therapeutics letter ©

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Using Framingham for primary prevention cardiovascular risk assessment

Therapeutics Letter 62 outlined an approach to estimate the potential benefits of treating mild hypertension by using the results of a meta-analysis. Another approach used by clinicians is the Framingham risk calculator, which incorporates age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, presence or absence of diabetes, and smoking (yes or no) in a mathematically derived formula to provide a prediction of risk of cardiovascular disease (CVD). Novel risk factors such as CRP, LpPLA, IL-6, D-dimer, homocysteine, folate, Vitamin B6, leptin and plasminogen are not included, and interestingly a recent publication concludes that their routine measurement are "not warranted for risk assessment".[1] Another study suggests that using apo B-apo A-I ratio adds little to the predictive value of the Framingham Risk Score.[2] As with most calculators, family history and weight are not variables and so clinicians must use clinical judgment when these factors are considered important.

What are you calculating with a Framingham calculator?

Some Framingham calculators calculate the risk of overall CVD while some calculate coronary heart disease (CHD) risk. Total CHD in Framingham was defined as angina, unstable angina, MI, or death from CHD and early risk tables used this definition. More recent calculators in cardiovascular guidelines calculate the risk of "hard" CHD endpoints (MI and CHD deaths) which are roughly 2/3 to 3/4 of total CHD.

A cardiovascular event is defined in the Framingham equation as myocardial infarction, new angina, ischaemic stroke, transient ischaemic attack (TIA), peripheral vascular disease (PVD), congestive heart failure (CHF) and cardiovascular-related death.

If you are using a calculator you must check what you are actually calculating.

Over what period of time is the risk being calculated?

Most of the calculators calculate either a 5 or 10-year risk (approximately twice the 5-year risk). While some people advocate longer periods, such as lifelong risk, this is unhelpful because most people have a "high" life-time risk of CVD. One approach has been to use these calculators to show patients how a patient's risk

compares to similarly aged patients without these risk factors and some researchers have developed risk models to estimate the change in "cardiovascular age" associated with modifying specific risk factors.[3]

What would be the estimate of CHD and CVD risk in our patient (TL 62) if we used the Framingham formulas?

Mr. EBP is a 55-year-old man, his BP is 146/94, he does not have diabetes and does not smoke. While Mr. EBP did not have his cholesterol measured, let's assume his total cholesterol is 5 mmol/L and his HDL is 1.25 mmol/L. From the five trial meta-analysis of people with an average BP of 160/98 mmHg (TL 62) drug therapy (versus placebo) reduced a combined endpoint of total strokes and heart attacks from 4% to 3.2% over a period of 5 years.

Using Framingham our patient would be predicted to have a 10-year 16% overall CVD risk and a 11% chance of total CHD (see Table). In our previous Letter, in the five studies (54% male, average age 51 years, average baseline BP 160/98 mmHg, and most with no evidence of cardiovascular disease) the actual total MI plus stroke incidence was 4% over 5 years or 8% for 10 years. The Framingham estimate at 16% is higher, but it includes more outcomes: new angina, TIAs, PVD and CHF.

In the Table some of the numbers from Framingham are presented (calculated using the published formulas incorporated into a spreadsheet). The columns in orange are the numbers for our patient and the other columns are provided to show the impact of changes in SBP or total cholesterol on estimated risk.

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
Web: www.ti.ubc.ca

Effects of blood pressure on 10 year risks*

SBP mm/Hg	136	146	156
overall CVD	14%	16%	18%
CHD	9%	11%	12%

*55-year-old male, non-smoker, non-diabetic, total cholesterol 5 mmol/L and HDL 1.25 mmol/L

Effects of cholesterol on 10 year risks**

Total cholesterol mmol/L	4	5	6
overall CVD	13%	16%	19%
CHD	8%	11%	13%

**55-year-old male, non-smoker, non-diabetic, with SBP of 146 mmHg and an HDL of 1.25 mmol/L

How can one use these numbers to estimate benefit of treatment?

This requires extrapolation from the evidence.

A. You could simply use the Table and estimate what would happen if the patient had a blood pressure of 136 instead of 146 mmHg: the 10-year CVD risk decreases from 16% to 14%, the 5-year risk would decrease from 8% to 7%, resulting in a 1% ARR.

B. You could take the predicted 10-year risk of 16% and convert it to a 5-year risk of 8% and multiply it by the average RRR of 31% (CI 25 to 37) over 5 years for combined MI and stroke in meta-analyses of all antihypertensive trials.[4] This predicts a 2.4% absolute risk reduction in CVD.

