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Cardiovascular Disease Prevention: Part 1, What Works—What Doesn't?

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ABSTRACT: Data that validate cardiovascular risk factor reduction are sufficiently powerful to justify specific interventions in primary care. Thanks largely, but not exclusively, to the Framingham Heart Study, you can confidently tell patients that their risk of heart disease and stroke is significantly decreased by smoking cessation, normalization of lipid profiles, and blood pressure control. Exercise, treatment of depression, stress management, and techniques for mitigating anger and hostility may also help prevent cardiovascular disease; however, the data supporting these interventions are not as solid. Although a nonmodifiable risk factor (such as family history, age, sex, and nontreatable predisposing or genetic condition) cannot be directly altered, its presence may prompt interventions to change other modifiable risk factors, thereby lowering cardiovascular disease risk.

The concept of cardiovascular risk factors was introduced by the Framingham Heart Study researchers, and much of our current understanding in this area derives from their ongoing work.[1,2] Only a leap of faith, however, transformed an initial identification of high-risk markers into an understanding of the causes of disease. Even bolder intellectual steps were required to reinterpret risk factors as predictors of future cardiovascular events and to infer that modifying such risk factors might reduce the likelihood of cardiovascular disease.

Certainly, the value of intervention has been shown for some—although by no means all—types of cardiovascular risk reduction. In this article (the first of a two-part series), I briefly review how risk is assessed, outline the spectrum of risk factors for cardiovascular disease, and discuss which interventions are known to be effective. In a second article (page 2973), I will explain how to integrate these interventions into primary care.

HOW TO THINK ABOUT RISK

To apply risk-based treatment recommendations, it is necessary to differentiate persons at high risk from those at low risk. Risk may be presented in terms of absolute risk, relative risk, or the number needed to treat.[3,4] Without explanation, data can be misleading or difficult to understand. To be meaningful, the end points (eg, future cardiovascular events) and the nature and duration of risk should be also specified.

Absolute risk reduction. This is the most straightforward method of measuring risk reduction. Absolute risk reduction is an expression of the change in the probability of an outcome (in percent) and is calculated as the difference in outcomes between two groups (placebo and treatment) in a study.

For example, the difference in the event rate for a group of patients receiving active treatment and the rate for a group receiving placebo is the absolute risk reduction. However, in many studies, the event rates tend to be low and their differences are small

Table 1 – Different perspectives on cardiovascular risk*

End point	Study	Relative risk reduction (%)	Absolute risk reduction (%)	Number needed to treat
Nonfatal MI/CAD death	4S[7]	31	8.6	11
	WOSCOPS[5]	30	2.4	42
CABG/PTCA	4S[7]	34	5.9	16
	WOSCOPS[5]	32	0.8	125
Events in diabetic patients	4S[7]	32	18.7	5
Stroke	4S[7]	37	1.6	62
	CARE[10]	32	1.2	83

MI, myocardial infarction; CAD, coronary artery disease; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; 4S, Scandinavian Simvastatin Survival Study; WOSCOPS, West of Scotland Coronary Prevention Study; CARE, Cholesterol and Recurrent Events.

*Similar relative risk reductions can correspond to widely disparate absolute risk reductions and numbers needed to treat.

Adapted from Moriarty PM. *Am J Cardiol.* 1998.[4]

and therefore difficult to interpret. For instance, if the risk of an event is 8% with placebo and 5% with treatment, the absolute risk reduction is 3%.

Relative risk reduction. The relative risk reduction is the difference in risk between two groups divided by the average (or placebo group) risk. Although relative risk reduction is larger than the absolute risk reduction and makes a greater impact on our understanding of the benefit of an intervention, it is not necessarily more meaningful.

In the example given above, the difference in the amount of risk shown for a group of patients receiving active treatment and for a group receiving placebo is divided by the risk in the placebo group. If the absolute risk reduction is 3%, the relative risk reduction is 3% divided by 8%, or 37.5%—a number that more easily catches our attention but which can also be misleading.

Number needed to treat. An increasing number of clinical investigators and clinicians are using the concept of the number needed to treat. This concept can be readily grasped by physicians, patients, and the public; thus, it is becoming more widely used in making comparisons and clinical decisions. The number needed to treat is the inverse of the absolute risk reduction.

