Cardiovascular Protection Paradigms: Is Change on the Horizon?

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Recent trials of patients with cardiovascular disease (CVD) have provided a wealth of data regarding diagnosis, risk factors, and treatment. Aggressive risk factor management has been shown to improve patient survival, reduce recurrent events and the need for interventional procedures, and improve the quality of life in patients with known CVD. There have been impressive reductions in blood pressure and low-density lipoprotein cholesterol levels, and improved diabetes control. Medical therapy with options such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and aspirin has been shown to have positive effects. Patients in current trials are more likely to be receiving appropriate treatment upon study entry than were patients in older trials. Changes in the risk profile of high-risk patients have reduced the overall rates of cardiovascular events and will continue to affect outcomes in randomized clinical trials. Such changes should be considered in the design of new clinical trials and in the interpretation of current data.

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Key words: Cardiovascular disease • Blood pressure • Low-density lipoprotein cholesterol • Angiotensin receptor blockers • Angiotensin-converting enzyme inhibitors

Despite the tremendous progress made in cardiovascular medicine, cardiovascular disease (CVD) still remains a dominant problem in the general population, affecting the majority of adults over the age of 60 years. Coronary heart disease (CHD) accounts for approximately one-half of all cardiovascular events, and the lifetime risk of developing CHD remains high. In the Framingham Heart Study of 7733 participants aged 40 to 94 years who were initially free of CHD,[1] data indicated that the lifetime risk of developing CHD for individuals at age 40 was 49% for men and 32% for women. For

those who were free of disease at age 70, the lifetime risk was 35% in men and 24% in women.

The term *CVD* encompasses 4 major areas: 1) CHD manifested by myocardial infarction (MI), angina pectoris, heart failure (HF), or coronary death; 2) cerebrovascular disease manifested by stroke and transient ischemic attack; 3) peripheral vascular disease (PVD) manifested by intermittent claudication; and 4) aortic atherosclerosis and thoracic or abdominal aortic aneurysm. CHD is the most prominent form of CVD and accounts for more than 1.1 million new cases per year.[2] CHD alone accounts for 20% of all deaths annually.[3] There are also more than 700,000 cases of fatal and nonfatal stroke per year.[4,5] Almost 62 million people in the United States have some form of CVD, making it the preeminent public health problem in the nation.[2] CVD leads to 1.5 million percutaneous coronary interventions[6] and more than 570,000 surgical revascularizations each year,[7] with an overall annual cost exceeding $352 billion (as calculated in 2000).[8]

This article will examine the latest data from large, randomized trials in patients with CVD. It will consider how new findings may modify previous recommendations.

CVD Risk Factors

Recent experimental studies in animals and humans have identified the mechanisms by which the major cardiovascular risk factors of hypertension, dyslipidemia, diabetes, and smoking may lead to CVD. Risk factors influence and contribute to the development of endothelial dysfunction, which leads to increased endothelial permeability to lipoproteins and other plasma constituents, resulting in increased expression of leukocyte adhesion molecules and entry of leukocytes into the arterial intima. The resulting inflammatory process leads to the development of atherosclerotic plaque: monocytes convert to macrophages, which engulf lipids and become foam cells; smooth muscle cell migration leads to formation of a fibrous cap; and foam cell death leads to formation of a necrotic core. Plaques with thin caps may become unstable and rupture, producing atherothrombosis and clinical events. Arterial thrombosis is the underlying cause of the majority of vascular events, such as MI, ischemic stroke, and vascular death. Atherothrombosis was indeed the leading cause of death among the more than 56.5 million people who died in 2000 worldwide.[9]

The presence of vascular disease in one vascular bed significantly increases the likelihood of disease in other vascular distributions. For this reason, the National Cholesterol Education Program (NCEP) report considered that the presence of noncoronary atherosclerotic vascular disease carried the same risk for future cardiac events as did CHD. Peripheral arterial disease is therefore considered a CHD equivalent.[10]

