Framingham Risk Score Inadequately Predicts Cardiac Risk in Young Patients Presenting with a First Myocardial Infarction

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Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. The Framingham Risk Score (FRS) was derived from the Framingham Heart Study (FHS) cohort and was designed to predict 10-year risk of hard coronary events, including mortality due to coronary heart disease and non-fatal myocardial infarction (MI) by considering the presence or absence of important risk factors. The FRS is calculated by taking into account age, sex, smoking status, total cholesterol, high-density lipoprotein cholesterol and systolic blood pressure.1,2 The FRS is a widely adopted and well-validated tool to assess the risk for a first cardiac event, and focuses on absolute risk of disease rather than on modification of individual risk factors.1-10 It is also useful in guiding the intensity of risk factor interventions.2

It has been shown that the vast majority of individuals with CVD carry at least one antecedent, traditional risk factor such as smoking, diabetes, hypertension and/or hypercholesterolaemia.11 Exposure to high levels of these risk factors throughout life increases atherosclerotic burden,12,13 resulting in an increased risk for future clinical CVD events.14,15 Conversely, the absence of established risk factors is associated with very low lifetime risk for CVD and markedly longer survival.15 The FHS cohort comprised primarily of middle-aged Caucasian men, and in middle-aged adults, measurement of traditional risk factors is a surrogate for atherosclerotic burden and hence, indicative of the risk of clinical CVD.

However, the same cannot be said for younger adults. Even though the atherosclerotic process begins at a young age in relation to traditional risk factor burden,16 clinical CVD events do not occur until much later.17,18 This means that while the majority of people of a relatively younger age are defined as low risk using existing risk algorithms, a low short-term risk in younger subjects may not reflect...
their true lifetime risk.

Additionally, diabetes mellitus is not traditionally considered when computing the FRS. Recently, diabetes mellitus is considered a coronary artery disease (CAD) equivalent because patients with diabetes without known CAD were found to have similar cardiac event rates as patients without diabetes who had a prior MI. The Singapore National Health Survey 2004 reported that the proportion of Singapore residents with previously undiagnosed diabetes mellitus was 49.4%. Thus, there is an underestimation of the prevalence of diabetes mellitus and therefore cardiac risk burden in the population.

We hypothesized that the FRS underestimates cardiovascular risk in young adults and this may in part be because of a higher incidence of newly diagnosed diabetes mellitus amongst the young.

Materials and Methods

Study Sample and Risk Factor Assessment

This is a retrospective medical case note review. We investigated 1267 patients who were admitted to our institution between January 2002 and November 2007 with a first MI. Baseline demographics, smoking history, other co-morbidities (including hypertension, diabetes and hypercholesterolemia) and current treatments for them were obtained from review of case notes. Other data collected included blood pressure on admission, fasting serum lipids and fasting blood glucose levels.

The 10-year FRS was calculated for each patient using their admission demographics and fasting lipid profiles. The risk predictors used were age, total serum cholesterol, serum high-density lipoprotein, systolic blood pressure, treatment for hypertension (if any), and smoking status.

Exclusions

During the period of January 2002 and November 2007, 1744 patients were admitted for acute MI, of whom 1267 were recruited. The remaining 477 (27%) patients with pre-existing diabetes mellitus and vascular disease were excluded.

Statistical Analyses

Patients were divided into 3 groups based on their age: group A (<40 years), group B (40 to 64 years) and group C (≥65 years). For each group, based on the FRS, patients were divided into risk deciles – the first decile corresponding to a 10-year CVD risk of 3% or less, the tenth corresponding to a risk of more than 30%, and the remainder falling in between at approximately equal intervals apart.

The distribution of risk deciles and the sensitivity of the FRS in identifying at least intermediate risk subjects (10-year risk for cardiac events >10%) were computed for each age group. The one-way ANOVA test with post hoc multiple comparisons was used to compare between groups. P < 0.05 was considered statistically significant. All analyses were performed using SPSS version 16.0 for Windows.

Institutional Review Board Approval

The study was approved by the National Health Group institutional review board.

