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# Performance of coronary risk calculators: the "ROC-Sensitivity Paradox".

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| **Abstract:** | Background<br>Statin therapy in primary prevention is guided by predicted absolute risk of future cardiovascular disease. Clinical performance (e.g. sensitivity and specificity) of risk calculators depends on the recommended decision threshold.<br><br>Design<br>We aimed to assess if clinical performance for detecting subclinical carotid atherosclerosis (TPA80) could be improved by lowering decision thresholds in younger age groups.<br><br>Methods<br>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=2,942) and Switzerland (CH, N=2,202).<br><br>Results<br>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 decision thresholds varied widely from 39% for DE-FRAM-CVD to 5% for CH-AGLA. Lowering of the decision threshold increased sensitivity substantially at the expense of minor losses in specificity, but the sensitivity generally remained <45% at the 90% specificity threshold.<br><br>Conclusion<br>Current thresholds of American and European coronary risk calculators have a low |

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| | sensitivity for TPA80 consistent with a clinically relevant "ROC-sensitivity paradox", notably in younger individuals. Assessing subclinical atherosclerosis, such as TPA80, may improve sensitivity to detect younger subjects at high coronary risk. |
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# Performance of coronary risk calculators: the "ROC-Sensitivity Paradox".

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# Abstract

## Aims

Statin therapy in primary prevention is guided by predicted absolute risk of future cardiovascular disease. Clinical performance (e.g. sensitivity and specificity) of risk calculators depends on the recommended decision threshold. We aimed to assess if clinical performance for detecting subclinical carotid atherosclerosis (TPA80) could be improved by lowering decision thresholds in younger age groups.

## Methods and Results

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 $mm^2$ (TPA80), a coronary risk equivalent, in age groups 40-55, 56-65, 66-75 from Germany (DE, N=2,942) and Switzerland (CH, N=2,202). 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 decision thresholds varied widely from 39% for DE-FRAM-CVD to 5% for CH-AGLA. Lowering of the decision threshold increased sensitivity substantially at the expense of minor losses in specificity, but the sensitivity generally remained <45% at the 90% specificity threshold.

## Conclusion

Current thresholds of American and European coronary risk calculators have a low sensitivity for TPA80 consistent with a clinically relevant "ROC-sensitivity paradox", notably in younger individuals. Assessing subclinical atherosclerosis, such as TPA80, may improve sensitivity to detect younger subjects at high coronary risk.

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**Keywords**

atherosclerosis, risk-prediction, statin-indication, carotid plaque

## Introduction

The publication of the 2013 ACC/AHA risk assessment and cholesterol guidelines created debates about high numbers of patients recommended to treat with statins in the USA[1]: over 80% of patients aged 60 years or older would require statins[2]. In Europe and Switzerland, the SCORE and the PROCAM risk calculators are used in primary care to stratify coronary risk. The performance of the SCORE and the PROCAM risk calculators to detect subjects with high coronary risk is an important public health issue in order to identify and treat the atherosclerotic epidemic early and with high sensitivity and specificity.

The comparison of different risk calculators has shown considerable need for recalibration, since risk overestimation occurred in four out of five risk calculators when applied to the MESA cohort[3]. Further, both the SCORE and SCORE-HDL models overestimate risk in the contemporary Copenhagen General Population Study by a factor of 5.0 and 3.6 respectively despite a sensitivity of 42% and 26% for the detection of fatal cardiovascular disease[4]. Attempts to recalibrate calculators have been made, e.g. using historical mortality data from the MONICA project[5]. However, the translation of historical data to contemporary risk may be a source of bias because of changes of disease prevalence over time. Further, calibration of risk calculators may reduce the performance at the clinical level, where effective prevention should take place: for the clinician, the decision thresholds of coronary risk are used to target preventive therapies to those at high risk. If such thresholds have a low sensitivity, deterioration in the performance of risk assessments may occur because of high numbers of false negative test results, despite excellent results from ROC analysis[4,6]. Therefore attempts were made in a recent Framingham Offspring Study to improve coronary risk stratification by reducing risk thresholds to lower levels of coronary risk in younger subjects, which increases the sensitivity performance of a test at the expense of only a minor decrease in specificity [6]. These findings were confirmed in the Copenhagen General Population Study[4].

An elegant way to evaluate the performance of coronary risk equations in real-life uses coronary risk derived results from various calculators in patients admitted for a first myocardial infarction: an extraordinary low sensitivity was observed for the SCORE threshold of 5% fatal cardiovascular disease risk in 10 years [4,7]. Instead of waiting until a myocardial infarction occurs, atherosclerosis imaging offers another way to evaluate coronary risk equation performance on behalf of contemporary data: subjects having a coronary risk equivalent e.g. defined by the total carotid plaque burden. Compared to coronary calcifications, total carotid plaque burden has similar prognostic information and reclassification ability[8]. Hence, such information about the total plaque burden can be used to test risk calculators for their performance before the eventual occurrence of an acute coronary event[9].

For the purpose of this study, we selected a well-validated coronary risk equivalent in order to test the performance of various risk calculators and to look at the effect of different coronary risk thresholds on sensitivity and specificity in three different age groups.

# Methods

### Subject selection

Both groups of subjects were assessed at the practice based level as described elsewhere[10]. In the Swiss 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 Imaging Center in Koblenz, all subjects were referred within a working medicine setting[11]. Subjects had to be free of cardiovascular symptoms or diseases. Laboratory values, blood pressure and medical history were measured locally and entered into a data spread-sheet (Excel, Microsoft, Richmond, USA).

### Carotid Imaging

Presence and burden of longitudinal carotid plaque surface was imaged with a high resolution ultrasound linear transducer using a 7.5–12.0 MHz probe, which identified all plaques defined by intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed up to compute the value for 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)[12].