Most of the important cardiovascular risk factors have been identified and validated by the Framingham Heart Study; they include cigarette smoking, elevated blood pressure (BP), elevated serum total and low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and advanced age. Although individually these risk factors can initiate the atherosclerotic process, coexistence of multiple risk factors dramatically increases the risk of vascular complications (Figure 1). These observations have been confirmed worldwide. The INTERHEART study[11] was conducted in 262 centers in 52 countries around the world. A total of 15,152 incident cases of acute MI and 14,820 matched control subjects with no history of CHD were examined. The study identified 9 potentially modifiable factors that accounted for over 90% of the population-attributable risk of a first MI: smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, inadequate consumption of fruits and vegetables, regular alcohol consumption, and inadequate physical activity. Population-attributable risk for each of these factors is presented in Table 1. The large number of participants in the study made it possible to determine that there were no significant geographical variations in the population-attributable risk for the 9 risk factors. It was concluded that the principles of CVD prevention should be similar around the world.

Many individuals in the general population have at least 1 risk factor for CHD, and over 90% of CHD events occur in individuals who have at least 1 risk factor.[12,13] Absence of major risk factors predicts low risk of CHD. About 8% of cardiovascular events occur in patients with marginal or borderline elevation of traditional risk factors.

Framingham Risk Score

The model most frequently used is the one developed by the Framingham Heart Study.[13] This model incorporates age, sex, LDL and HDL cholesterol, BP, diabetes status, and smoking status to derive an estimated risk of developing CHD within 10 years. A validation study found that the Framingham CHD predictors performed well for prediction of CHD events in both black and white subjects.[14]

The Framingham risk score was modified by the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in