If the absolute risk reduction is 3%, the number needed to treat is 1 divided by 0.03, or 33.3, to prevent one event for the *specific* intervention studied during the *specific* period of the study. If the absolute risk reduction were larger, fewer patients would have to be treated to see it. The larger the absolute risk reduction, the smaller the number needed to treat in order to prevent an event.

Nature and duration of assessed risk. To understand the benefit of a risk-reducing therapy, one must know *which* outcomes are being tracked and for *how long* (eg, the 5-year risk of having a myocardial infarction [MI] or stroke). Both factors must be explicit in order to interpret study data. This is particularly important to consider in the elderly, for whom—for example—stroke prevention may be much more meaningful than the risk of death.

Mortality may be a preferred end point among clinical trial investigators because it is unambiguous and easy to measure. It may be less meaningful—or desirable—to patients in a study, for whom quality-of-life end points that relate to symptom relief, amount of medication required, or more subjective criteria may be of greater importance.

Comparing risk. Consideration of the number needed to treat makes it possible to compare the implications of risk when absolute risks vary greatly while relative risks appear similar (Table 1). For example, in the West of Scotland Coronary Prevention Study (WOSCOPS), the relative risk reduction for coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) as end points was 32%, the absolute risk reduction was 0.8%, and the number needed to treat to prevent this end point (CABG or PTCA) was 12[illegible] patients.[5,6] In the Scandinavian Simvastatin Survival Study (4S), analysis of the same end points in a group of patients at much higher risk yielded a similar relative risk reduction (34%) and an absolute risk reduction of 5.9% while the number needed to treat to obviate the need for CABG or PTCA was only 16, almost an order of magn

tude fewer than that needed in WOSCOPS.[6,7] Furthermore, to reduce the number of cardiovascular events among persons with diabetes mellitus in the 4S—even though the relative risk reduction was 32%—only 5 patients needed to be treated.

Global risk assessment. This method of estimating risk takes multiple risk factors—as well as the level of each factor—into account. One recently developed coronary disease prediction algorithm is based on readily available information, including age, presence of diabetes, smoking status, total serum cholesterol level, low-density lipoprotein (LDL) cholesterol level, high-density lipoprotein (HDL) cholesterol level, and blood pressure.[8] Such a method of risk estimation is attractive because high-risk persons can be targeted for therapy, while low-risk persons can avoid therapy.

This prediction algorithm emphasizes the importance of both the number of risk factors and their severity. Thus, the more risk factors that are present and the greater their severity, the higher the risk of coronary disease. In addition, the algorithm focuses on the whole patient and is thus helpful in patient education and for compliance. This practical, cost-effective approach to population-based preventive medicine can be readily implemented in primary care.

SPECTRUM OF RISK FACTORS

The 27th Bethesda Conference of the American College of Cardiology, which was held to help clarify the role of risk factor management in patients at high risk for cardiovascular disease, proposed four risk factor categories.[9] Risk factors were categorized according to the evidence that their modification or management affects outcomes in coronary heart disease (CHD). They are grouped in descending order of importance for direct management (Table 2).

Risk factors *proved* to lower CHD risk when modified. From a practical perspective, the most important risk factors are those for which interventions have been proved to reduce the incidence of CHD events. The risk factors include cigarette smoking, elevated serum LDL cholesterol level, hypertension (especially when left ventricular hypertrophy [LVH] is present), and thrombogenic factors. These risk factors affect many persons; for example, approximately 25% of the general population smokes, 30% have high levels of LDL cholesterol, and 30% have hypertension.

No specific "thrombogenic" factors are recommended for measurement. Rather, inclusion of this "factor" is meant to indicate that either antiplatelet (aspirin) or anticoagulant (heparin or warfarin) therapy has been *proved* to lower risk.

