Predictive Value of Clinical Risk Assessment Tools and Guidelines for 10 year Coronary Heart Disease Risk in Practice Based Primary Care Subjects: a Prospective Pilot Study

Michel Romanens, 24th November 2003

Abstract

Background: Risk for developing myocardial infarction derived from risk tables in primary care subjects in Switzerland may over- or underestimate risk. Coronary calcifications, a biological marker of risk, may improve the performance of risk tables.

Design: Prospective cross sectional monocenter study.

Methods: We used coronary calcium score percentiles > 50 (CS%>50) as a surrogate marker for 10 year myocardial infarction risk. CS%>50 was compared to several risk charts, was used to reclassify subjects in the intermediate risk category assessed by Framingham risk scores (FRS) and was used to calculate a cohort specific correction factor for FRS and PROCAM. Results from risk charts were entered into the Bayes formula as the pretest risk estimates.

Results: 100 subjects (54 ± 11 years, 44 women) were assessed. Sensitivity of FRS to detect CS%>50 was 47% and specificity was 85%. NCEP III and Swiss guidelines had sensitivities of 53% and 67% respectively (p NS), and lower specificities of 66% and 67% than FRS (p<0.05). In 21 subjects with intermediate risk assessed by FRS, CS%>50 derived posttest probabilities shifted 16 (76%) into the low risk category and 5 subjects (24%) into the high risk category. Cohort specific correction factors were 0.68 for FRS and 0.64 for PROCAM.

Conclusion: In our Swiss German cohort, risk tables tended to overestimate risk. A biological risk marker (calcifications of coronary arteries), may allow to improve risk prediction in primary care subjects with intermediate risk and helps to calculate cohort specific correction factors of risk derived from risk charts.

Introduction

Coronary heart disease (CHD) presents as myocardial infarction or sudden death in 60% of the cases (1). Therefore, early detection of individuals at risk for CHD is crucial to promote risk modifying behaviors and initiate appropriate medical management (2-6). Accordingly, cardiovascular risk assessment tools such as the Framingham risk charts (7, 10) and PROCAM (9) are used to guide preventive measures in both the American and European continent (7-11). Though useful, these risk assessment tools miss a substantial portion of patients at risk of an event and have not been validated in several European countries where there might be a greater prevalence of low risk populations (6). An example of such low risk countries is Switzerland where life style and genetic heritage make a “French paradox” very likely. Hence, measurements of atherosclerosis burden may provide additional information to allow refinement of risk assessment.
In this pilot study we used a very sensitive biological marker for the 10 year risk to develop hard coronary events (fatal or non fatal myocardial infarction) obtained from percentiles of coronary calcifications above the 50th percentile (CS%>50), a strong marker of CHD risk (12-15). First, we aimed to compare CS%>50 with the risk obtained from several coronary risk charts. Second, we aimed to improve risk prediction in intermediate risk patients, where about one third of coronary events occur within 10 years (9). Third, we aimed to perform an adjustment for risk by calculating posteriorer probabilities based on the Bayes formula in order to correct for the results of coronary risk charts. These calculations may be helpful for working groups elaborating new guidelines to create region-specific correction factors.

Methods

Patient Selection

Three primary care physicians participated in this prospective cross sectional study. Their practices are located in Olten and Trimbach, Switzerland, an area with approximately 20,000 total rural and urban inhabitants. The 3 physicians were asked to recruit 100 subjects randomly selected from consecutive patients entering their practices between the hours their of 9 to 10 o’clock in the morning. Subjects aged 35 to 75 years were included if they had no known cardiovascular disease, severe claustrophobia, chronic arrhythmias such as atrial fibrillation and frequent premature ventricular contractions, life expectancy below two years or unwillingness to give informed written consent. Women of childbearing age and not using birth methods were further excluded. All imaging studies were performed centrally at the Rodiag Institute, Olten, Switzerland. The study was approved by the Ethics Committee of the Canton Solothurn, Switzerland.