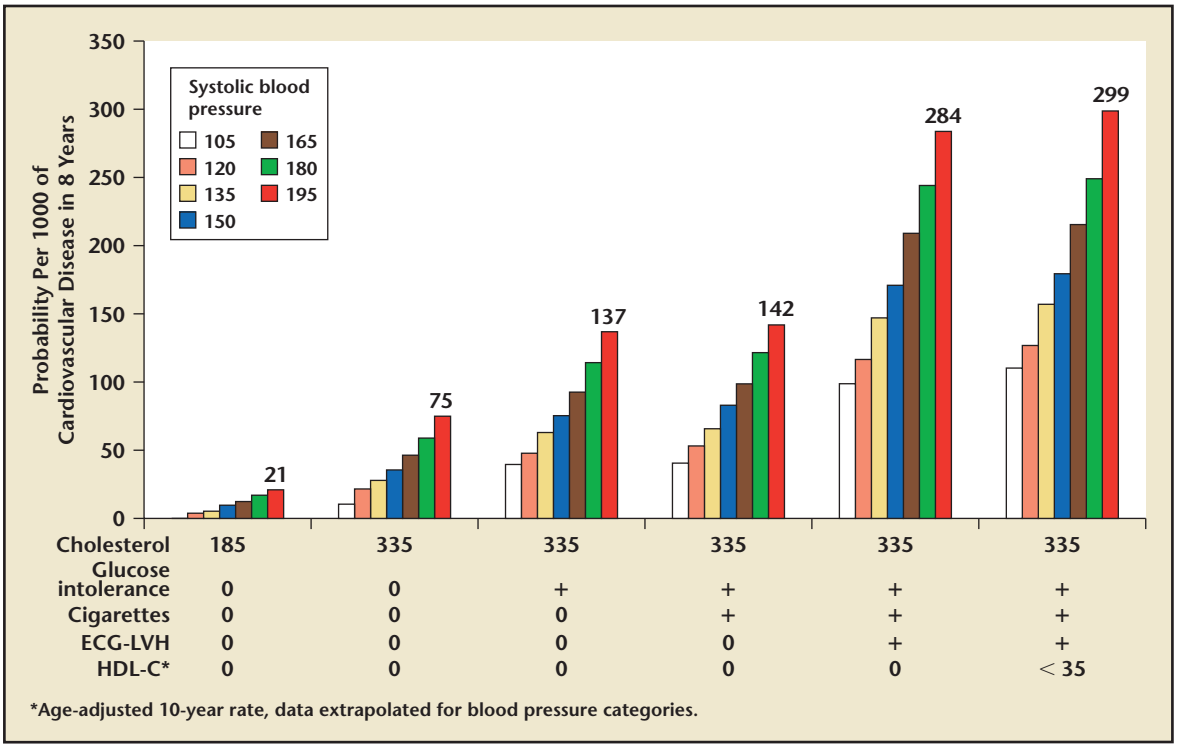

Figure 1. *Synergistic effect of cardiovascular risk factors. Data from women are shown. ECG, electrocardiogram; LVH, left ventricular hypertrophy; HDL-C, high-density lipoprotein cholesterol. Data from Wilson et al*[12] *and Kannel WB.*[55] www.medreviews.com

Table 1
OR and PAR of 9 Factors for Myocardial Infarction: The INTERHEART Study

Risk Factor	OR	PAR (%)
Apolipoprotein B/Apolipoprotein A_1	3.2	49
Smoking	2.9	36
Psychosocial factors	2.7	33
Abdominal obesity	1.6	20
Hypertension	1.9	18
Diabetes mellitus	2.4	10
Consumption of fruits and vegetables	0.7	15
Regular physical activity	0.8	12
Alcohol consumption	0.9	7

OR, odds ratio; PAR, population-attributable risk. Reprinted from *The Lancet*, Volume 364. Yusuf S et al. Effect of potentially modifiable risk factors associated with MI in 52 countries. Pages 937-952.[11] Copyright © 2004, with permission from Elsevier.

Adults (Adult Treatment Panel [ATP] III) for use in their recommendations for dyslipidemia screening and treatment.[10] The modifications include elimination of diabetes from the algorithm (because it was considered a CHD equivalent), broadening of the age range, and inclusion of hypertension treatment and age-specific points for smoking and total cholesterol.

The Framingham/ATP III criteria were used to estimate the distribution of CHD risk in the United States in an analysis of data from the National Health and Nutrition Examination Survey (NHANES) III among 11,611 patients (aged 20 to 79 years) without self-reported CHD, stroke, peripheral vascular disease, or diabetes.[15] The 10-year CHD risk results and the proportion of patients in each category were as follows: low risk (< 10% CHD risk at 10 years), 82% of patients; intermediate risk (10% to 20%), 16% of patients; and high risk (> 20%), 3% of patients. Not surprisingly, the frequency of high-risk patients increased with age and was greater in men than women.

Risk Evaluation in Europe

Other models have been developed in an attempt to provide better predictive accuracy for European patients. The largest was developed by the Systematic Coronary Risk Evaluation (SCORE) project,[16] which included data on more than 200,000 patients pooled from cohort studies in 12 European countries. Variables incorporated into the model include age, sex, systolic BP, total cholesterol, HDL cholesterol, and cigarette smoking. The mean follow-up was 13 years, with an endpoint of cardiovascular death. A unique aspect of SCORE is that separate risk scores were calculated for high- and low-risk regions of Europe. The predictive value of SCORE was high in each study cohort.

