The Challenges and Benefits of Cardiovascular Risk Assessment in Clinical Practice

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Practice Challenges:

1. How do busy health professionals identify the risk tools that can help them in clinical practice?
2. What are the strengths and weaknesses of the currently available risk model?
3. How should risk models be used?

Objectives:

1. Provide a framework for evaluating the scientific validity of risk assessment models
2. Discuss the characteristics of risk assessment tools that are necessary to engage patients and health care professionals.

Background

The potential benefits of modifying cardiovascular risk factors among individuals with known cardiovascular disease are no longer debated. Strong and consistent clinical trial data have clearly demonstrated that reducing blood pressure and/or modifying blood lipids will reduce the risk of secondary cardiovascular events, and increase longevity. These treatments also appeared to be highly cost-effective (1).

Primary prevention is more problematic as many individuals with elevated blood pressure or blood lipid abnormalities may still be at relatively low, short term risk of a cardiovascular event due to young age, gender, or the absence of other risk factors (2). Accordingly, expert guidelines for the treatment of hypertension or dyslipidemia recommend the use of global risk assessment to guide treatment decisions among individuals without diagnosed cardiovascular disease (3-6). Risk factor management can then be targeted to those individuals who will benefit the most given the high absolute risk of the cardiovascular event over the next five to 10 years.
Cardiovascular risk assessment in routine clinical practice holds many promises including: reassuring low-risk individuals, motivating high-risk individuals to modify their lifestyle or adhere to medical therapy and track an individual’s progress as risk factors come under control.\(^{(7;8)}\) Risk assessment can also be used to improve the allocation of finite healthcare dollars to ensure that one gets the biggest bang for the buck by reducing cardiovascular events among those individuals in whom the risk is most imminent.

There are also a number of challenges in asking busy health professionals to incorporate routine risk assessment into their daily clinical practice. First and foremost, risk assessment takes time whether it is performed using web-based applications, computer programs, hand-held risk calculators, or printed risk tables. Data entry is simply time-consuming even if only a few risk factors must be measured and imputed into the risk calculation. Additional time is required if one wishes to share these results with individual patients and their families. With a few exceptions, health professionals are rarely reimbursed for the additional time and effort this requires.

A second challenge is to demonstrate that the risk assessment tools do in fact accurately identify those at increased risk. Accordingly, despite the potential usefulness of cardiovascular risk assessment in primary care practice, the vast majority of patients seen in physicians’ offices have never had their cardiovascular risk assessed. Nonetheless, pharmacotherapy for dyslipidemia and hypertension in Canada will cost nearly $5 billion this year while the majority of treated individuals will remain sedentary and overweight and as many as half will not adhere with prescribed pharmacotherapy. What then can be done to realize the full potential of risk assessment?

**Choice of Risk Models**

Over a dozen multivariable risk models have been developed. The ones that tend be the most useful in clinical practice are those based on at least several thousand individuals who are representative of the general population. This will typically include men and women ranging in age from approximately 30 to 70 years. While sample size is important, the number of cardiovascular outcomes that occur during the follow-up period is perhaps the most important determinant of the resulting model’s accuracy. As a general rule, most multivariable techniques require 10 to 20 outcomes for each additional independent risk factor entered into the model. Accordingly, given that most models include five to 10 risk factors, a minimum of 50 to 200 outcomes is required to build these models.

Model performance is usually evaluated based on external validity or the accuracy of the model when tested on a cohort of individuals different from those the model was developed on. Model discrimination refers to the ability of the risk equations to discriminate between those who will and will not develop the outcome of interest. This is usually assessed using the area under receiver operating characteristic (ROC) curve or Harrell’s C. statistic were a value of one indicates a perfect test and 0.5 a test that performs no better than chance alone \(^{(9)}\). Values between 0.75 and 0.85 are commonly observed for the most clinically useful risk equations.

Model calibration refers to how closely the predicted outcomes match those that are actually observed during the external validation \(^{(10)}\). In most instances, the model will require recalibration if one wants to accurately predict the number of events that occur in a new population as the
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underlying event rate is rarely identical in different cohorts. Nonetheless, risk factors tend to have the same relative impact in different populations. Accordingly, a risk model developed in a northern European population where the absolute event rate is high can perform accurately in the low risk southern European population after recalibration to adjust for the lower absolute event rate.

The net reclassification index (NRI) is a recently developed measure to compare how different models perform in classifying individuals into specific risk categories (11). For instance, if treatment guidelines require that individuals be classified into 10-year risk categories of less than 10%, 10% to 19%, and 20% or above, the NRI can be used to see if the addition of a novel risk factor to the model will result in individuals who develop the outcome being classified in a higher risk category while those who do not develop the outcome are classified in a lower risk category.