Imaging Method

Coronary calcium screening was performed with a multi-slice computed tomography scanner (MSDT, Aquilion, Toshiba, Tokyo, Japan) with prospective triggering (starting at 50% of the R wave). Images (2 mm slice thickness) were transferred to a workstation for quantification of coronary calcium using NetraMD Software (ScImage Palo Alto, California, USA). High risk for fatal and nonfatal myocardial infarction was defined as coronary calcium score percentile (CS%) > 50 (ten year risk for fatal and nonfatal myocardial infarction ≥ 20 %). Percentiles were obtained by comparing the calculated scores with the published scores of 10,122 asymptomatic subjects screened by electron beam tomography (EBT). (19) Interobserver variability for CS% calculation was 0.2±1.3% in 96 subjects randomly selected from a database of 240 subjects in our imaging center and the interscan variability was 6±7%.

Assessment of Risk and Statistical Methods

Risk comparisons were based for all tests on estimates for the occurrence of fatal and non-fatal myocardial infarction within 10 years. For the calculation of risk according to the Framingham Risk Score (FRS) (16) the following variables were initially considered: age, gender, smoking status, diabetes mellitus and hypertension. According to the recommendations of the Adult Treatment Panel III (ATP-III), risk was then calculated for each patient based on age, gender, smoking status, total cholesterol, HDL cholesterol, and systolic blood pressure (10).
The PROCAM risk was calculated for the 45 men aged 35-65 years enrolled in our cohort using the variables gender, age, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, smoking habits, diabetes mellitus and family history for premature CAD (9). Total cholesterol, triglycerides, HDL-cholesterol, and glucose were measured after an 8-hour fast.

Coronary calcium score percentiles (CS%) were used to adjust risk calculated according to FRS and PROCAM. Posterior probabilities were calculated with the Bayes formula using published sensitivities and specificities for risk of future myocardial infarction (20). The risk was adjusted using correction factors that were calculated by dividing posttest risk derived from CS% by the pretest risk derived from either FRS or PROCAM.

Data were compiled in an Excel data sheet (Microsoft, Redmond, WA, USA) and further analyzed using GB-STAT version 9.0 (Dynamic Microsystems, 2000, Silver Spring, MD, US) using Chi²-statistics. For statistical analysis, the level of significance was set at < 0.05.

The study was approved by the local ethical committee operating for the canton of Solothurn, Switzerland.

Results

Patient characteristics and risk derived from a Framingham Risk Score

Of 304 subjects screened, 88 (29 %) were excluded because of age below 35 years or above 75, 47 (15 %) because of known vascular disease such as previous myocardial infarction or stroke, life expectancy below two years, inability to understand German, frequent arrhythmias, severe claustrophobia, and 69 (23%) did not consent to participate. 100 were entered into the study. Patient characteristics are given in table 1.

A Framingham Risk Score (FRS) was calculated to assess risk for future fatal and non fatal myocardial infarction as described (16). Risk estimates to detect 10 year risk for fatal and nonfatal myocardial infarction showed 24 subjects to be at low (5-9%) and 35 at very low risk (< 5%), while 21 subjects were classified in the intermediate risk category (10-19%) and 20 subjects in the high risk category (≥ 20%, figure 1). The mean 10 year FRS risk for the entire cohort was 10.6 %.

Coronary calcium percentiles

Sixty five subjects had no detectable coronary calcifications on MSDT. In the 35 subjects with coronary calcium, the percentiles were widely distributed between the 10th and the 99th percentile (figure 2).

Performance of different risk assessment strategies to detect CS%>50

Table 2 summarizes sensitivities, specificities, positive and negative predictive values, and accuracies of the different cardiovascular risk assessment tools.
Swiss guidelines (sensitivity 67%, \( \chi^2 = 1.22, p = 0.269 \)) but not NCEP III (sensitivity 53%, \( \chi^2 = 0.18, p=0.715 \)) tended (p=NS) to increase sensitivity in comparison to FRS (sensitivity 47%).

The specificity of FRS for prediction of a CS ≥ 50% was 85%. NCEP III and Swiss guidelines showed lower specificities of 66% (\( \chi^2 = 7.12, p = 0.008 \)) and 67% (\( \chi^2 = 7.23, p = 0.007 \)) respectively, when compared to FRS.