Risk Factor Modification

Recognition of the importance of risk factors in the development of CVD leads to aggressive treatment and multidisciplinary approaches. Results from many randomized clinical trials repeatedly demonstrated the benefits of risk factor control in patients with no demonstrable vascular disease (primary prevention), but more importantly in patients with established CVD (secondary prevention). Implementation of risk factor modification has been cumbersome, but multidisciplinary efforts are bearing fruit. Patients are more involved in their own care, physicians better understand the significant value of risk factor modification, and results are moving in the right direction. Risk of development of CVD has been decreasing, and mortality and recurrent events have been dramatically reduced. As mounting data are published documenting the benefits of aggressive reduction of BP and LDL cholesterol, as well as of diabetes control, the target values are being revised downward. Thus, the target systolic BP is now below 140 mm Hg for most patients, below 130 mm Hg in diabetic patients and patients with coronary artery disease (CAD), and below 120 mm Hg in patients with nephropathy. In patients with HF, the best BP is the lowest BP tolerated.[17,18] Similarly, targets for LDL cholesterol have been revised downward. Numerous placebo-controlled trials in both primary and secondary prevention have shown that statin therapy can reduce LDL cholesterol by 30% to 40% and reduce cardiovascular events by 24% to 37%.[19] More recently, comparative studies have shown continuous improvement with lower levels of achieved LDL cholesterol. Recent guidelines recommend LDL levels below 70 mg/dL in very high-risk patients with CAD or a history of acute coronary syndromes (ACS).[20]

Treatment of Hypertension

The cardiovascular risk of elevated systolic and diastolic BP is linear, continuous, and graded. Systolic BP above 115 mm Hg or diastolic BP above 75 mm Hg is associated with increased risk of stroke and MI.[21] A large body of evidence supports the notion that systolic BP is a much stronger risk predictor than diastolic BP.[22] In fact, in patients older than 60 years, there is an inverse relationship between diastolic BP and cardiovascular risk.[23] In the older age group, pulse pressure becomes an important factor. Data from the Multiple Risk Factor Intervention Trial (MRFIT)[24] indicate that after the age of 60 years, patients with the highest systolic and lowest diastolic BP have the greatest risk of cardiovascular complications. A large meta-analysis of 61 studies[21] that included close to 1 million subjects also indicated a strong association between systolic and diastolic BP and cardiovascular risk. In this analysis, for every 20 mm Hg increase in systolic pressure or 10 mm Hg increase in diastolic pressure, there was a doubling of cardiovascular risk. Following the landmark studies of the Veterans Administration in the late 1960s and early 1970s, several studies have shown the benefit of BP control. Meta-analyses of 18 placebo-controlled trials with more than 48,000 patients demonstrated that even modest reductions in BP can result in substantial benefit.[25,26] Moser and Hebert[26] have shown that even a 4- to 6-mm Hg reduction of diastolic BP can reduce HF by 52%, strokes by 38%, cardiovascular mortality by 21%, and fatal or nonfatal MI by 16%. In most of these trials, systolic BP was reduced to levels between 140 and 160 mm Hg. There was no evidence, therefore, that reduction of systolic BP below 140 mm Hg provides additional benefit.

Three trials that achieved systolic BP below 140 mm Hg demonstrated substantial reduction of cardiovascular events in high-risk patients. Data from the Heart Outcomes Prevention Evaluation (HOPE),[27] European Trial On Reduction of Cardiac Events with Perindopril in Stable Coronary Artery (EUROPA),[28] and Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[29] trials suggest that reducing the BP below previously recommended goal levels is beneficial in high-risk patients. Although the HOPE and EUROPA trials have been interpreted to demonstrate a specific benefit of angiotensin-converting enzyme (ACE) inhibitors in patients at increased risk, the results of CAMELOT and other data suggest that the benefit of ACE inhibitor therapy in these trials was due to BP reduction. A goal of BP equal to or below 130/80 mm Hg is recommended in patients with CVD.

Benefits Beyond BP Control

Following these and many other similar publications, a hotly debated question surfaced: Is there benefit beyond BP control? To answer this question, several studies have been designed comparing treatment regimens from different classes of antihypertensive medications; these trials have been summarized in meta-analyses and review articles. The largest of these publications included over 158,000 patients. This analysis failed to demonstrate any benefit in the primary endpoint of major cardiovascular events,[18] but interestingly suggested that there may be benefit in stroke prevention from regimens that included angiotensin receptor blockers (ARBs) or calcium channel blockers. The 2 major trials that compared ARBs with other regimens are the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[30,31] and the Study on Cognition and Prognosis in the Elderly (SCOPE) study.[32]