In Canada, a number of models have been proposed for general use by primary health care providers (3-6) including the following (presented in chronological order of the publication dates).

The Framingham Model

Multivariable risk assessment equations to predict cardiovascular events were first developed by the Framingham Heart Study group. The Framingham equations remain the most widely used around the world and have evolved over more than 40 years since the first models were developed on risk factors such as age, gender, total cholesterol, systolic or diastolic blood pressure, and the presence of diabetes, smoking, and left ventricular hypertrophy. The original Framingham cohort and the Offspring cohort typically provide three to five thousand individuals (age 30-75 years), followed for five to 15 years, with several hundred outcomes occurring during this period including hard cardiovascular events such as fatal and nonfatal myocardial infarction plus sudden-death (12;13). Other hard endpoints include strokes (fatal and non-fatal) as well as soft endpoints such as angina pectoris, coronary insufficiency; and other complications of atherosclerosis including revascularization procedures, congestive heart failure, and transient ischemic attacks (14).

The current Framingham equations include the total cholesterol/HDL ratio, systolic blood pressure, age, gender, smoking status, and may also include the presence of diabetes (13). A secondary model for estimating the risk of recurrent events among individuals who already have known cardiovascular disease has also been published (15). However the resulting model does not appear to be particularly robust, includes only a few risk factors, and has not been extensively validated.

The Framingham equations have been shown to discriminate well between those who will and will not develop a cardiovascular event over five to 10 years (16). The Framingham risk equations also perform well in most populations outside of the United States with appropriate recalibration based on the incidence of cardiovascular disease in the population of interest (17). The Framingham models focusing on hard cardiac endpoints, including those published in 1991 by Anderson et al. or 1998 by Wilson et al., have been extensively tested and externally validated on other populations in the United States, Europe, Asia and Canada (17;18). The more recent Framingham equations including soft cardiac endpoints, published by D’Agostino et al in 2008, remains to be externally validated (14).
The Framingham model has been validated in a Canadian cohort. It has been shown to accurately forecast cardiovascular deaths in the Canadian Lipid Research Clinic (LRC) Follow-up cohort without additional calibration(19).

An online version is available at http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof

The Cardiovascular Life Expectancy Model

The Cardiovascular Life Expectancy model is a Markov model developed to calculate short-term risk as well as long term life expectancy. Using the 15% random sample from the LRC Follow-up Cohort (age 30-79 years) from the United States and Canada, the model can be used to calculate the risk of coronary death and cerebrovascular death as a function of age, gender, the total cholesterol/HDL ratio, mean blood pressure, smoking status, and the presence of diabetes(20). The model has been externally validated and shown to reasonably estimate the results of published clinical trials over 5-10 years of follow-up. It has also been validated in selected populations including individuals with or without previously diagnosed CVD or diabetes(21;22). The life expectancy estimates have also been shown to closely approximate published Canadian and American life tables(2;23).

The 10-year results forecasted with the cardiovascular life expectancy model tend to be very similar to those using the Framingham equations with very small differences between the two(19). Once the 10-year Framingham Risk has been calculated, the only advantage associated with using this Markov model is the opportunity to estimate the long-term impact of risk factors over the entire life expectancy. One can also use the model to estimate an individual’s life-expectancy before and after treating one or more risk factors.

An online version is available at www.myhealthcheckup.com, www.monbilansante.com, or www.chiprehab.com. The 2010 version allows the user to choose “hard coronary events” or also include the “soft coronary events” published by the Framingham group and recently recommended by the 2009 Canadian Lipid Guidelines(4). An adjustment is also now available for the presence of a family history of premature coronary disease.

The individual’s “Cardiovascular Age” is also calculated as their age minus the difference between their estimated remaining life-expectancy (adjusted for their coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex. For instance, a 50 year old with a life expectancy of 25 more years (versus 30 years for the average Canadian) would be assigned a Cardiovascular Age of 55.

The Cardiovascular Life Expectancy model has been validated in a Canadian cohort. A model based only on American LRC data, has been shown to accurately forecast cardiovascular deaths in the Canadian LRC cohort without additional calibration(19).

The Systematic Coronary Risk Evaluation (SCORE) Model

The SCORE model was developed on a pooled data set of 12 European population cohorts (age 40-65 years) including both low risk populations in southern Europe and high risk populations in northern
Europe\cite{24}. Accordingly, model is easily calibrated for these 12 European countries. Ease of calibration was one of the primary objectives of the SCORE model which focuses only on the fatal cardiovascular events [coronary death and non-coronary atherosclerotic death]. This provides a reasonably simple platform to recalibrate for different countries where cardiovascular mortality rates are readily available while non-fatal event rates are not. On the other hand, fatal cardiovascular events does not match up with the risk categories currently recommended in most Canadian and American guidelines which focus on fatal and non-fatal “hard outcomes” (fatal and non-fatal MI, sudden death) or, in the case of the 2009 Canadian Lipid guidelines may also includes “soft outcomes” such as angina, coronary insufficiency, transient ischemic attack, congestive heart failure and revascularization procedures.

