Education

Éducation

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This article has been peer reviewed.

Can Med Assoc J 1997;157:422-8

Primary prevention of heart disease and stroke: a simplified approach to estimating risk of events and making drug treatment decisions

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Abstract

LONG-TERM POPULATION-BASED STUDIES have identified and quantified risk factors for cardiovascular and cerebrovascular (CCV) events. In addition, a number of well-designed clinical trials have shown that various drug therapies that reduce these factors decrease the risk of some CCV events. In the practice of evidence-based medicine, data from clinical trials should inform treatment decisions. The clinician and patient, however, are faced with the difficult task of assessing the patient's particular risk and likelihood of benefit on the basis of the results of large, randomized trials. To assist clinicians and their patients in arriving at treatment decisions, the authors provide simple nomograms for estimating the risk of a CCV event for an individual patient and suggest an approach to estimating the potential benefit of drug therapy for primary prevention.

Résumé

DES ÉTUDES REPRÉSENTATIVES DE LONGUE DURÉE ont permis de définir et de quantifier les facteurs de risque d'accidents cardiovasculaires et cérébrovasculaires (CCV). En outre, des études cliniques bien conçues ont démontré que diverses pharmacothérapies qui réduisent ces facteurs diminuent aussi le risque de certains accidents CCV. Dans la pratique de la médecine fondée sur des données probantes, les données d'études cliniques devraient éclairer les décisions relatives au traitement. Le clinicien et le patient ont toutefois la tâche difficile d'évaluer le risque particulier pour le patient et l'avantage probable en fonction des résultats d'études randomisées de grande envergure. Afin d'aider les cliniciens et leurs patients à prendre des décisions relatives au traitement, les auteurs présentent des nomogrammes simples pour évaluer le risque d'accident CCV dans le cas d'un patient en particulier et suggèrent une façon d'estimer l'avantage que peut offrir une pharmacothérapie en ce qui concerne la prévention primaire.

The decision to treat a patient who has no history of cardiovascular or cerebrovascular (CCV) disease with long-term preventive drug therapy should be based on an assessment of the likely benefit of such treatment relative to the chance of a CCV event. This information should be presented to the patient in a manner that facilitates informed decision-making.[1] The best information that clinicians can bring to these decisions is that arising from large population-based studies and randomized controlled trials. Despite the increasing availability of such information, both primary care physicians and specialists tend to substantially overestimate the risk of CCV events and the likely benefits of primary prevention with drug therapy.[2,3] One possible reason for this is the lack of a simple means for relating the outcomes of large epidemiologic and intervention studies to individual patients. This is a classic example of how it can be difficult to apply the principles of evidence-based medicine to individual patient care. Various attempts have been made to develop tools to assist clinicians in quantifying risk of CCV events.[4–6] In most cases, these methods require the clinician to use a computer or to sum up risk factor points and then transfer this information to tables or

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nomograms. In addition to being cumbersome, these methods do not include estimates of drug therapy benefit.

To overcome these difficulties, we have developed simple nomograms (Figs. 1 and 2) for estimating the risk of CCV events in individual patients. In addition to simplifying the determination of risk, these nomograms allow the clinician and patient to visualize the interplay between risk factors and to observe the impact on risk when various factors are added or removed. Table 1 provides examples from the literature of risk reductions associated with long-term (approximately 5 years) drug therapy. In the following discussion we outline how this technique can be used in practice.

Estimating risk

The nomograms presented in Figs. 1 and 2 display the risks relative to age, sex and other risk factors of cardiovascular events over a 5- or 10-year period and of cerebrovascular events over a 10-year period in patients with no history of CCV disease. Cardiovascular events are defined as angina, unstable angina, myocardial infarction (MI) and death from coronary artery disease (CAD). Cerebrovascular events are defined as atherothrombotic brain infarction, transient ischemic attack, cerebral embolism, intracerebral hemorrhage or subarachnoid hemorrhage. The nomograms were created using the most recent data from the Framingham Study cohort, which have been manipulated by the Framingham Study investigators to create risk factor scores and somewhat complex methods of calculating risk.[4,5] The method for using the nomograms is explained in the figure caption.