For statin treatment, primary prevention trials have shown a 26% (CI 19 to 32) reduction in CHD in men but not in women (see TL 48). This man's 5-year CHD risk is 5.5% (1/2 of the 10-year risk) and so a 1.4% absolute benefit in CHD would be predicted.

Many groups have defined specific, yet arbitrary risk percentages, or blood pressure/cholesterol treatment thresholds. **These thresholds are all arbitrary and opinion-based and rarely if ever take into account individual patient preference.** Interestingly, one study suggested that less than 1/3 of patients (with or without a history of heart disease) would take a "safe" drug if the absolute chance of reducing a heart attack over 5 years was ≤ 5%.[5] Using statins for secondary prevention produces less than a 5% absolute reduction in heart attacks over 5 years. A study reporting preferences of health professionals and lay people concluded that personal decisions would often be at odds with recommendations in "evidence-based" guidelines.[6]

Has anybody done a systematic review of the accuracy and impact of risk assessment?

Yes. They found 17 epidemiologic studies assessing the accuracy of the Framingham risk scores and **concluded that scores were inaccurate**, tending to underestimate risk in high risk populations and overestimate risk in low risk populations. They also found 4 RCTs assessing the impact of risk assessment, which showed that CV risk assessment had little or no impact on the overall number of people treated.[7]

Nonetheless, if one truly wishes to engage in shared-informed decision making, patients need to be provided with at least a ballpark estimate of their risks and the potential for benefit. Despite the limitations, using Framingham or some other risk engine at least allows clinicians some objective approach to risk estimation. However, clinicians need to be aware that only limited validation has been done in a Canadian population.[8] Using a Framingham score at least provides more information than simply using a blood pressure or cholesterol level to identify patients needing treatment.

What are some limitations of using a Framingham calculator?[9]

- no risk prediction beyond 12 years
- no confidence intervals around the estimate
- less accurate for patients with extremes of risk factors
- if your patient is "dissimilar" to the population studied, risk assessment is more inaccurate - e.g. non-U.S. populations, Japanese men, Hispanic men, Native-American women, men and women younger than age 30 or older than age 65, and diabetics.

Conclusions

- If you use Framingham to calculate risk, make sure you know what endpoints are included and over what period of time.
- Framingham risk assessment has a number of limitations and there is a lack of evidence of its impact on prescribing practice or health outcomes.
- **Risk assessment needs to be studied in RCTs as compared to standard care:**

- to determine the impact on prescribing in patient populations with different risks at baseline;
- to see if patients presented with risk estimates feel more informed and make different treatment decisions.

The draft of this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

1. Folsom AR, Chambless LE, Ballantyne CM, et al. *An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study.* Arch Intern Med. 2006; 166(13):1368-73.
2. van der Steeg WA, Boekholdt SM, Stein EA, et al. *Role of the apolipoprotein B–apolipoprotein A-I ratio in cardiovascular risk assessment: a case-control analysis in the EPIC-Norfolk.* Ann Intern Med. 2007;146:640-8.
3. Grover SA, Paquet S, Levinton C, et al. *Estimating the benefits of modifying risk factors of cardiovascular disease: A comparison of primary vs. secondary prevention.* Arch Intern Med. 1998;158:655-662
4. Mulrow C, Lau J, Cornell J, Brand M. *Pharmacotherapy for hypertension in the elderly.* Cochrane Database of Systematic Reviews. 1998; Issue 2. Art. No.: CD000028. DOI: 10.1002/14651858.
5. Trewby PN, Reddy AV, Trewby CS, et al. *Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs.* Clin Med. 2002; 2(6):527-33.
6. Lewis DK, Robinson J, Wilkinson E. *Factors involved in deciding to start preventive treatment: qualitative study of clinicians' and lay people's attitudes.* BMJ. 2003; 327(7419):841-5.
7. Brindle P, Beswick A, Fahey T, Ebrahim S. *Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review.* Heart. 2006; 92(12):1752-9.
8. Grover SA, Hemmelgarn B, Joseph L, Milot A, Tremblay G. *The role of global risk assessment in hypertension therapy.* Can J Cardiol 2006. 22(7):606-13.
9. Sheridan S, Pignone M, Mulrow C. *Framingham-based tools to calculate the global risk of coronary heart disease: a systematic review of tools for clinicians.* J Gen Intern Med. 2003; 18(12):1039–1052.