Coronary calcium percentiles as a possible modifier of FRS derived risk estimates

The Bayes formula was used to compute posttest-probabilities with the FRS risk estimates as the pretest value (20). Five of 21 (24%) intermediate risk subjects were reclassified into the high risk group and 16 (76%) into the low risk group. Eleven of 20 (55%) subjects with high risk defined by FRS were reclassified into the low risk group and two subjects into the intermediate risk group. In the low risk group, only 2 of 51 subjects (3%) were reclassified as high risk subjects, while 48 (94%) remained in the low risk group.

Coronary calcium percentiles as a possible marker to calculate population specific correction factors

By adjusting the risk estimates based on a posttest probability risk obtained by CS% (see table 3), the average FRS 10 year risk for myocardial infarction decreased from 10.6% to 7.2%, yielding a correction factor of 0.68. Using this correction factor, accuracy to detect CS%>50 increased from 79% to 82% at the expense of sensitivity (20% versus 47%, all p=NS).

The PROCAM algorithm showed a sensitivity of 67% and a specificity of 87% to predict a CS%>50. Using a posttest risk obtained by CS% (see table 3), PROCAM 10 year risk for myocardial infarction decreased from 10.8% to 6.9%, yielding a correction factor of 0.64. Using this correction factor, accuracy to detect CS%>50 increased from 84% to 87% at the expense of sensitivity (67% versus 33%).
Discussion
The European guidelines for coronary risk estimates were published in 1998 (25) and were based on data from the Framingham study cohort. Risk estimation in the Framingham paradigm includes soft (angina) as well as hard CHD events and has been shown to markedly overestimate risk in an Italian cohort (6). The European Task Force was aware of these issues and called for national adjustments to their guidelines for cardiovascular risk assessment (25). Since the publication of these European guidelines, there has been a shift of paradigm in risk prediction. Prediction of soft events has been removed from the recent NCEP III guidelines (10), from the PROCAM algorithm (9) and from the new European guidelines termed EU-SCORE (26). As a consequence, the specificity of the PROCAM algorithm (9) could be increased to 95%. This high specificity of PROCAM leads to a very high accuracy (91%), but to a very low sensitivity (33%) to detect future myocardial infarctions (9). Similarly low sensitivity and high specificity was published for global cardiovascular mortality risk derived from the EU-SCORE (26).

Our study subjects were randomly selected from a Swiss German primary care setting. As a cohort they allow to calculate coronary risk estimates in the German part of Switzerland which has not been done recently. The Swiss population is at relatively low risk for coronary events, comparable to Mediterranean countries such as Italy and France (22), but there are no data on coronary risk in the Swiss German part of Switzerland, a region which did not participate in the MONICA project (24). Further, none of the widely used risk assessment charts (8-11,16) have been validated for a Swiss and more specifically for a Swiss German population, and generally very few data exist in low risk populations. Therefore, we aimed to find a reasonable surrogate marker of outcome. For this purpose we have chosen a coronary calcium score percentile above 50. This test has been shown in a U.S. cohort to be a highly sensitive (93%) but not very specific (specificity 52%) biological or “imaging” marker to detect the 10 year risk for myocardial infarction (19).

The first aim of our study was to compare CS%>50 with risk charts for the occurrence of 10 year risk of hard coronary events (fatal or nonfatal myocardial infarction). The European Task Force guidelines includes risk derived from the original Framingham cohort (FRC) also for soft coronary events (e.g. angina) (25). We therefore chose a modification of FRC as reported by S. Grundy which allows to calculate 10 year risk estimates derived from the original Framingham cohort for hard coronary events only (16). Based on this risk estimation, we show that Swiss guidelines for the treatment of cholesterol published in 1999 (8) show a better sensitivity (67%) to detect CS%>50 than FRS (47%, p NS), however at a significant loss of specificity (67% versus 85%, p=0.007) when compared to FRS. This may lead to overtreatment and most probably increase cost. When we applied NCEP III guidelines (10) to our population, we observed a lower sensitivity (53%), similar to the low sensitivity we found for FRS. Furthermore, NCEP III had a lower specificity than FRS (66% versus 85%, p=0.008). Therefore, the application of NCEP III guidelines is inadequate in Swiss primary care subjects.