Sample case

Consider the case of a 58-year-old man who smokes, has a systolic blood pressure of 160 mm Hg, a total serum cholesterol level of 6.70 mmol/L and an HDL cholesterol level of 1.40 mmol/L. He has no history of diabetes and his electrocardiogram exhibits no evidence of left ventricular hypertrophy. To estimate this patient's 5-year absolute risk of cardiovascular disease, the clinician should use Fig. 1 and carry out the following steps.

1. Find the patient's age (58) on the age scale for men.
2. Trace a line upward to the corresponding square on the 5-year risk line. The corresponding value on the y axis (3%) is the absolute 5-year risk of a cardiovascular event in 58-year-old men, taking only age and sex into account.
3. Identify the relevant risk factor adjustment scores to take the patient's other risk factors into account. Smoking counts as 4 points; therefore move 4 squares to the right. The patient now has a 6% risk. His systolic blood pressure of 160 mm Hg counts as another 4 points; move another 4 squares to the right. The patient now has a risk of 9%. His total serum cholesterol level of 6.70 mmol/L counts as 3 points; move 3 squares to the right. The patient's risk is now 13%. The HDL cholesterol level of 1.40 mmol/L reduces his risk adjustment score by 1 point; move 1 square to the left. The patient's overall 5-year risk is 12%.
4. To determine the patient's 10-year risk, now trace a line upward to the 10-year line. This patient's current risk of experiencing a cardiovascular event in the next 10 years is 23%.

Unfortunately, there are no data that permit us to quantify risk factors such as family history, sedentary life style, weight or ethnic background. The Framingham investigators use systolic blood pressure instead of diastolic blood pressure in their risk estimates because, although both correlate well with overall risks, systolic blood pressure can be determined more accurately and is a stronger predictor of CAD, especially in elderly people.[4]

The data from the Framingham Study identify a composite of all possible cardiovascular events that make up this patient's overall risk. Approximately 70% of the cardiovascular events in the male cohort of the study population were either MI or death from CAD. (In the female cohort, these events accounted for approximately 40% of the cardiovascular events.[8]) Thus, the sample patient's risk of MI or death from CAD is roughly 8% within 5 years and 16% within 10 years. Another way of looking at the numbers is that the patient has a 92% chance of not having an MI or dying of CAD even though he has a number of risk factors. The patient's risk of a cardiovascular event other than an MI or death from CAD is approximately 4% within 5 years.

This patient's risk for experiencing a cerebrovascular event in the next 10 years can be estimated in the same manner, using the nomogram in Fig. 2. After all noted risk factors are accounted for, the best estimate of the patient's absolute 10-year risk of a cerebrovascular event is 10%. In the Framingham Study, transient ischemic attacks accounted for approximately 25% (20% in women) of cerebrovascular events.[9] Therefore, this patient's chance of a fatal or nonfatal stroke during the next 10 years is estimated to be approximately 7.5%, or roughly 4% over the next 5 years.[9]

Limitations

Although this approach offers a reasonable estimate of a patient's risk, it has certain limitations. The nomograms should be used only in patients with no history of CCV disease for the purpose of making decisions about primary prevention. The risk factor adjustment scores for blood pressure and cholesterol levels assume that the values have

Using the nomograms

To estimate a patient's risk of a cardiovascular or cerebrovascular event, select the appropriate nomogram and carry out the following steps.

1. Find the patient's age on the appropriate scale (men or women).
2. Trace a line upward to the corresponding square on the 5- or 10-year risk line (Fig. 1) or the 10-year risk line for men or women (Fig. 2). The corresponding value on the y axis is the patient's absolute risk, taking only age and sex into account.
3. To take other risk factors into consideration, identify the risk factor adjustment score (in the large box) for each risk factor present in the patient. If the score is a positive number, move to the right up the risk line the appropriate number of squares. (Each square equals 1 point.) If the score is a negative number, move to the left the appropriate number of squares. Repeat this in series for each risk factor. Once all risk factors have been considered, find the corresponding value to determine the patient's estimated overall risk. (See text for sample case.)

Fig. 1: Five- and 10-year risk of a cardiovascular event in patients with no history of cardiovascular disease.
Cardiovascular events are defined as angina, unstable angina, myocardial infarction or death from coronary artery disease.