### 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[13]), the pooled risk equation (PCE) and the Framingham risk calculator for major cardiac (FRAM-CHD) and major cardiovascular events (FRAM-CVD). The PROCAM risk was calculated manually online, since the algorithm is not published. For Switzerland, PROCAM risk was multiplied by the factor 0.7 (according to the Swiss AGLA guidelines 2014[14]). The SCORE risk was calculated using the algorithm published by Conroy[15] and the SCORE-HDL[16] risks were calculated as previously described by Descamps[17].

### Computation of statin indication

Subjects recommended for statin therapy were based on the 2013 ACC/AHA cholesterol guideline for age-specific (40 to 55 years, 56 to 65 years, and 66 to 75 years) and sex-specific (women and men) groups. Therefore, subjects exceeding risk thresholds in Tables 5 to 7 were computed as having a treatment indication for a statin, irrespective of LDL levels.

### Statistics

We used MedCalc software (Version 13.3.3.0) to calculate ROC curves and their comparisons[18]. For comparison of risk calculators (Tables 5 to 7), 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 $p < 0.05$.

## Results

### Patient characteristics

We assessed 2202 healthy Swiss and 2294 healthy German subjects. Subjects characteristics are shown in Table 1. On average, the Swiss group was older than the German group (57 ± 9 versus 46 ± 10 years) with more women (49% versus 34%). The assessment of 10-year risk for both groups showed that most subjects were in the low risk category. The prevalence of TPA80 was higher in Switzerland than in Germany (22% versus 15%). Lipid profiles were comparable.

### Prevalence of TPA80 for different age groups and sex

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).

### C-Statistics for the Evaluation of coronary risk calculators

Using ROC curves, 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 some significant difference among the calculators (Table 4): especially the CH-AGLA risk calculator showed a significantly lower area under the curve (AUC 0.743), while the same was true for the DE-PCE risk calculator (AUC 0.769). Uniformly good and comparable performance was found both for the FRAM-CVD and the SCORE and the SCORE-HDL risk calculators.

### 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).

### Effect of different risk thresholds on sensitivity and specificity to detect TPA80 by sex and age groups for SCORE, PROCAM and CH-AGLA.

Tables 5 to 7 show the sensitivity and specificity by age groups and various risk thresholds for PROCAM and SCORE for women and men respectively to detect TPA80. As expected, by increasing risk thresholds sensitivity is reduced to zero or near zero, with specificities at near 100% or 100%.

**Age group 40 to 55:** in Swiss women at the SCORE threshold of 0.75%, 12% would be treated with a statin with a sensitivity of 39% and a specificity of 89%, while in Swiss men a threshold of 1.88% shows a sensitivity of 34% and a specificity of 79% with 23% qualifying for statins.

In German women the sensitivity of SCORE 0.75% was 41% (7% with statin indication), for German men at a threshold of 1.88%, sensitivity was 43 (16% with statin indication). Similar results were found for AGLA and PROCAM at the 10% risk threshold. The recommendation of the Swiss Medical Board (SCORE ≥ 7.5% for a statin indication[19]) had a sensitivity of 0% for Swiss and German men and women.

**Age group 56 to 65:** in Swiss women and at a SCORE threshold of 2.5%, 17% would be treated with a statin with a sensitivity of 32% and a specificity of 85%, while in Swiss men at a threshold of 2.5% 69% qualified for statins with a sensitivity of 76% and a specificity of 34%. In German women, the sensitivity of SCORE at 2.5% was 13% (12% with statin indication), for German men at a threshold of 2.5%, sensitivity was 74% (66% with statin indication). Similar results were found for AGLA and PROCAM at the 10% risk threshold.

The recommendation of the Swiss Medical Board (SCORE ≥ 7.5% for a statin indication[19]) had a sensitivity of 0% for Swiss and German men and women.

**Age group 66 to 75:** For this age group we have no data from Germany. In Switzerland, women at the risk threshold of SCORE of 3.75% showed a sensitivity of 68%, a specificity of 55% and a statin indication in 53%. In men, the SCORE threshold of 5% had a sensitivity of 81% and a specificity of 30% with a statin indication in 77%.

The recommendation of the Swiss Medical Board (SCORE ≥ 7.5% for a statin indication[19]) had a sensitivity of 12% for Swiss men and women.

**Sensitivity of different risk thresholds to detect TPA80 for each risk calculators by age groups**

Appendix Tables 8 and 9 show the sensitivities for each risk calculator at three different thresholds (1%, 2% and 5% for SCORE; 5%, 10% and 20% for the remainders) and for the age group 40-55 (Table 8) and the age group 56-65 (Table 9).

**Age group 40 to 55:** the CH and DE prevalence of TPA80 was 11% and 13% respectively. At the SCORE threshold of 1%, sensitivity was 61% (SCORE-HDL 55%) in Switzerland and was 69% (SCORE-HDL 59%) in Germany respectively. At the FRAM-CVD/PCE/PROCAM/AGLA risk threshold of 5%, sensitivities were 95%, 61%, and 36% in Switzerland and 96%, 68%, and 64% in Germany. For the intermediate risk threshold (SCORE 2.0%, FRAM-CVD/PCE/PROCAM/AGLA 7.5%), sensitivities were 26% and 21% for the SCORE calculators and 81%, 37%, and 23% in Switzerland and were 34% and 27% for the SCORE calculators and 88%, 48%, and 47% in Germany. For the high risk threshold (SCORE 5.0%, FRAM-CVD/PCE/PROCAM/AGLA 20%), sensitivities were 2% and 1% for the SCORE calculators and 22%, 3%, and 2% in Switzerland and were 3% and 2% for the SCORE calculators and 13%, 4%, and 12% in Germany.

