups above the 15% level, and was present in 57% in Swiss men aged 66 to 75 years (Table 2).

3.3. Sensitivity and Specificity of high risk coronary risk thresholds for the detection of TPA80

Using high risk thresholds for high coronary risk (5% for the SCORE and SCORE-HDL risk calculators, 20% for the remaining cardiovascular risk calculators), global sensitivity to detect TPA80 showed some variability, but was generally below 20% in Switzerland and Germany. Of note, CH-AGLA had a sensitivity of only 5% (Table 3).

3.4. C-Statistics of coronary risk calculators (Fig. 1)

We found that the performance of all cardiovascular risk calculators was similar in Switzerland and Germany, but with slightly higher values for Germany and with significant differences among calculators (Supplemental Table I): especially CH-AGLA showed a significantly lower area under the curve (AUC 0.743), while the same was true for the

Table 1
Baseline Characteristics, average and prevalence of cardiovascular risk and average TPA for Switzerland (CH) and Germany (DE).

Country	CH			DE		
Number of subjects (N)	2202			2942		
Female, N, %	1082		49%	989		34%
Mean age (N ± SD)	57	±	9	46	±	10
Family history for CAD (N, %)	386		18%	660		22%
Current smoker (N, %)	458		21%	770		26%
Blood pressure systolic, mm Hg mean ± SD	129	±	16	123	±	16
TPA mm^2 mean ± SD	52	±	50	36	±	50
Individuals with TPA ≥ 80 mm^2 (N, %)	484		22%	452		15%
Total cholesterol, mmol/l, mean ± SD	5.9	±	1.2	5.9	±	1.2
HDL cholesterol, mmol/l, mean ± SD	1.5	±	0.5	1.4	±	0.4
LDL cholesterol, mmol/l, mean ± SD	3.7	±	1.0	3.8	±	0.9
Triglycerides, mmol/l, mean ± SD	1.5	±	0.9	1.7	±	1.2
FRAM-CHD	9.0	±	7.1	6.5	±	6.0
% individuals with risk <10%	67%			79%		
FRAM-CVD	13.2	±	9.8	9.3	±	8.4
% individuals with risk <10%	47%			66%		
SCORE	2.4	±	2.6	1.1	±	1.4
% individuals with risk <5%	87%			99%		
SCORE-HDL	1.8	±	2.0	0.8	±	1.2
% individuals with risk <5%	93%			99%		
PCE	8.0	±	7.4	7.8	±	13.8
% individuals with risk <10%	70%			80%		
PROCAM	6.2	±	7.3	4.3	±	6.2
% individuals with risk <10%	81%			87%		
AGLA	4.3	±	5.1			
% individuals with risk <10%	89%					