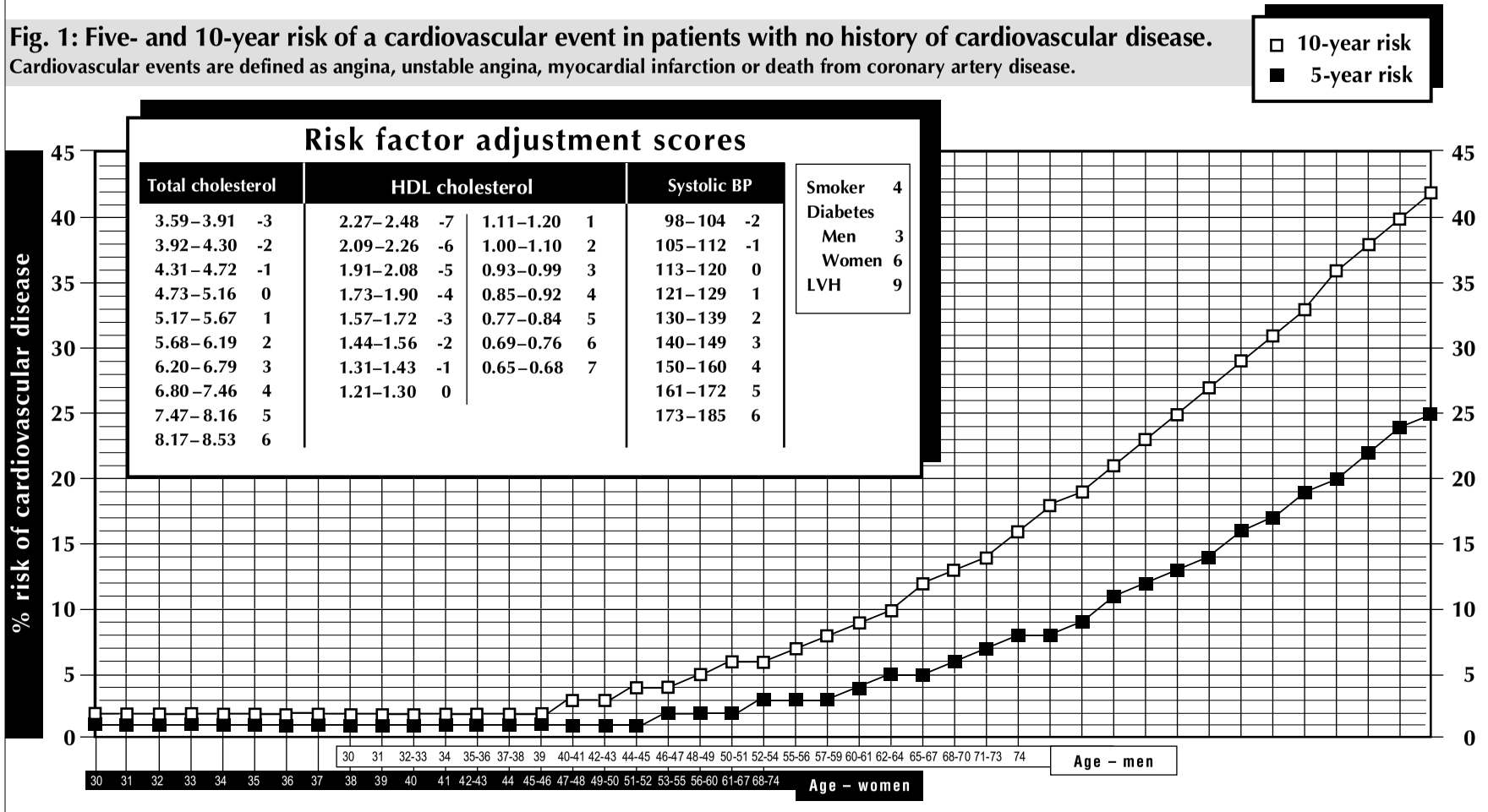

Figure based on material in Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation* 1991;83:356-62.

Fig. 2: Ten-year risk of a cerebrovascular event in patients with no history of cerebrovascular disease.
Cerebrovascular events are defined as atherothrombotic brain infarction, transient ischemic attack, cerebral embolism, intracerebral hemorrhage and subarachnoid hemorrhage.