The model was developed primarily for individuals without diagnosed cardiovascular disease or diabetes. The risk equations are based on age, gender, systolic blood pressure, smoking status and total cholesterol levels alone or the total cholesterol/HDL ratio.

The SCORE model has been validated in a number of populations. It has not yet been validated in a Canadian cohort\cite{19}.

An online version is available at http://www.scorecanada.ca

The Reynolds Risk Score

The Reynolds Risk Score was developed using data from two different American populations: the Women's Health Study (women age 45 and older who were free of CVD and cancer) and the Physicians Health Study II (male physicians age 50-80 years who were free of CVD, diabetes and cancer) \cite{25;26}. The Reynolds model is similar to the Framingham model but includes two additional risk factors: a family history of premature coronary disease and high sensitivity c-reactive protein (hsCRP).

There is good data demonstrating that a family history of premature coronary disease will increase the risk of a CVD event by 1.5 to 2 fold among individuals under the age of 60 without diagnosed CVD, diabetes\cite{27}. The major debate surrounding the Reynolds Risk Score is whether or not the addition of hsCRP is useful once the traditional Framingham risk factors and family history are known. Unlike family history, hsCRP requires additional laboratory testing and given the low specificity of hsCRP for inflammation in the coronary arteries, false positives may occur due to inflammation in other parts of the body. The two primary papers that described the model were only able to demonstrate a slight improvement in the model’s discriminating ability over the traditional Framingham risk factor for men (C statistic increased from 0.699 to 0.708, p<0.001) while absolutely no improvement in the C statistic was noted in the female cohort. There are concerns that of the two risk factors added in the Reynolds Score, family history is the more important and hsCRP may add little additional information. This was confirmed by the Framingham investigators when they added hsCRP measurements to the Framingham model and could not demonstrate any significant improvement in the C statistic\cite{28}.

A number of concerns have also been expressed regarding the Reynold’s Risk Score. For women these include the fact that the score was developed on a cohort of health professionals participating in a
clinical trial rather than a sample representative of the general population\textsuperscript{(29)}. Risk factors such as blood pressure, were not measured but self reported and the prevalence of cigarette smoking was low thereby underestimating the contribution of these traditional risk factors. Among men, similar concerns include the questionable generalizability of a model developed on a physician cohort, median age 63 years, where only 3.2% were smokers and the median systolic blood pressure was low at 128mmHg.

The Reynolds Risk Score has not yet been extensively validated in other populations. It has also not been validated in a Canadian Cohort. It is available online at \url{http://www.reynoldsriskscore.org/}

**How Should Cardiovascular Risk Assessment be Used in Routine Clinical Practice?**

Multifactorial risk assessment has been proven to more accurately identify those at increased risk of a cardiovascular event compared to treatment guidelines focusing only on blood lipid levels or simply counting the number of risk factors present in a specific patient.

Treatment guidelines commonly recommend classifying individuals into 10year risk categories including Low Risk (<10%), Medium Risk (10-20%) and High Risk (>20%)\textsuperscript{(4)}. Thresholds for initiating treatment (such as LDL cholesterol levels above 3.5mmol/l) and therapeutic targets (such as reduce LDL to <2mmol/l) are then defined based on one's risk category. However, there are increasing concerns that this approach, based on short term 10-year risk, will result in the under-treatment of younger individuals who have significant elevations in one or more risk factors but whose absolute risk level remains low given their age\textsuperscript{(7;17)}. This issue is particularly apparent among younger women, below the age of 60, whose life-time risk of developing cardiovascular disease is substantial even though an event is unlikely to occur over the next 10 years. On the other hand, focusing only on short term risk may also result in the over-treatment of elderly individuals whose absolute risk is high in large part due to their advanced age while the long-term benefits of therapy may be relatively modest given their remaining life expectancy and the presence of other co-morbidities.

For instance, if one calculates the 10-year Framingham Risk (hard outcomes only) of a 42 year old man without a family history of premature coronary disease, total cholesterol level of 6.5mmol/l, LDL level of 4.5mmol/l, HDL level of 1.1mmol/L, borderline hypertension of 138/88 and no other risk factors, his risk is only 4.2% over the next 10 years. Current guidelines would not recommend treating his blood lipids as he is categorized as low risk. Nonetheless his life expectancy is reduced by 0.7 years on average by virtue of his multiple borderline risk factors and he can be told that he has the Cardiovascular Age of someone 42.7 years old (\url{www.myhealthcheckup.com}). Lipid therapy could reduce his total cholesterol 25% and LDL 35%, while his HDL could be raised 20% resulting in a 2.6% absolute drop in his risk to 1.6%. When the potential life-time benefits are calculated, his “Cardiovascular Age” would drop from 42.7 years to 40.9 years or an estimated increased life expectancy of 1.8 years. The potential benefits of treatment might seem quite attractive to many such patients.