The LIFE study included 9193 patients with hypertension and left ventricular hypertrophy (LVH) randomized to an atenolol-based regimen or a losartan-based regimen. BP was reduced significantly by 30.2/16.6 mm Hg and 29.1/16.8 mm Hg in the losartan-based and atenolol-based groups, respectively, yet the group of patients randomized to losartan demonstrated 25% fewer fatal and nonfatal strokes (0.75, 95% confidence interval [CI], 0.63-0.89; $P = .001$). In a subgroup of 1326 patients with isolated systolic hypertension and LVH—a population at high risk for stroke—results were more impressive.[31] These patients were also randomized to losartan-based or atenolol-based regimens. BP was reduced by 28/9 mm Hg in both the losartan-based and atenolol-based arms. In this population, losartan reduced nonfatal and fatal stroke 41% better than atenolol (10.6 vs 18.9 events per 1000 patient-years; relative risk [RR], 0.60; 95% CI, 0.38-0.92; $P = .02$).[33,34]

The SCOPE trial assessed the effect of candesartan on cardiovascular outcomes in elderly patients with mild to moderate hypertension. Patients were randomized to receive standard therapy alone (mostly diuretics, n = 2460) or with candesartan, 8 to 16 mg/d (n = 2477). Nonfatal stroke was reduced by 28% ($P = .04$) in the candesartan-treated group as compared with the control group. There was also a nonsignificant 11% ($P = .19$) reduction in major cardiovascular events. Among patients included in the SCOPE study, 1518 had isolated systolic hypertension.[33] In this subgroup of patients, those randomized to candesartan had 42% fewer strokes (RR, 0.58; 95% CI, 0.33-1.00; $P = .050$ unadjusted; $P = .049$ adjusted for baseline risk) despite little difference in systolic and diastolic BP. Another group of patients in the SCOPE study who benefited substantially were those with history of stroke. In this group, the risk reduction with candesartan was 64% ($P = .004$). Other cardiovascular events demonstrated nonsignificant trends in favor of candesartan.[33] These results, in parallel with the results of the patients with isolated systolic hypertension in the LIFE study, suggest that this high-risk group of patients can potentially benefit from regimens that include ARBs.

This observation is of great interest and confirms the findings of the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study.[34] This study was a prospective, randomized, double-blind, placebo-controlled, multicenter trial designed to assess the safety of modest BP reduction by candesartan in the early treatment of stroke. Patients were included if they had an acute ischemic stroke with a motor paresis and severe hypertension. The primary endpoint was a composition of the patient's morbidity (functional status measured with modified Rankin Scale and Barthel Index, degree of motor deficit by National Institutes of Health Scale) and mortality rates after 3 months. Patients were randomized to candesartan or placebo within 24 hours for 7 days. Thereafter, all subjects received candesartan for the remaining treatment period, and BP was controlled by increasing the candesartan dose or by adding other antihypertensive agents. The study was terminated prematurely when researchers saw beneficial effects of early treatment with candesartan. The cumulative 12-month mortality and the number of vascular events was 47.5% lower in the early candesartan treatment group, although there was no significant difference in long-term systolic and diastolic BP.

A third study to examine the effect of an ARB in the prevention of stroke was the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study.[35] This study was the first to compare an ARB with calcium channel blockers in secondary stroke prevention. In hypertensive stroke patients, for the same level of BP control, eprosartan was more effective than nitrendipine in reducing cerebrovascular events (incidence density ratio [IDR], 0.75; 95% CI, 0.58-0.97; $P = .03$) and cardiovascular events (IDR, 0.75; 95% CI, 0.55-1.02; $P = .06$). The mechanism by which ARBs may reduce the risk of stroke has not been clearly understood, and different hypotheses have been proposed. These include a specific effect of angiotensin II type 1 (AT_1) receptor blockade in the brain flow or hemodynamics, greater reduction in central BP by ARBs, or

the reduction on atrial fibrillation (AF).[36] It is well known from the literature that chronic or paroxysmal AF is associated with high risk of stroke in nonanticoagulated patients. Consequently, it is reasonable to assume that prevention of AF will result in a lower risk of stroke, which has been validated in the LIFE study.[36]