**Age group 56 to 65:** the CH and DE prevalence of TPA80 was 25% and 41% respectively. At the SCORE threshold of 1%, sensitivity was 96% (SCORE-HDL 90%) in Switzerland and was 94% (86%) respectively in Germany. At the FRAM-CVD/PCE/PROCAM/AGLA risk threshold of 5%, sensitivities were 99%, 88%, and 51% in Switzerland and 99%, 88%, and 75% in Germany. For the intermediate risk threshold (SCORE 2.0%, FRAM-CVD/PCE/PROCAM/AGLA 7.5%), sensitivities were 77% and 62% for the SCORE calculators and 92%, 72%, and 36% in Switzerland and were 74% and 62% for the SCORE calculators and 93%, 76%, and 58% for FRAM-CVD/PCE/PROCAM in Germany. For the high risk threshold (SCORE 5.0%, FRAM-CVD/PCE/PROCAM/AGLA 20%), sensitivities were 19% and 12% for the SCORE calculators and 39%, 6%, and 4% in Switzerland and

were 20% and 12% for the SCORE calculators and 48%, 8%, and 18% for FRAM-CVD/PCE/PROCAM in Germany.

**Comparison of expected risk defined by coronary risk calculators at 10 years**

When SCORE was set at 1.0%, Swiss calibration factors were 0.8 for SCORE-HDL (DE 0.7), for Swiss PROCAM 2.6 (DE 3.9), for Swiss PCE 3.3 (DE 7.1), for Swiss FRAM-CHD 3.8 (DE 5.9) and for Swiss FRAM-CVD 5.50 (DE 8.5). AGLA without the correction factor of 0.7 had a calibration factor of 1.8 as compared to SCORE.

## Discussion

To the best of our knowledge, this is the first study to correlate carotid plaque burden with the performance of coronary risk calculators in Europe. Our study serves to determine the sensitivities of currently used coronary risk calculators to detect a coronary risk equivalent defined by a measure of the total plaque burden of both carotid arteries in healthy subjects from Germany and Switzerland. Further, by using various age groups and gender we further could define clinically relevant thresholds of coronary risk in order to improve sensitivities.

**C-statistics, sensitivity, specificity performance of coronary risk calculators for Germany and Switzerland at the high risk threshold**

We assessed sensitivity, specificity and discriminatory performance (area under curve (AUC)) of American and European risk calculators to detect a coronary risk equivalent defined by the total carotid plaque burden (TPA80) in a practice-based setting in our 5,145 subjects from the German Koblenz (N=2942) and the Swiss Olten area (N=2202), where the prevalence of TPA80 ranged from 4% in younger women to 57% in elderly men (Table 2). While results from ROC curves showed equally acceptable discriminatory performance to detect TPA80 with AUC ranging from 0.74 for CH-AGLA to 0.87 for DE-SCORE-HDL (Table 4), the high risk threshold for SCORE (5%) and for the remainder of the calculators (20%) had sensitivities below 30% except for CH-FRAM-CVD (39%) and DE-FRAM-CVD (39%). Extremely low sensitivity (< 10%) was observed for CH-AGLA (5%), DE-SCORE-HDL (7%), DE-PCE (6%), while specificity remained above 97% except for CH-FRAM-CVD with 87% (Table 3). Reliance on high risk thresholds would therefore largely eliminate statin indications in primary care with the exception of FRAM-CVD. These findings were 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[4]. Therefore, at the population level, there exists a paradox between high values found for ROC analysis (> 0.70) with low sensitivities for fatal and non-fatal cardiovascular outcomes (< 30%).

**Effect of lowering risk thresholds on sensitivity and specificity of AGLA/PROCAM and SCORE**

We could replicate the results of the Framingham Offspring Study when using our surrogate marker of risk for incident myocardial infarction for the coronary risk calculators PROCAM/AGLA and SCORE, calculators that are most widely used in continental Europe[6]. Only at a threshold of 0.75% had the SCORE calculators acceptable sensitivities and specificities in men and women aged 40-55, which is 10 times lower than a recent recommendation from the Swiss Medical Board about statins[19].

**Comparison of sensitivities for various risk thresholds, age groups, and coronary risk calculators**

We compared the sensitivity performance of various coronary risk calculators including the pooled US risk equation (PCE) and the Framingham risk calculators for incident cardiac (FRAM-CHD) and

cardiovascular (FRAM-CVD) events by the age groups 40 to 55 and 56 to 65, by country but not by sex and found very low sensitivities especially for the SCORE calculators and confirm the study results by Mortensen et al., who found similar results: of 162 men and 85 women with a first myocardial infarction, only 8% and 1% respectively would have qualified for a statin treatment before the event when using a cutoff of SCORE 5% or more[7].

For SCORE and SCORE-HDL, we could replicate the results from the Copenhagen General Population Study, where lower risk thresholds (e.g. 1% instead of 5% 10 year risk) increased the sensitivity for fatal and non-fatal cardiovascular events from SCORE 26% (SCORE-HDL 17%) to 79% (SCORE-HDL 71%) in men and women aged 40-65 years[4]. Further, we could replicate the counter-intuitive finding that the addition of HDL in the SCORE model reduced the sensitivity of SCORE-HDL when compared to SCORE (Tables 8 and 9).

**The ROC-Sensitivity paradox, down-calibration and the AGLA risk calculator**

Our results indicate that subjects with expression of coronary risk equivalents in mid-life remain frequently undetected (sensitivity below 75%), when conventional or age specific thresholds for intermediate or high cardiovascular risk are used to stratify their coronary risk. By selectively lowering risk thresholds especially in younger age groups, higher sensitivity with only minor losses in specificity (and treatment costs) can be obtained. But, even when we adopt the various risk thresholds for an eventual statin therapy in the age groups 40 to 65, important issues about low sensitivity remain. Therefore, the conundrum of risk prediction is not resolved[20]. If thresholds for statins should maintain a specificity of at least 90%, Tables 5 to 7 show that sensitivities usually remain below 25% (especially in women), a similar finding in the Framingham Offspring Study[6].