On the other hand, consider a 75 year old man with exactly the same risk factors who would have a 10-year Framingham Risk of 21% and current guidelines would recommend treatment as he is categorized as high risk even though his absolute risk is below average for Canadian men of his age.
This risk would drop to 17.5% following the same response to lipid therapy as the previously mentioned younger man. While the 3.5% drop in 10-year risk is greater than the absolute risk reduction calculated for the 42-year-old, his “Cardiovascular Age” would be reduced less (0.8 years) reflecting the more limited time horizon over which the benefits associated with treatment could be realized.

A second problem with Low, Medium, and High risk categories is that they are completely arbitrary. There is no scientific evidence to support treating someone with a 20% risk differently from someone with a 10% risk. To treat patients differently on the basis of risk levels of 11% vs 9% makes even less sense particularly when small changes in blood lipids or blood pressure from one day to the next can move one’s risk profile a couple of percentage points up or down.

If one accepts that arbitrary treatment thresholds based on absolute risk categories makes little sense, there is little reason to try and make minor improvements in risk prognostication. Existing Framingham models have been shown to have very good discriminating ability usually in the range of 75% to 85%. If perfect discrimination is 100% there is not that much room for improvement. Accordingly it should not be surprising that the addition of hsCRP improves risk discrimination often by no more than 1% compared to traditional Framingham risk factors.

Model calibration also becomes less of a concern when categorical risk levels no longer drive treatment decisions as it really does not matter if ones risk is 11% or 9% but rather whether ones risk is elevated relative to a clinically useful standard. What should the standard be for defining an elevated risk? Should all elderly individuals be considered to be at increased risk just because they are older? Are all men at increased risk due to their gender? Are all young women under the age of 40 at low risk no matter how many risk factors they have? Two possibilities have been proposed. One is to compare an individual’s increased risk relative to individuals with no risk factors or and ideal risk profile such as non-smokers with blood pressure of 120/80 and a total cholesterol/HDL ratio of 4. Alternatively one can define increased relative risk as a risk level above the average risk of individuals of the same age and sex in ones community. Accordingly one’s risk is only compared to the average risk of one’s peers. In either situation it does not matter if the risk model over-estimates or under-estimates risk in a specific population as both and individual patient’s risk profile and the frame of reference will be inflated or deflated similarly to the ideal risk profile or the average risk of one’s peers.

If one focuses on relative risk rather than absolute risk the debate surrounding which model to use and how much to calibrate that model becomes irrelevant. One can choose any model with a high discriminating ability and apply it to Canadian population data to define the ideal or average risk for each age and sex group. The only question that then remains is whether a specific patient’s risk is elevated compared to one of these norms and how much that risk can be reduced by treating modifiable risk factors. Clinicians can use this information to help inform their clinical decisions while evaluating the patient’s preferences rather than make arbitrary decisions based only on the absolute risk level.

While helping health professionals make more informed decisions, risk profiles can also provide useful information to patients. An initial assessment can be used to engage the patient in modifying
their lifestyle including smoking cessation, weight loss, and increased physical activity. If this is unsuccessful, a risk profile can also be used to help a patient understand the need for pharmacotherapy. In addition, follow-up profiles can be used to quantify the potential benefits of adhering to both lifestyle changes and pharmacotherapy. Knowing one’s Cardiovascular Age has been shown to be increase the odds of reaching lipid targets by 26% overall and up to 69% among those whose Cardiovascular Age was at least 7 years greater than their chronological age(30).

**Conclusions**

In conclusion, multifactorial cardiovascular risk assessment has been shown to improve our ability to identify those individuals most likely to suffer a cardiovascular event over the next 10 years and treatment guidelines have evolved to incorporate this information into daily clinical decision making. The choice of risk model is of little consequence as long as the discriminating ability is good with a C statistic of at least 75% or more. Categorical risk levels as currently defined by Low, Medium, and High, risk are arbitrary and over simplify complicated decisions that should be based on the patient’s relative risk, age, the presence of other co-morbidities, remaining life-expectancy and individual patient preferences. There is no evidence that any one of the newer risk models is significantly better than the Framingham risk models. Once the 10 year Framingham risk is calculated, the Cardiovascular Age of an individual can be used to compare the life-time risk and life expectancy of that individual to Canadians of the same age and sex. These two estimates of short and long-term risk have been shown in a randomized clinical trial to improve the management of both dyslipidemia and hypertension among Canadian patients followed in a primary care setting(30;31).
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