The second aim of our study was to test the ability of CS%>50 to better assess patients with intermediate risk in common risk assessment tools. About 33% of myocardial infarctions have been observed to occur in these intermediate risk patients (9). For this purpose, we reclassified patients assessed with FRS (16) according to their coronary calcium percentiles using posterior probabilities based on the Bayes formula. Expectedly (6,23), 16 out of 21 (76%) intermediate risk subjects
could be reclassified into the low and 5 (24%) into the high risk category. Therefore, these results, albeit obtained in a small study, show that most intermediate risk subjects defined by FRS are in fact low risk subjects.

The third aim of this pilot study was to obtain an estimate of correction factors that could be used to regionally adjust risk obtained from risk charts with the extension of a biological marker of risk, e.g. a CS%>50. National correction factors have been suggested in the PROCAM Pocket Guide 2003 based on the MONICA data (24): 0.61 for the Italian speaking part and 0.55 for the French speaking part of Switzerland (24). However, no correction factor is available for the Swiss German population, which originally did not participate in the MONICA project. We calculated a correction factor for FRS: 10 year myocardial infarction risk was estimated to be 10.6% for the entire cohort of 100 subjects. The posttest risk estimate decreased to 7.2% with coronary calcium scoring, yielding a correction factor of 0.68. Using this correction factor, accuracy to detect CS%>50 increased from 79% to 82% and specificity from 85% to 93% at the expense of sensitivity (20% versus 47%, all p=NS). The correction factor of 0.68 is comparable to the correction factors derived from MONICA data for the Swiss Italian population (0.61) and the Swiss French population (0.55). In contrast to the other correction factors, our correction factor relates to persons very recently investigated.

The same calculations were also applied to PROCAM risk estimates of 10 year risk to develop a myocardial infarction. The PROCAM algorithm, which is only valid for men aged 35-65 years, was applied to our 45 men aged 35-65 years. In these men, the PROCAM algorithm performed well with a good sensitivity of 67% and a high specificity of 87% to detect CS%>50. Again, using a posttest risk obtained by coronary calcium score percentiles (see table 3), PROCAM 10 year risk for myocardial infarction decreased from 10.8% to 6.9%, yielding a correction factor of 0.64. Using this correction factor, accuracy to detect CS%>50 increased from 84% to 87% at the expense of sensitivity (33% versus 67%, all p=NS).

**Study Limitations**

This study has several limitations. First, the best gold standard (i.e., event rates of myocardial infarction in a prospective cohort study) was not available in this study. We substituted this gold standard with a surrogate marker of risk for myocardial infarction. Absence of coronary calcium is correlated with a very low event rate for fatal and nonfatal myocardial infarction of 2/1000/year in middle-age asymptomatic subjects (14,21). Therefore, it is reasonable to argue that absence of coronary calcium in intermediate risk subjects defined by FRS and PROCAM may help to identify true low risk subjects. Although unproven, risk related to coronary calcification may be lower in low risk populations such as the Swiss than in the US cohort, from where our CS%>50 surrogate marker was originally obtained (19), the correct reclassification of intermediate subjects into low risk subjects appears even more evident. Further, posttest risk calculations cannot be performed with high precision using other markers of risk, such as the ankle-arm-index (17) or carotid intima-to-media thickness (18).

Second, we had to adopt data from the EBCT risk prognostication database (19) into MSDT imaging, since a similar normal database allowing for calculation of accurate posttest-probabilities (20) is neither available for MSDT nor for EBCT in Europe. Once the results from the Rotterdam (27) and the Heinz Nixdorf Recall Study (28)
are available, the CS%>50 used in our study may be substituted by European data. However, all such outcome data will be inaccurate as well because medical interventions reduce risk in subjects originally identified to have high risk coronary calcifications. This is true for all event studies assessing risk tools.

**Conclusions**

This pilot study uses a very sensitive ("oversensitive") biological marker of risk (CS%>50) as a comparator for risk obtained from risk charts in a Swiss German cohort derived from a population at low coronary risk. Despite using this oversensitive marker, CS%>50 reclassified 76% of our intermediate risk subjects assessed by FRS into the low risk group. Therefore, CS%>50 may allow to improve risk prediction in intermediate risk patients, where, according to PROCAM, about one third of coronary events occur within 10 years (9). New guidelines or risk assessment tools such as PROCAM or the EU-SCORE have higher specificity and accuracy but entail an unacceptable loss of sensitivity. This may leave up to about two thirds of subjects, who would have needed preventive therapy, undetected even in a low risk population. Therefore, coronary calcifications may help to identify the subject at higher than the expected intermediate risk, e.g. by using CS%>75. Finally, our CS%>50 derived correction factors show an overestimation of risk in our pilot cohort with the use of FRS and PROCAM. Therefore, such an algorithm may be helpful to calculate correction factors in different areas in Europe in which data from prospective observational studies are lacking.