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 is a composite of those with disease (true positives) and is low, when positives are missed frequently (false negatives). Although ROC analysis show generally good discriminatory performance of coronary risk calculators externally[3], reliance on recalibration based upon 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[3,4,6]. Such a down-calibration was performed with the Swiss AGLA coronary risk calculator, which is the German PROCAM coronary risk calculator simply multiplied by 0.7[21], therefore reducing coronary risk as compared to Germany by 30%. This down-calibration may be the cause for the extremely low sensitivities found for AGLA to detect TPA80. Either calibration factors are set to increase sensitivity globally – irrespective of age groups – or age groups are chosen and coronary risk thresholds are defined in order to have acceptable sensitivities. However, waiting to recalibrate coronary risk calculators until hard coronary events occur, may create a source of bias especially in Europe, where higher coronary risks are likely to be transferred by migration from low-income countries[22]. Further, calibration factors are different for different populations, since we found for SCORE risk of 1.0% an equivalent risk for Swiss PCE of

3.33% (DE 7.09%) and for FRAM-CVD in CH 5.5% (DE 8.45%). The reason for such differences warrants further investigation.

**Total carotid plaque burden, long-term coronary outcome and prevalence in the younger population**

Use of carotid imaging, especially of the total plaque burden such as measurable by the total plaque area allows for cardiovascular risk prediction[8,23,24]. As confirmed by in the long-term Tromsø study, TPA80 – a rapid and cheap test that does not need expensive radiology, radiation exposure and software – is a high risk finding for incident myocardial infarction[12]: 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. Considering further that some subjects were treated with preventive medication, TPA80 (which by inference is the amount of TPA from the right and left carotid artery) is a true coronary risk equivalent with a high confidence. Further, a high prevalence of atherosclerosis identified by imaging in middle-aged subjects was recently confirmed by the PEMA study[25]. Imaging of atherosclerosis, where appropriate expertise is available, transfers coronary risk from stratification derived from population based data to individualization as outlined in Mayo Clinic guidelines [26].

We found that one in six men aged 40 to 55 years had a silent coronary risk equivalent (Table 3). Earlier preventive therapy may therefore better protect 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[29]; a 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].

**Need for individualized risk assessments in the younger population**

Recent Guidelines from the U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline[31] recommend against additional screening tests because improved risk prediction appears too low when assessed by ROC analysis and reclassification improvement (NRI)[32]. However, these recommendations are not derived from specific age groups, where effects of reclassification may become much higher in younger subjects, nor do they take into consideration that both ROC and NRI analysis reduce emerging test performance to an average, while medicine operates at the individual level, where much larger reclassification effects may occur, e.g. using the Bayes kernel to determine the posttest-risk for an individual[33]. A 50-year old woman with a CH-FRAM-CVD

risk of 7% and TPA80 has an arterial age of 75 years[10] and a posttest risk of 35%[34]. Therefore, instead of repeating risk factor based screening every two years as suggested by these guidelines, assessments for carotid plaque burden are likely to detect important cardiovascular risk earlier in the younger, and allows for a more rapid decision making with respect to the initiation of preventive therapies[24]. Imaging of carotid artery global plaque burden may be more efficient than coronary risk calculators based risk stratification with respect to public health issues in an increasingly restrictive statin prescription environment in Europe[7]: it would allow for an individualized detection and earlier allocation of preventive therapies. Based upon our observations, men aged 40-55 and women aged 56-65 may be candidates for carotid imaging screening, since the prevalence of high risk atherosclerosis is at least 14% with a number needed to image of about one in five to seven to detect TPA80. Further, atherosclerosis imaging lends 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[35] and cost-efficiency analysis found acceptable costs for an PCE risk down to 3%[36]. Based upon our calibration factors, this would correspond to a CH-SCORE risk of 0.57 (DE =0.34).

**Limitations**

Our work has some limitations: it examines practice based groups of subjects that cannot be generalized to the whole population. However, this may also be viewed as a strength of the study, since practice based subjects may serve as an external validation 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 validation. 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[37–40].

Further, we do not present hard coronary outcome data in this study. However, there is high confidence for TPA80 being a true coronary risk finding, and we could confirm the poorer sensitivity performance of SCORE-HDL versus SCORE, originally described in the Copenhagen General Population Study[4]. Therefore, from an ethical point of view, we believe that subjects with relevant amounts of atherosclerosis should be offered effective preventive treatments. This is also in line with the recommendations of US and European guidelines, to treat atherosclerosis evidenced by imaging medically[1,41,42].

Although we cannot provide a comparison of TPA with coronary calcium scoring (CAC), we found that 14% of 1766 subjects with PCE ≥7.5% had no visible plaque in the carotid arteries. This number is lower than the 44% found with zero CAC in the MESA study[43,44]. However, zero CAC does not exclude soft plaque and depending on various populations screened, a varying number of subjects may have advanced soft coronary plaque. In a comparative observation of Swiss subjects (N=432), where both CAC and TPA could be assessed (VARIFO data on file), we found that severe CAC (Agatston

score > 400 found in 54 out of 432 subjects) was present in only 2 subjects with zero TPA, while in 151 subjects with zero CAC, significant amounts of TPA (>50 $mm^2$) were present in 40 (26%) of subjects and moderate amounts of TPA (>25 $mm^2$) where present in 77 (51%) of subjects; similar observations were made in the BIOIMAGE and the PESA studies[8,25]. Therefore, early carotid plaque formation may be more valuable for life time risk assessments, where event may occur more than 10 years after the initial risk assessment with CAC. A direct comparison of TPA and CAC for risk assessment e.g. in those with PCE ≥7.5% may be needed with observation times over 10 to 20 years, since there are no very long-term data on risk in subjects with zero CAC, a problem that may become more prominent, when younger subjects are assessed by CAC.