Results

Baseline Characteristics

The mean age was 54.7 ± 11 years, and 88.4% were males. Table 1 shows baseline characteristics of the 3 different age groups. History of cigarette smoking and hyperlipidaemia were the predominant cardiovascular risk factors among the young. The incidence of newly diagnosed diabetes mellitus is higher in groups A and B as compared to group C (12.0% risk for cardiac events >10%) were computed for each age group. The one-way ANOVA test with post hoc multiple comparisons was used to compare between groups. P < 0.05 was considered statistically significant. All analyses were performed using SPSS version 16.0 for Windows.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (&lt; 40)</th>
<th>Group B (40-64)</th>
<th>Group C (≥65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>92</td>
<td>921</td>
<td>254</td>
</tr>
<tr>
<td>Age, y</td>
<td>35.3 ± 4.0</td>
<td>52.2 ± 6.5</td>
<td>70.7 ± 4.1</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>55.4</td>
<td>61.5</td>
<td>67.3</td>
</tr>
<tr>
<td>Malay</td>
<td>15.3</td>
<td>24.0</td>
<td>22.5</td>
</tr>
<tr>
<td>Indian</td>
<td>29.3</td>
<td>14.5</td>
<td>10.2</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94.6</td>
<td>92.4</td>
<td>71.7</td>
</tr>
<tr>
<td>Female</td>
<td>5.4</td>
<td>7.6</td>
<td>28.3</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.79 ± 1.18</td>
<td>5.59 ± 1.15</td>
<td>5.30 ± 1.20</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
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</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>0.97 ± 0.25</td>
<td>1.03 ± 0.25</td>
<td>1.11 ± 0.31</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.98 ± 1.22</td>
<td>3.75 ± 1.00</td>
<td>3.54 ± 1.03</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.24 ± 1.35</td>
<td>1.85 ± 1.15</td>
<td>1.53 ± 0.74</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>131.2 ± 19.3</td>
<td>136.1 ± 23.1</td>
<td>140.2 ± 27.2</td>
</tr>
<tr>
<td>P = 0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>78.9 ± 13.7</td>
<td>81.8 ± 16.2</td>
<td>77.8 ± 16.3</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, %</td>
<td>73.9</td>
<td>57.8</td>
<td>38.6</td>
</tr>
<tr>
<td>P = 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed DM, %</td>
<td>12.0</td>
<td>13.2</td>
<td>7.1</td>
</tr>
<tr>
<td>P = 0.027</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

DBP: diastolic blood pressure; DM: diabetes mellitus; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure.
smokers and higher incidence of newly diagnosed diabetes mellitus, which constitutes a coronary artery disease risk equivalent. Similar finding was noted by Zarich et al.22

This has important public health implications. In order to develop a targeted approach, where persons who are truly high risk are identified and receive individualised intervention, an effective and accurate risk algorithm must be in place. This might be so for older patients, but as yet no such risk-stratifying strategy exists for younger patients. The accuracy of the currently available methods for risk estimation in this age range is yet to be elucidated, and our results are among the first to examine systematically their performance when applied to young adults.

The propensity for these methods to classify young individuals inappropriately as “low risk” underscores some important limitations to these models and their current application in clinical practice.6 While the Framingham risk algorithm reflects the importance of age in predicting absolute risk,6 the result is that typically only older patients exceed thresholds for treatment. Younger patients, on the other hand, may be missed even though they carry significant risk factor burden. This, and the false sense of security such an age-weighted risk algorithm generates, denies treatment to a large proportion of those that need it.

In order to minimise the bias of weighting by age, some authors have proposed using relative risk estimates in place of age-dependent absolute risk estimates for individuals with low short-term risk, where comparisons are made only to age-similar individuals.23,24 Others have argued for estimation of absolute lifetime risks.25,26 While the FRS may not identify subjects with low short-term but high lifetime risk for CVD (probably due to changes in risk factor status over time), lifetime risk estimates avoid this problem of age-dependency. This allows the identification of younger individuals who are truly at high risk, providing the window

**Fig. 1. Deciles of total points allocated by FRS in younger age group (group A), middle-age group (group B) and older age group (group C).**

<table>
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<th>Group A (&lt;40)</th>
<th>Group B (40-64)</th>
<th>Group C (≥65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;10%)</td>
<td>63.0</td>
<td>29.3</td>
<td>14.2</td>
</tr>
<tr>
<td>Intermediate (10%-20%)</td>
<td>27.2</td>
<td>50.3</td>
<td>49.6</td>
</tr>
<tr>
<td>High (&gt;20%)</td>
<td>9.8</td>
<td>20.4</td>
<td>36.2</td>
</tr>
</tbody>
</table>

*P* <0.001

**Discussion**

This study highlighted several important findings. The majority of young patients who presented with a first MI were classified by the FRS as low risk (10-year risk for cardiac events <10%). Yet risk factor burden within this group was remarkably high, due in part to the higher prevalence of
for intensive lifestyle modification or early initiation of medical therapy. Finally, another strategy would be to use similar 10-year risk estimates for this patient population, but with lower, age-specific, limits for the definition of “high-risk”. However, the drawback is that even then those individuals in the highest quartile of risk by FRS may not be the same individuals at highest lifetime risk; the FRS is shown to be a poor indicator of lifetime risk amongst younger men.26

Future research is needed to clarify if any of these strategies are effective in the identification of “high-risk” young individuals. Once identified, these strategies must then be evaluated further in clinical and public health settings to determine their efficacy.