Many of these risk factors respond—at least in part—to behavioral modifications, such as dietary and

Table 2 – Spectrum of risk factors for coronary heart disease

Category 1 (risk factors proven to reduce the incidence of CAD events when modified)
Cigarette smoking
Elevated serum LDL cholesterol level
Hypertension (especially when left ventricular hypertrophy is present)
Thrombogenic factors
Category 2 (risk factors likely to lower the incidence of CAD events when modified)
Diabetes mellitus
Physical inactivity
Low HDL cholesterol level
Obesity
Postmenopausal status
Category 3 (risk factors that might lower the incidence of CAD events if modified)
Psychosocial factors (anger, depression, hostility, stress)
Elevated triglyceride level
Elevated Lp(a) lipoprotein level
Elevated homocysteine level
Oxidative stress
Excessive alcohol consumption or abstinence
Category 4 (risk factors that cannot be modified but which may prompt interventions to change other modifiable risk factors)
Age
Gender
Nontreatable predisposing or genetic conditions
Family history
Physical characteristics (such as height, baldness, earlobe crease)

CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Adapted from Pasternak RC et al. *J Am Coll Cardiol.* 1996.[9]

CLINICAL HIGHLIGHTS

- Risk factors that have been *proved* to lower the likelihood of cardiovascular events when modified include smoking, high levels of low-density lipoprotein (LDL) cholesterol, hypertension (especially if left ventricular hypertrophy is present), and thrombogenic tendencies (that is, the patient is not receiving antiplatelet or anticoagulant therapy). These risk factors affect many persons; for example, 30% of the general population have high levels of LDL cholesterol and/or hypertension and 25% smoke.
- Risk factors that are *likely*—but not proved—to reduce cardiovascular risk when modified include diabetes mellitus, physical inactivity, low levels of high-density lipoprotein (HDL) cholesterol, obesity, and post-menopausal status. About 50% of the general population are sedentary, 25% are obese, 15% have low levels of HDL cholesterol, and 10% have diabetes.
- Risk factors that *may* lower cardiovascular risk when modified include psychosocial factors, such as anger and depression; elevated levels of triglyceride, Lp(a) lipoprotein, and homocysteine; oxidative stress; and excessive alcohol consumption or abstinence.

lifestyle changes. Risk factor modification is appropriate even for patients with no symptoms. The magnitude of benefit, however, is usually greater for patients at highest risk—that is, those with overt cardiovascular disease.

Risk factors *likely* to lower risk when modified. When present, these factors clearly increase the risk of cardiovascular disease, but the evidence showing that modification reduces risk is not quite as strong. Risk factors in this category include diabetes, physical inactivity, low HDL cholesterol levels, obesity, and postmenopausal status. Approximately half of the general population is physically inactive, 25% are obese, 15% have low HDL cholesterol levels, and 10% have diabetes.

These risk factors are amenable to both lifestyle changes and medical treatment. While convincing, large-scale, randomized clinical trials have not proved the benefits of treatment, optimizing the control of these factors seems likely to be beneficial in most cases.

Risk factors that *might* lower risk when modified. These have attracted much attention in the lay press, but little conclusive evidence exists that their modification actually reduces the risk of cardiovascular events. They include psychosocial factors; elevated triglyceride, Lp(a) lipoprotein, and homocysteine levels; oxidative stress; and either excessive alcohol consumption or abstinence. Approximately 25% of the general population has homocysteinemia, 20% has high triglyceride levels, and 10% has elevated levels of Lp(a) lipoprotein.

While emerging data suggest that anger, hostility, depression, and social isolation have deleterious effects on cardiovascular risk, there is no definite proof that mitigating these psychosocial factors reduces morbidity or mortality. Similarly, modifying triglyceride, Lp(a) lipoprotein, and homocysteine levels; antioxidant use; and moderate alcohol intake may be beneficial; however, firm data showing reductions in event rates are not yet available. Thus, these factors should generally not be primary targets of risk modification.

Risk factors that cannot be modified or that do not alter risk when modified. Family history, age, sex, and nontreatable predisposing or genetic conditions are nonmodifiable risk factors. An MI, coronary intervention (such as CABG surgery or PTCA), or sudden death before age 55 in a male first-degree relative or before age 65 in a female first-degree relative constitutes a strongly positive family history for premature coronary disease. Although a nonmodifiable risk factor cannot be directly altered, its presence may prompt interventions to change other, modifiable risk factors, thereby lowering cardiovascular disease risk. ■

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Editor's note: In a second article on page 2973, Dr Pasternak explains how to integrate cardiovascular risk reduction strategies into daily practice.