Finally, validation 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 guidelines is widely accepted for the PCE calculator[45,46].

## Conclusion

In our practice-based group of 5,145 subjects without cardiovascular disease, we find a clinically relevant "ROC-sensitivity paradox": Discriminatory performance of all coronary risk calculators assessed by ROC analysis to detect TPA80 were acceptable; however, with respect to coronary risk prevention at the individual level, where high sensitivity should exist to detect subjects with a coronary risk equivalent derived from the total carotid plaque burden, we observed a poor sensitivity of risk factor-based assessments when using recommended decision thresholds. We note that improvement in sensitivity can be achieved by lowering risk thresholds for the initiation of a statin therapy without major losses in specificity, similar to the results of the recent Framingham Offspring Study. Furthermore, we note that using established calibration factors, FRAM-CVD outperformed other coronary risk calculators both in Switzerland and Germany when using the 5% and 10% risk thresholds.

However, even when adopting age-specific risk thresholds, sensitivity remains almost uniformly below 30% if specificity is maintained at 90% or more. Therefore a problem emerges, especially in younger subjects with coronary risk equivalents, when coronary risk calculators are used for clinical decision making. This may pose an important public health problem for the early prevention of atherosclerotic burden. Further we show that high ROC values of coronary risk calculators do not 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, further reduces the detection rate of subjects with future events by calibrating excessively in favor of the majority: those without future cardiovascular events.

The addition of carotid plaque burden imaging offers a solution to the risk stratification conundrum, in that a more individualized diagnostic strategy may allow for a more tailored and earlier preventive therapy. Further studies would be helpful to assess the return on investment of our imaging approach.

**manuscript word count: 4918**

# Tables

## 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% | | | |

## Table 2: Prevalence (N, %) of TPA80 by age groups and sex for CH and DE

| | | CH | | DE | |
|---|---|---|---|---|---|
| **TPA80** | **Age Group** | **N** | **%** | **N** | **%** |
| **Women** | **40-55** | 18 | 4.5 | 27 | 4.4 |
| | **56-65** | 60 | 14.0 | 45 | 25.7 |
| | **66-75** | 78 | 36.3 | | |
| | | | | | |
| **Men** | **40-55** | 79 | 15.7 | 195 | 17.5 |
| | **56-65** | 150 | 37.2 | 179 | 48.2 |
| | **66-75** | 97 | 56.7 | | |
| | | | | | |
| **All** | **40-55** | 97 | 10.7 | 222 | 12.8 |
| | **56-65** | 210 | 25.2 | 224 | 41.0 |
| | **66-75** | 175 | 45.3 | | |

**Table 3: sensitivity (SENS) and specificity (SPEC) of coronary risk calculators at the high risk threshold (SCORE 5%, 20% remainders) to detect TPA80**

| Switzerland (CH, N=2202) | SENS | 95%CI | SPEC | 95%CI |
|---|---|---|---|---|
| **SCORE** | 32.64 | 28.5 - 37.0 | 92.08 | 90.7 - 93.3 |
| **SCORE-HDL** | 19.21 | 15.8 - 23.0 | 96.33 | 95.3 - 97.2 |
| **PCE** | 17.36 | 14.1 - 21.0 | 96.39 | 95.4 - 97.2 |
| **FRAM-CHD** | 21.07 | 17.5 - 25.0 | 95.81 | 94.8 - 96.7 |
| **FRAM-CVD** | 39.05 | 34.7 - 43.6 | 87.14 | 85.5 - 88.7 |
| **PROCAM** | 12.81 | 10.0 - 16.1 | 97.09 | 96.2 - 97.8 |
| **AGLA** | 5.17 | 3.4 - 7.5 | 98.95 | 98.3 - 99.4 |

| Germany (DE, N=2942) | SENS | 95%CI | SPEC | 95%CI |
|---|---|---|---|---|
| **SCORE** | 11.73 | 8.9 - 15.1 | 99.4 | 99.0 - 99.7 |
| **SCORE-HDL** | 7.3 | 5.1 - 10.1 | 99.64 | 99.3 - 99.8 |
| **PCE** | 6.42 | 4.3 - 9.1 | 93.29 | 92.2 - 94.2 |
| **FRAM-CHD** | 18.14 | 14.7 - 22.0 | 98.71 | 98.2 - 99.1 |
| **FRAM-CVD** | 39.38 | 34.8 - 44.1 | 94.9 | 94.0 - 95.7 |
| **PROCAM** | 15.27 | 12.1 - 18.9 | 98.8 | 98.3 - 99.2 |

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# Appendix

## Table 4: Area under the curve (AUC) of risk calculators to detect TPA80 and level of significance for the differences in AUC results

| Switzerland (CH) | AUC | 95%CI | p |
|---|---|---|---|
| **SCORE** | 0.773 | 0.755 to 0.790 | <0.0001 |
| **SCORE-HDL** | 0.782 | 0.764 to 0.799 | <0.0001 |
| **FRAM-CHD** | 0.765 | 0.747 to 0.782 | <0.0001 |
| **FRAM-CVD** | 0.767 | 0.749 to 0.785 | <0.0001 |
| **PCE** | 0.778 | 0.760 to 0.795 | <0.0001 |
| **AGLA** | 0.743 | 0.725 to 0.762 | <0.0001 |

| Switzerland (CH) | SCORE | SCORE-HDL | FRAM-CHD | FRAM-CVD | PCE |
|---|---|---|---|---|---|
| **SCORE** | | | | | |
| **SCORE-HDL** | P = 0.0075 | | | | |
| **FRAM-CHD** | P = 0.3312 | P = 0.0062 | | | |
| **FRAM-CVD** | P = 0.4613 | P = 0.0100 | P = 0.0991 | | |
| **PCE** | P = 0.3653 | P = 0.3014 | P = 0.0331 | P = 0.0610 | |
| **AGLA** | P = 0.0030 | P < 0.0001 | P = 0.0035 | P = 0.0008 | P < 0.0001 |