While the absolute event rates in younger patients are low, individual risk factors already present at this age are significant and strong predictors of future clinical events. In a cohort of male medical students, serum total cholesterol was a strong and independent predictor of future CVD events over the course of 27 to 42 years of follow-up.18 Forty years of follow-up of young adults (aged 30 to 39) in the FHS found similar associations between total cholesterol and both cardiovascular and all-cause mortality.22 The Chicago Heart Association Detection Project in Industry showed that major coronary disease risk factors such as age, serum total cholesterol, blood pressure, and cigarette smoking were observed to be strong and independent risk factors for CHD death in younger adults (aged 18 to 39) in long-term follow-up.17

These risk factors promote subclinical asymptomatic atherosclerosis from a young age if present. The earliest evidence of this emerged from autopsy studies from the Korean28 and Vietnam29 wars, in which significant subclinical coronary atherosclerosis was present among young individuals who died of non-CVD-related causes. It has been shown that premature atherosclerosis does not affect all young adults equally and is associated with the presence of major cardiovascular risk factors.30 More recently, the Bogalusa Heart Study has shown that these traditional risk factors are significantly associated with the accumulation of aortic and coronary atherosclerosis in a population aged 2 to 39 years.16 As noted above, these risk factors increase the risk for future clinical CVD events through an increase in atherosclerotic burden.12-15

On the other hand, despite its inadequacy in predict in predicting cardiovascular risk in young individuals, a recent local study by Lee et al21 showed that FRS is still a better predictor for cardiovascular death than metabolic syndrome as set out by the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) in individuals with an average age of 38.5 years.

Cost-effectiveness of interventions is an important consideration from a public health standpoint. Accurately identifying individuals at the highest risk using a global risk assessment tool like the FRS provides a framework within which clinical decisions may be made. Given the example of cholesterol-lowering drug therapy, prior studies have shown that from a societal standpoint, the greatest benefit is achieved when the highest risk individuals are treated with statin drugs.32 Applying this to the younger population, while it may not be cost-effective to treat the majority of young adults with intermediate risk factor burden with statins, it would likely be cost-effective to treat only the very highest risk young adults. Primary prevention with therapeutic lifestyle changes, however, may be implemented more ubiquitously: prior estimates suggest that in men with a variety of risk factor levels, primary prevention with diet can be a very cost-effective strategy.32 Without more accurate risk estimates, large proportions of the younger population may be incorrectly classified as “low risk” and the message of therapeutic lifestyle change may not be effectively communicated to them.

Limitations

Our study has some limitations. Firstly, the study sample is predominantly male (88.4%). Prior studies have shown that there are clear gender differences in coronary heart disease, and that established risk factors have a varied impact on disease risk for both sexes.33,34 Secondly, while FHS cohort is predominantly Caucasian, the ethnic make-up of the present study cohort is Asians. It has been shown that the ability of the FRS to accurately predict CVD risk in cohorts of different ethnic make-ups varies considerably, and that recalibration of the FRS is necessary for local application.35,36 That being said, the FRS tends to overestimate CVD risk in Asians.34 Finally, the present study did not take into consideration other known cardiovascular risk factors such as family history, obesity (BMI), hyperhomocysteinaemia, and inflammatory markers. Indeed, elevated C-reactive protein blood levels has been shown to predict the risk of MI.37

Conclusion

The movement towards global risk assessment has certainly served us well. However, while the FRS has been useful in predicting 10-year coronary risks accurately amongst older patients, it inadequately predicts cardiac risk in young patients despite substantial risk factor burden. This could be in part due to a higher proportion of young patients having undiagnosed diabetes mellitus, a coronary artery disease risk equivalent. Future clinical guidelines should consider alternative strategies to better estimate and communicate CVD risk to the young adult population. Perhaps these alternatives may overcome the inherent bias of age-weighted risk algorithms, and incorporate certain recently discovered cardiovascular risk factors.
REFERENCES


March 2010, Vol. 39 No. 3