In the LIFE study, new-onset AF occurred in 150 patients randomized to the losartan-based regimen versus 221 patients randomized to the atenolol-based regimen (6.8 vs 10.1 per 1000 patient-years; RR 0.67; 95% CI, 0.55-0.83; $P < .001$), despite similar BP reduction. There were fewer strokes in patients who developed new-onset AF in the losartan treatment arm when compared with those in the atenolol treatment arm (19 vs 38; HR = 0.49; 95% CI, 0.29-0.86; $P = .01$).[36] Similar results were obtained in patients with chronic AF. A total of 342 patients with AF were assigned to losartan- or atenolol-based therapy for 1471 patient-years of follow-up. Stroke occurred in 18 patients in the losartan treatment group as compared with 38 in the atenolol treatment group (HR = 0.55; 95% CI, 0.31-0.97; $P = .039$).

Management of High-Risk Patients

The benefit of ACE inhibitors in high-risk patients with normal ejection fraction was first demonstrated in the HOPE study.[15] HOPE was a double-blind, randomized, multicenter clinical study that evaluated the role of the ACE inhibitor ramipril in patients who were at high risk for cardiovascular events but who did not have evidence of LV dysfunction or HF. Patients who were at least 55 years of age were eligible for the study if they had a history of CAD, stroke, peripheral vascular disease, or diabetes plus at least 1 other cardiovascular risk factor (hypertension, increased total cholesterol, low HDL cholesterol, cigarette smoking, or microalbuminuria). Patients were randomized to receive ramipril, 10 mg/d, in addition to standard therapy or matching placebo for a mean of 5 years. The primary composite outcome was MI, stroke, or cardiovascular death. A total of 651 patients (14%) randomized to the ramipril group reached the primary composite endpoint as compared with 826 patients (17.8%) randomized to the placebo group (RR, 0.78; 95% CI, 0.70-0.86; $P < .001$). Treatment with ramipril reduced cardiovascular mortality by 26% (6.1% vs 8.1%; $P < .001$ in the placebo group), MI by 20% (9.9% vs 12.3%), stroke by 32% (3.4% vs 4.9%), total mortality by 16%, revascularization procedures by 15%, and HF by 23%. These results, as impressive as they are, have been criticized since the degree of BP lowering by ramipril may have been greater than what was reported at study end. This difference in BP could account for all or a portion of the outcome findings. At baseline, 46% of the HOPE population had hypertension, and these patients benefited the most from ramipril therapy. The mean BP at entry was 139/79 mm Hg in both groups. BP decreased on average by 3.3 mm Hg systolic and 1.4 mm Hg diastolic in the ramipril-treated group and by 0.66 mm Hg systolic and 1.1 mm Hg diastolic in the placebo-treated group.

This high-risk population benefited from ACE inhibitor therapy added to standard therapy. The event rate was fairly high and allowed for substantial improvement with ACE inhibition. Since the publication of the results of the HOPE trial, awareness of the benefits of risk factor modification (primarily BP control, lipid management, tight glycemic control, and smoking cessation) has led to increased utilization of cardiovascular risk-reducing therapies in high-risk patients. Thus, the background therapies of populations recruited for more recent studies have evolved considerably. The Prevention of Events with an ACE inhibitor (PEACE) study,[37] for example, included a similar population to the one included in the HOPE trial. The trial randomized 8290 high-risk patients to trandolapril or placebo.[37] The study failed to demonstrate any significant benefit from trandolapril therapy added to standard background treatment. The primary endpoint was similar in the trandolapril group and the placebo group. To interpret the predominantly negative findings of PEACE in the context of the positive findings of HOPE, the authors compared the baseline characteristics of patients in both trials. At baseline, the patients in the PEACE trial had an average ejection fraction of 58% and normal creatinine and serum levels. Their average BP was 133/78 mm Hg, which was the level of BP achieved with ramipril treatment in HOPE. Patients in the PEACE trial received more intensive medical therapy for risk factors than did those in HOPE. At baseline, 70% of patients in PEACE as compared with 29% in HOPE were on lipid-lowering drugs. More patients in PEACE were on aspirin, β-blockers (Table 2), and underwent revascularization at study entry. Intensive medical therapy and risk factor modification reduced the risk of cardiovascular events in the placebo arm of the PEACE trial to the point that there was no further benefit from ACE inhibition. In fact, as shown by the authors, the risk in the placebo arm of the PEACE study was lower than the risk of the treated patients in the HOPE study[37] (Figure 2).