| Germany (DE) | AUC | 95%CI | p |
|---|---|---|---|
| **SCORE** | 0.868 | 0.856 to 0.880 | <0.0001 |
| **SCORE-HDL** | 0.867 | 0.854 to 0.879 | <0.0001 |
| **FRAM-CHD** | 0.856 | 0.843 to 0.868 | <0.0001 |
| **FRAM-CVD** | 0.859 | 0.846 to 0.871 | <0.0001 |
| **PCE** | 0.769 | 0.754 to 0.784 | <0.0001 |
| **PROCAM** | 0.830 | 0.816 to 0.844 | <0.0001 |

| Germany (DE) | SCORE | SCORE-HDL | FRAM-CHD | FRAM-CVD | PCE |
|---|---|---|---|---|---|
| **SCORE** | | | | | |
| **SCORE-HDL** | P = 0.6090 | | | | |
| **FRAM-CHD** | P = 0.0066 | P = 0.0009 | | | |
| **FRAM-CVD** | P = 0.0320 | P = 0.0150 | P = 0.0024 | | |
| **PCE** | P < 0.0001 | P < 0.0001 | P < 0.0001 | P < 0.0001 | |
| **PROCAM** | P < 0.0001 | P < 0.0001 | P < 0.0001 | P < 0.0001 | P < 0.0001 |

**Table 5: PROCAM and SCORE thresholds, percent of subjects qualifying for statin therapy, sensitivities, specificities and positive and negative predictive values to detect TPA80 for Germany**

| Women | | | PROCAM | | | Women | | | SCORE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** | **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** |
| **40 - 55** | | | | | | **40 – 55** | | | | | |
| 3.0 | 6% | 37 | 96 | 28 | 97 | 0.75 | 7% | 41 | 95 | 27 | 97 |
| 4.0 | 3% | 26 | 98 | 41 | 97 | 1.00 | 1% | 15 | 99 | 44 | 96 |
| 5.0 | 2% | 15 | 99 | 33 | 96 | 1.25 | 1% | 4 | 99 | 25 | 96 |
| 7.5 | 1% | 7 | 99 | 33 | 96 | 1.88 | 0% | 0 | 100 | 0 | 96 |
| 10.0 | 0% | 4 | 100 | 33 | 96 | 2.50 | 0% | 0 | 100 | - | 96 |
| 15.0 | 0% | 0 | 100 | 0 | 96 | 3.75 | 0% | 0 | 100 | - | 96 |
| 20.0 | 0% | 0 | 100 | - | 96 | 5.00 | 0% | 0 | 100 | - | 96 |
| **56 - 65** | | | | | | **56 - 65** | | | | | |
| 3.0 | 51% | 62 | 53 | 31 | 80 | 0.75 | 85% | 89 | 17 | 27 | 81 |
| 4.0 | 35% | 42 | 67 | 31 | 77 | 1.00 | 66% | 71 | 35 | 28 | 78 |
| 5.0 | 29% | 38 | 75 | 34 | 78 | 1.25 | 51% | 58 | 51 | 29 | 78 |
| 7.5 | 12% | 20 | 91 | 43 | 77 | 1.88 | 25% | 31 | 78 | 33 | 77 |
| 10.0 | 9% | 20 | 95 | 56 | 77 | 2.50 | 12% | 13 | 88 | 29 | 75 |
| 15.0 | 3% | 7 | 98 | 50 | 75 | 3.75 | 5% | 4 | 95 | 25 | 74 |
| 20.0 | 2% | 4 | 98 | 50 | 75 | 5.00 | 1% | 2 | 99 | 50 | 75 |
| **Men** | | | **PROCAM** | | | **Men** | | | **SCORE** | | |
| **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** | **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** |
| **40 - 55** | | | | | | **40 – 55** | | | | | |
| 3.0 | 60% | 84 | 45 | 24 | 93 | 0.75 | 58% | 88 | 48 | 27 | 95 |
| 4.0 | 49% | 76 | 57 | 27 | 92 | 1.00 | 44% | 76 | 63 | 30 | 93 |
| 5.0 | 39% | 71 | 68 | 32 | 92 | 1.25 | 33% | 66 | 74 | 35 | 91 |
| 7.5 | 24% | 52 | 82 | 38 | 89 | 1.88 | 16% | 43 | 90 | 47 | 88 |
| 10.0 | 17% | 45 | 89 | 48 | 88 | 2.50 | 8% | 28 | 96 | 61 | 86 |
| 15.0 | 7% | 23 | 96 | 55 | 85 | 3.75 | 2% | 11 | 100 | 88 | 84 |
| 20.0 | 4% | 14 | 99 | 69 | 84 | 5.00 | 1% | 4 | 100 | 88 | 83 |
| **56 - 65** | | | | | | **56 - 65** | | | | | |
| 3.0 | 91% | 92 | 11 | 49 | 60 | 0.75 | 100% | 100 | 0 | 48 | - |
| 4.0 | 87% | 91 | 17 | 50 | 65 | 1.00 | 100% | 99 | 0 | 48 | 0 |
| 5.0 | 79% | 84 | 27 | 52 | 65 | 1.25 | 99% | 99 | 2 | 49 | 80 |
| 7.5 | 61% | 68 | 45 | 54 | 60 | 1.88 | 84% | 91 | 21 | 52 | 71 |
| 10.0 | 47% | 57 | 63 | 59 | 61 | 2.50 | 66% | 74 | 42 | 54 | 63 |
| 15.0 | 25% | 33 | 82 | 63 | 57 | 3.75 | 32% | 42 | 78 | 64 | 59 |
| 20.0 | 15% | 21 | 91 | 69 | 55 | 5.00 | 15% | 24 | 93 | 77 | 57 |