**Acknowledgements:**

We are grateful to the participating general practitioners (Markus Annaheim, Simon Heiniger, and Andreas Schweizer) and the technical assistance of Ms A. Reitshammer. Special thanks are owed to the Chairman of the Rodia Diagnostic Centers, Switzerland, Mr. Kiou Afchani, for the support for this study.
References
1 Murabito J. Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation. Circulation 1993;88:2548-555
5 Grover SA, Coupal L, Xiao-Ping H. Identifying adults at increased risk of coronary artery disease. JAMA 1995;274:801-06
10 Executive Summary of the third report of the national cholesterol education program. NCEP Adult Treatment Panel III. JAMA 2001;285:2486-497
17 Newman, A. B., Shemanski, L., Manolio, et al. Ankle-Arm index as a


21  Verschuren W et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA. 1995;274:131-36


24  Tunstall H et al. for the WHO MONICA Project. Lancet 1999; 353: 1547-1557


Tables and Figures

Table 1: Clinical characteristics of the study group (N=100)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>54.6±10.7</td>
</tr>
<tr>
<td>Male / Female</td>
<td>56 / 44</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
</tr>
<tr>
<td>Smokers</td>
<td>30</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>14</td>
</tr>
<tr>
<td>Office hypertension (&gt; 140 mm Hg)</td>
<td>34</td>
</tr>
<tr>
<td>Cholesterol (mmol/l), mean±SD</td>
<td>5.8 ± 1.1</td>
</tr>
<tr>
<td>HDL (mmol/l), mean±SD</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides (mmol/l), mean±SD</td>
<td>1.7 ± 0.8</td>
</tr>
<tr>
<td>LDL (mmol/l), mean±SD</td>
<td>3.8 ± 1</td>
</tr>
<tr>
<td>Glucose (mmol/l), mean±SD</td>
<td>5.9 ± 2.5</td>
</tr>
<tr>
<td>Aspirin users</td>
<td>6</td>
</tr>
<tr>
<td>Statin users</td>
<td>7</td>
</tr>
<tr>
<td>Antihypertensive drug users</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 2: Performance of different risk assessment tools to detect CS%>50

<table>
<thead>
<tr>
<th></th>
<th>FRS</th>
<th>FRSc</th>
<th>AGLA</th>
<th>NCEP III</th>
<th>PROCAM</th>
<th>PROCAMc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>47</td>
<td>20</td>
<td>67</td>
<td>53</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Specificity</td>
<td>85</td>
<td>93</td>
<td>67</td>
<td>66</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>PPV</td>
<td>35</td>
<td>33</td>
<td>26</td>
<td>21</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>NPV</td>
<td>90</td>
<td>97</td>
<td>92</td>
<td>88</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Accuracy</td>
<td>79</td>
<td>82</td>
<td>67</td>
<td>66</td>
<td>84</td>
<td>87</td>
</tr>
</tbody>
</table>

FRS: Framingham Risk Charts.
FRSc: FRS corrected for CS% posttest probability, correction factor 0.68
AGLA: Swiss guidelines for risk management.
PROCAM: German risk guidelines applied to 45 men aged 35-65 years
PROCAMc: PROCAM corrected for CS% posttest probability, correction factor 0.64
Table 3: Sensitivities And Specificities For CS% To Detect 10-Year Risk For The Combined End Point Of Fatal And Nonfatal Myocardial Infarction (Modified from Callister et al) (20)

<table>
<thead>
<tr>
<th>CS%</th>
<th>Risk</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-74</td>
<td>20-34</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>75-89</td>
<td>35-64</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>90-99</td>
<td>≥ 65</td>
<td>46</td>
<td>90</td>
</tr>
</tbody>
</table>
Figure 1: Framingham risk estimation (FRS) (16).

Figure 2: Distribution of coronary calcium score percentiles