Table 2
Background Therapy in the HOPE[27] and PEACE Trials[37]

Medication	HOPE (%)	PEACE (%)
Aspirin	75.3	90
β-blocker	39.2	60
Lipid lowering	28.4	70
Calcium channel blockers	46.3	36
Diuretics	15.3	13

HOPE, Heart Outcomes Prevention Evaluation; PEACE, Prevention of Events with an ACE inhibitor.

Table 3
Relative Risk Reduction in Recent Trials of Patients at High Risk for Cardiovascular Events

Study	Population	N	RRR (%)
CURE[38]	ACS, clopidogrel	12,562	20
COMMIT[39]	Acute ST-elevation MI, clopidogrel	42,852	9
CHARM-Added[40]	Heart failure class II-IV, ACE inhibitor	2248	16
IDEAL[41]	CHD, lipid lowering	8888	11
PROVE IT[42]	CAD, ACS, lipid lowering	4162	16
TNT[43]	CAD, lipid lowering	10,001	22
SPARCL[44]	Stroke, TIA, lipid lowering	4731	16
COURAGE[45]	Medical therapy vs PCI in stable CAD	2287	−5

RRR, relative risk reduction; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ACS, acute coronary syndrome; COMMIT, Clopidogrel Metoprolol Myocardial Infarction Trial; MI, myocardial infarction; CHARM, Candesartan in Heart failure–Assessment of Reduction in Mortality and Morbidity; ACE, angiotensin-converting enzyme; IDEAL, Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; CHD, congestive heart failure; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; CAD, coronary artery disease; TNT, Treating to New Targets; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; PCI, percutaneous coronary intervention.

Since then, several trials in high-risk patients have demonstrated that intensive and comprehensive medical therapy and risk factor modification can substantially reduce risk in high-risk patients, making it difficult for any intervention to further improve the risk of cardiovascular events. Thus, the relative risk reduction seen in the latest comparative studies in CVD has been getting smaller and smaller. Examples of such studies are shown in Table 3.