**Table 6: AGLA and SCORE thresholds, percent of subjects requiring preventive therapy, sensitivities, specificities and positive and negative predictive values to detect TPA80 for Switzerland, women only**

| Women | | | AGLA | | | Women | | | SCORE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** | **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** |
| **40 - 55** | | | | | | **40 – 55** | | | | | |
| 3.0 | 5% | 22 | 95 | 18 | 96 | 0.75 | 12% | 39 | 89 | 15 | 97 |
| 4.0 | 4% | 17 | 96 | 17 | 96 | 1.00 | 6% | 28 | 95 | 20 | 97 |
| 5.0 | 2% | 0 | 98 | 0 | 95 | 1.25 | 2% | 22 | 99 | 44 | 96 |
| 7.5 | 1% | 0 | 99 | 0 | 95 | 1.88 | 1% | 6 | 99 | 33 | 96 |
| 10.0 | 1% | 0 | 99 | 0 | 95 | 2.50 | 0% | 6 | 100 | 50 | 96 |
| 15.0 | 0% | 0 | 100 | - | 96 | 3.75 | 0% | 0 | 100 | - | 96 |
| 20.0 | 0% | 0 | 100 | - | 96 | 5.00 | 0% | 0 | 100 | - | 96 |
| **56 - 65** | | | | | | **56 - 65** | | | | | |
| 3.0 | 30% | 53 | 74 | 25 | 91 | 0.75 | 88% | 97 | 14 | 15 | 96 |
| 4.0 | 20% | 45 | 84 | 31 | 90 | 1.00 | 76% | 90 | 26 | 17 | 94 |
| 5.0 | 15% | 37 | 89 | 35 | 90 | 1.25 | 63% | 85 | 41 | 19 | 94 |
| 7.5 | 8% | 20 | 94 | 34 | 88 | 1.88 | 35% | 57 | 68 | 23 | 91 |
| 10.0 | 4% | 10 | 97 | 38 | 87 | 2.50 | 17% | 32 | 85 | 26 | 89 |
| 15.0 | 1% | 2 | 99 | 33 | 86 | 3.75 | 5% | 15 | 97 | 43 | 88 |
| 20.0 | 0% | 0 | 99 | 0 | 86 | 5.00 | 2% | 3 | 98 | 20 | 86 |
| **66 - 75** | | | | | | **66 - 75** | | | | | |
| 3.0 | 66% | 74 | 39 | 41 | 73 | 0.75 | 100% | 100 | 0 | 36 | - |
| 4.0 | 56% | 63 | 48 | 41 | 69 | 1.00 | 100% | 100 | 0 | 36 | - |
| 5.0 | 42% | 51 | 64 | 44 | 70 | 1.25 | 100% | 100 | 0 | 36 | - |
| 7.5 | 24% | 32 | 81 | 49 | 68 | 1.88 | 97% | 96 | 3 | 36 | 57 |
| 10.0 | 13% | 13 | 88 | 37 | 64 | 2.50 | 87% | 91 | 16 | 38 | 76 |
| 15.0 | 5% | 9 | 98 | 70 | 65 | 3.75 | 53% | 68 | 55 | 46 | 75 |
| 20.0 | 3% | 5 | 99 | 67 | 65 | 5.00 | 33% | 47 | 74 | 51 | 71 |

**Table 7: AGLA and SCORE thresholds, percent of subjects requiring preventive therapy, sensitivities, specificities and positive and negative predictive values to detect TPA80 for Switzerland, men only**

| Men | | AGLA | | | | Men | | SCORE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** | **cut** | **statin** | **SENS** | **SPEC** | **PPV** | **NPV** |
| **40 - 55** | | | | | | **40 – 55** | | | | | |
| 3.0 | 30% | 53 | 74 | 25 | 91 | 0.75 | 72% | 87 | 31 | 19 | 93 |
| 4.0 | 20% | 45 | 84 | 31 | 90 | 1.00 | 55% | 68 | 47 | 19 | 89 |
| 5.0 | 15% | 37 | 89 | 35 | 90 | 1.25 | 42% | 54 | 60 | 20 | 88 |
| 7.5 | 8% | 20 | 94 | 34 | 88 | 1.88 | 23% | 34 | 79 | 24 | 87 |
| 10.0 | 4% | 10 | 97 | 38 | 87 | 2.50 | 13% | 24 | 90 | 30 | 86 |
| 15.0 | 1% | 2 | 99 | 33 | 86 | 3.75 | 4% | 10 | 97 | 40 | 85 |
| 20.0 | 0% | 0 | 99 | 0 | 86 | 5.00 | 1% | 3 | 100 | 67 | 85 |
| **56 - 65** | | | | | | **56 - 65** | | | | | |
| 3.0 | 66% | 74 | 39 | 41 | 73 | 0.75 | 100% | 100 | 0 | 37 | - |
| 4.0 | 56% | 63 | 48 | 41 | 69 | 1.00 | 99% | 99 | 0 | 37 | 33 |
| 5.0 | 42% | 51 | 64 | 44 | 70 | 1.25 | 99% | 99 | 2 | 37 | 67 |
| 7.5 | 24% | 32 | 81 | 49 | 68 | 1.88 | 88% | 90 | 13 | 38 | 68 |
| 10.0 | 13% | 13 | 88 | 37 | 64 | 2.50 | 69% | 76 | 34 | 41 | 71 |
| 15.0 | 5% | 9 | 98 | 70 | 65 | 3.75 | 36% | 45 | 69 | 46 | 68 |
| 20.0 | 3% | 5 | 99 | 67 | 65 | 5.00 | 19% | 25 | 84 | 49 | 66 |
| **66 - 75** | | | | | | **66 - 75** | | | | | |
| 3.0 | 49% | 71 | 55 | 23 | 91 | 0.75 | 100% | 100 | 0 | 57 | - |
| 4.0 | 39% | 56 | 65 | 23 | 89 | 1.00 | 100% | 100 | 0 | 57 | - |
| 5.0 | 31% | 44 | 71 | 22 | 87 | 1.25 | 100% | 100 | 0 | 57 | - |
| 7.5 | 18% | 28 | 83 | 24 | 86 | 1.88 | 100% | 100 | 0 | 57 | - |
| 10.0 | 11% | 23 | 91 | 32 | 86 | 2.50 | 99% | 99 | 1 | 57 | 50 |
| 15.0 | 4% | 6 | 96 | 25 | 85 | 3.75 | 95% | 96 | 5 | 57 | 50 |
| 20.0 | 1% | 3 | 99 | 29 | 84 | 5.00 | 77% | 81 | 30 | 60 | 55 |