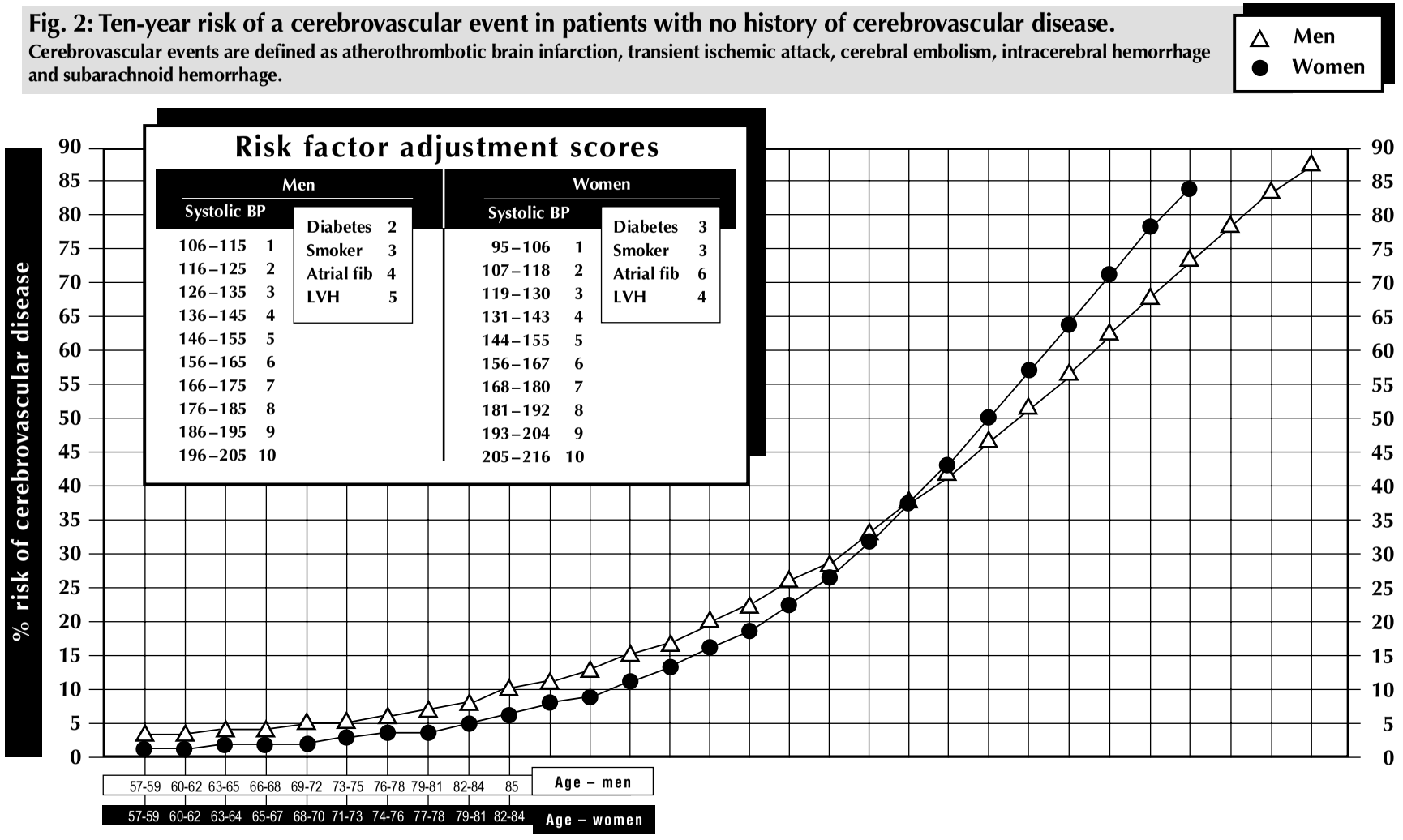

Figure based on material in D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication: the Framingham Study. *Stroke* 1994;25:40-3.

been measured in the absence of drug therapy. In addition, although factors such as weight, lifestyle and family history do contribute to the risk of CCV disease, it was not possible for the Framingham investigators to quantify the risks associated with each of these factors for individual patients.[4,5] Thus, for example, patients with a strong family history of CCV disease could be considered to have a greater absolute risk than that estimated. Conversely, those with no family history may have a somewhat lesser risk than the nomograms indicate. Also, the risk estimates may be less accurate for patients at the upper or lower extremes for risk factors that are continuous variables.[4]

We should also remember that the data used in these figures are based on risk estimates from the Framingham Study population and may not be representative of other populations such as those with very low rates of CCV disease.[4] Indeed, when these and similar data were used to predict the incidence of events among placebo-treated patients in clinical trials, the placebo groups often had lower event rates than had been predicted.[4] And finally, although it might be tempting to extrapolate the CCV risks beyond 10 years, there is no clear evidence to support such extrapolations.