**Table 8: Sensitivity of various thresholds of coronary risk calculators by age group 40-55, by country (CH and DE) to detect TPA80 at a prevalence of CH 11% and DE 13%**

| 40 - 55 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other / SCORE | CH-FRAM-CHD | CH-FRAM-CVD | CH-SCORE | CH-SCORE-HDL | CH-PCE | CH-AGLA | DE-FRAM-CHD | DE-FRAM-CVD | DE-SCORE | DE-SCORE-HDL | DE-PCE | DE-PROCAM |
| 0.0-2.5/1% | 96 | 100 | 61 | 55 | 90 | 64 | 98 | 100 | 69 | 59 | 92 | 81 |
| 0.0-5.0/2% | 86 | 95 | 26 | 21 | 61 | 36 | 91 | 96 | 34 | 27 | 68 | 64 |
| 0.0-7.5/3% | 66 | 81 | 11 | 8 | 37 | 23 | 68 | 88 | 17 | 13 | 48 | 47 |
| 0.0-10.0/4% | 48 | 70 | 7 | 4 | 24 | 19 | 51 | 75 | 6 | 4 | 34 | 40 |
| 0.0-12.5/5% | 28 | 55 | 2 | 1 | 14 | 8 | 39 | 59 | 3 | 2 | 22 | 27 |
| 0.0-15.0/6% | 19 | 40 | 1 | 1 | 8 | 5 | 28 | 50 | 2 | 1 | 14 | 20 |
| 0.0-17.5/7% | 13 | 28 | 1 | 1 | 3 | 3 | 22 | 39 | 1 | 0 | 8 | 15 |
| 0.0-20.0/8% | 10 | 22 | 1 | 0 | 3 | 2 | 13 | 30 | 1 | 0 | 4 | 12 |
| 0.0-22.5/9% | 3 | 18 | 0 | 0 | 1 | 1 | 9 | 25 | 0 | 0 | 2 | 10 |
| 0.0-25.0/10% | 3 | 13 | 0 | 0 | 1 | 1 | 5 | 21 | 0 | 0 | 1 | 7 |
| 0.0-27.5/11% | 2 | 10 | 0 | 0 | 0 | 0 | 4 | 13 | 0 | 0 | 1 | 6 |
| 0.0-30.0/12% | 0 | 8 | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 0 | 1 | 4 |

Other denotes FRAM, PROCAM, AGLA, PCE

**Table 9: Sensitivity of various thresholds of coronary risk calculators by age group 56-65, by country (CH and DE) to detect TPA80 at a prevalence of CH 25% and DE 41%**

| 56 - 65 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other / SCORE | CH-FRAM-CHD | CH-FRAM-CVD | CH-SCORE | CH-SCORE-HDL | CH-PCE | CH-AGLA | DE-FRAM-CHD | DE-FRAM-CVD | DE-SCORE | DE-SCORE-HDL | DE-PCE | DE-PROCAM |
| 0.0-2.5/1% | 100 | 100 | 96 | 90 | 100 | 77 | 100 | 100 | 94 | 86 | 96 | 89 |
| 0.0-5.0/2% | 91 | 99 | 77 | 62 | 88 | 51 | 92 | 99 | 74 | 62 | 88 | 75 |
| 0.0-7.5/3% | 80 | 92 | 50 | 34 | 72 | 36 | 83 | 93 | 51 | 34 | 76 | 58 |
| 0.0-10.0/4% | 65 | 87 | 31 | 21 | 51 | 23 | 72 | 86 | 31 | 22 | 59 | 50 |
| 0.0-12.5/5% | 48 | 76 | 19 | 12 | 35 | 16 | 59 | 79 | 20 | 12 | 38 | 40 |
| 0.0-15.0/6% | 34 | 63 | 12 | 8 | 22 | 10 | 45 | 70 | 13 | 7 | 23 | 28 |
| 0.0-17.5/7% | 23 | 50 | 6 | 3 | 14 | 7 | 32 | 60 | 8 | 4 | 13 | 21 |
| 0.0-20.0/8% | 16 | 39 | 5 | 2 | 6 | 4 | 23 | 48 | 4 | 2 | 8 | 18 |
| 0.0-22.5/9% | 11 | 30 | 4 | 1 | 3 | 4 | 16 | 42 | 3 | 1 | 4 | 13 |
| 0.0-25.0/10% | 10 | 22 | 2 | 1 | 1 | 2 | 11 | 31 | 2 | 1 | 2 | 9 |
| 0.0-27.5/11% | 6 | 17 | 2 | 0 | 1 | 1 | 8 | 25 | 2 | 1 | 1 | 5 |
| 0.0-30.0/12% | 4 | 14 | 0 | 0 | 0 | 1 | 5 | 18 | 1 | 0 | 0 | 4 |

Other denotes FRAM, PROCAM, AGLA, PCE

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