Despite these limitations, the method suggested offers a novel means of making a fast, reasonable and more explicit and visual estimate of an individual patient's absolute risk of CCV events over the next 5 or 10 years than is now possible.

Estimating the benefits of drug therapy for primary prevention

The potential benefits of long-term drug therapy in primary prevention can be determined from the estimate of the individual patient's absolute risk for an event and the relative risk reduction that has been shown with drug therapy. Clinicians should not be tempted to use the nomograms alone to estimate the benefits of risk reduction with drug therapy for their patients. Drug therapy that reduces 1 or more risk factors may not necessarily lead to stepwise reduction in an individual patient's risk of a CCV event as determined using the nomograms in Figs. 1 and 2. In fact, most drug trials have not demonstrated the overall benefit that one might expect on the basis of the risk factor reduction achieved. In addition, there is little evidence that multiple risk factor intervention has an additive effect in reducing the risk of an event.[10–12] For these reasons, we suggest that the results of primary prevention trials should be used to estimate an individual patient's potential relative risk reduction from drug therapy.

Table 1 outlines examples of the relative risk reductions for blood-pressure and cholesterol-lowering therapy in patients with no history of CCV disease. The data on blood pressure come from 2 meta-analyses of the use of diuretics and β-blockers in hypertension.[13,14] The data for cholesterol lowering come from the 3 available double-blind placebo-controlled randomized trials in which therapy with bile-acid sequestrants, fibric-acid derivatives and HMG–CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors were evaluated in hypercholesterolemia.[15–17] To date, there is no evidence that treatment of hypertension with angiotensin-converting enzyme inhibitors or calcium-channel blockers reduces the risk of CCV events, although trials are under way. In some cases there are no sex- or age-specific data on the benefit of pri-

Table 1: Relative risk reductions in myocardial infarction (MI) and stroke (S) in patients with no history of cardiovascular or cerebrovascular disease

	Men < 65*		Women < 65*		Men ≥ 65		Women ≥ 65	
Intervention	MI	S	MI	S	MI	S	MI	S
Blood pressure lowering								
Diuretics and/or β-blockers[13,14] (treatment for 5 years†)	14	42	14‡	42‡	19	35	19‡	35‡
Cholesterol lowering								
Bile-acid sequestrants[15] (treatment for 7 years§)	25	0	ND	ND	ND	ND	ND	ND
Fibric–acid derivatives[16] (treatment for 4 years§)	20	0	ND	ND	ND	ND	ND	ND
HMG–CoA reductase inhibitors[17] (treatment for 4.9 years§)	31	0	ND	ND	ND	ND	ND	ND

*2 of the 16 trials in the meta-analysis involved patients over 65.
†Diastolic blood pressure was lowered 5–6 mm Hg on average in nonelderly patients and 9 mm Hg on average in elderly patients; systolic blood pressure was lowered 10 mm Hg on average in nonelderly patients and 17 mm Hg on average in elderly patients.
‡Trials did not exclusively involve women, but most contained an important number of women: there is some evidence that the benefit might not be as great for women as for men.[7]
§Total cholesterol level was lowered on average 8.5% by cholestyramine, 11% by gemfibrozil and 20% by HMG–CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors.
ND = no data from randomized controlled trials.

mary prevention. In these groups, the clinician is required to form an opinion on the likelihood of benefit based on data from other groups of patients. We also do not know whether the benefit of treatment extends beyond 5–7 years. The duration of the trials is indicated in Table 1.

Sample case

Using our 58-year-old male patient with a 6% risk of MI or death from CAD and a 4% risk of stroke in the next 5 years, we then apply the relative risk reductions shown in Table 1. For ease of calculation we have rounded the relative risk reductions shown in the table to the nearest 5%. Clinicians should realize that the main point of these calculations is to appreciate the approximate magnitudes of the risks of CCV disease and of the potential benefits of therapies.

The potential benefit that would be obtained from the various interventions can be estimated as follows.

1. Reducing the patient's blood pressure (diastolic by 5–6 mm Hg and systolic by approximately 10 mm Hg) with drug therapy may reduce his risk of MI and death from CAD by about 15% (relative risk reduction) and his risk of stroke by about 40% (Table 1). Therefore, his risk of MI or death from CAD would decrease from 8% to 6.8% (absolute reduction 1.2%) and his risk of a stroke from 4% to 2.4% (absolute reduction 1.6%). A useful, more descriptive way to view the potential value of an intervention is in terms of the "number needed to treat" (NNT),[18] that is, the number of patients that must be treated to prevent 1 clinical event over a defined period. The NNT is calculated by dividing the absolute risk reduction into 100. In our example the NNT to prevent 1 MI or death from CAD over 5 years would be 83 (100/1.2). Although the prevention of 1 of these events is important for any individual patient, the clinician and patient should know that 82 of 83 patients so treated for 5 years would receive no measurable clinical benefit. Also, there is no way to tell who will be the 1 patient who does benefit. The NNT to prevent 1 stroke in our example is 63 (100/1.6); that is, 62 patients would receive no measurable benefit.
2. Reducing the patient's total cholesterol level with drug therapy by about 10%–20% may reduce his risk of MI or death from CAD by about 20%–30% (relative risk reduction) (Table 1). Therefore, his risk of MI or death from CAD would decrease from 8% to about 6% (using a 25% relative risk reduction). This is equivalent to an NNT for 5 years of 50. Cholesterol-lowering drug therapy would not reduce the patient's risk of stroke.

As most clinical trials provide data for approximately 5 years, there is currently no evidence that allows one to extrapolate accurately the benefit of drug therapy beyond that period. In addition, although it may be tempting to add the benefits of blood pressure lowering to those of cholesterol lowering, there is no evidence, as we mentioned earlier, that multiple risk factor intervention has an additive effect in reducing the risk of an event.[10–12]

Involving the patient

Patients should be involved in making decisions about their own therapy. Clinicians should explain the risks and benefits of therapy in a manner that the patient can understand. Results of a study by Hux and Naylor[19] reveal that patients may make very different decisions about long-term drug therapy depending on whether information from a trial is presented to them in terms of relative reduction, absolute reduction or NNT. Participants were asked to imagine that they had a particular risk factor, that an available drug had no side effects and that its cost would be covered by a plan. They were then asked whether they would be willing to take the drug if their physician suggested it. When the relative risk reduction was presented, 88% of the patients indicated they would take the drug. When the same results were presented in terms of absolute risk reduction, only 42% stated they would take the drug. Finally, when the information was presented as number needed to treat, only 31% of patients indicated that they would take the drug.

Once the patient understands the potential risks and benefits of drug therapy, the clinician should discuss other factors such as inconvenience, side effects, laboratory monitoring and cost that may affect acceptance of therapy. Once all these issues have been explained fully, the patient can make an informed decision about long-term primary prevention. If this information results in the rejection of therapy, this is the patient's perogative. If the information results in an informed acceptance of therapy, the chance of long-term adherance to drug therapy might be enhanced.

Our intention was to provide clinicians with a method for estimating the benefit of drug therapy for the primary prevention of CCV disease. However, reduction in or removal of risk factors by nonpharmaceutical means (e.g., smoking cessation, dietary modifications and exercise) can have an important impact on CCV disease.

Conclusion

We have developed nomograms and a table that are easy to use and provide a visual depiction for the clinician and patient of the interplay of individual risk factors for CCV events and potential benefit of drug therapy. We hope that these tools will help guide clinicians in evaluating and explaining to patients their risk of CCV events and that they will simplify discussion of the potential ben-

efits to be derived from some drug therapies. For many patients, the benefits of risk reduction with drug therapy may seem modest when considered in the manner presented. However, without reference to the individual's underlying risk, the projected benefits can be very misleading.[20] Unfortunately, many clinicians and the media focus on the relative risk reduction alone; this may result in an overestimation of both the risk of events and the potential benefits of drug therapy.

We thank Robin Ensom, PharmD, for his assistance in devising the nomograms.

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