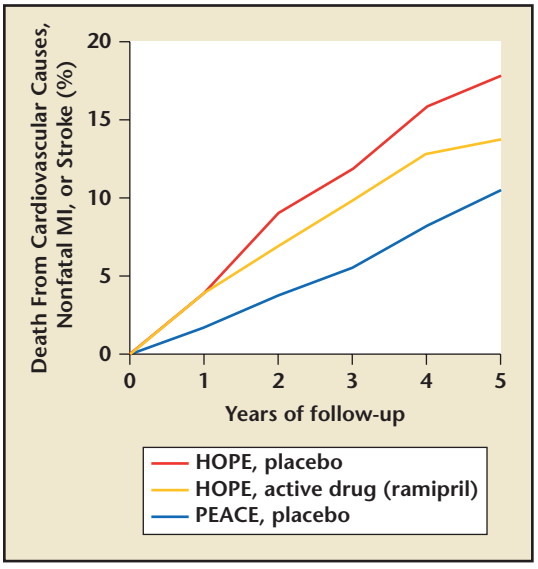

Figure 2. *Comparison of outcomes in the PEACE trial and HOPE. HOPE, Heart Outcomes Prevention Evaluation; PEACE, Prevention of Events with an Angiotensin-converting Enzyme Inhibitor. Data from Yusuf S et al[27] and Braunwald E et al.[37]*
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The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study[38] randomized 12,562 patients presenting with ACS to aspirin alone or to aspirin plus clopidogrel. The primary objective was to assess the benefit of dual antiplatelet therapy compared with aspirin alone. In 12 months, the study demonstrated a 20% reduction in the combined endpoint (death from cardiovascular causes, nonfatal MI, or stroke) with dual antiplatelet therapy. The benefit was substantial and statistically significant. The study was completed at approximately the same time as the HOPE trial, and patients were not aggressively treated with lipid-lowering drugs, β-blockers, or aspirin. The more recently published Clopidogrel Metoprolol Myocardial Infarction Trial (COMMIT)[39] randomized 42,852 patients with ST-elevation MI to aspirin alone or to aspirin plus clopidogrel. The primary objective was the prevention of recurrent events with dual antiplatelet therapy. The study demonstrated a statistically significant 9% reduction in the primary endpoint of death, reinfarction, or stroke, but the benefit was rather small. In this study, the

high-risk population enrolled was treated aggressively with lipid-lowering and other standard background therapy. The results of the Candesartan in Heart failure-Assessment of Reduction in Mortality and Morbidity (CHARM)-Added study[40] provide another example of moderate benefit of treatment with an ARB, candesartan, in a high-risk population treated aggressively and appropriately with background therapy. Patients were randomized to receive candesartan or placebo in addition to standard therapy. The study demonstrated a 16% reduction in the primary endpoint of cardiovascular death and HF hospitalizations, but the benefit was numerically small. Again the study was completed in an era when high-risk patients were treated aggressively. Thus, background therapy in the CHARM-Added study included ACE inhibitors (100%), β-blockers (55%), aspirin (51%), and lipid-lowering treatment (41%). Three lipid-lowering trials—Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL),[41] Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT),[42] and Treating to New Targets (TNT)[43]—compared less aggressive versus more aggressive lipid lowering in high-risk patients with CAD and/or ACS. The more aggressive cholesterol-lowering strategy reduced LDL cholesterol to a significantly lower level and resulted in a small but significant increase in protection from cardiovascular complications. Again, the benefit was small (Table 3), probably in part because the control groups were aggressively treated with background therapy, including less aggressive lipid lowering.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[44] randomized 4731 patients who had had a stroke within 1 to 6 months before study entry and no known CAD, to atorvastatin (80 mg) or placebo. The primary endpoint was recurrent fatal or nonfatal stroke. LDL cholesterol was reduced to 73 mg/dL in the atorvastatin-treated patients and remained at 129 mg/dL in the control group. The primary endpoint was 16% lower in the treated group ($P = .03$), with an absolute risk reduction of 2.2%. In this study, too, background therapy included antiplatelet agents (87%), ACE inhibitors (30%), β-blockers (18%), and dihydropyridines (15%).

Absolute Risk Reduction

It is apparent from recent clinical trials in high-risk patients that the landscape of CVD has changed. Medical therapy has incorporated the information collected in the past 2 decades, and high-risk patients are being treated more aggressively with CVD risk–reducing therapies. Medical therapy is effective in preventing many of the cardiovascular complications previously seen, and there may be limited room for improvement. The results of the recently published Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[45] study attest to this principle. The study randomized 2287 patients with stable CAD to optimal medical therapy or percutaneous coronary intervention (PCI). The primary endpoint was the occurrence of death or MI and the secondary endpoint was death, MI, or stroke. There was no difference between medical therapy and PCI for the primary or secondary endpoints, although PCI was more effective in preventing angina for the first 4 years of follow-up. It is interesting to look at the components of medical therapy in this study. Participants had all the characteristics of high-risk patients, but CAD, history of hypertension, diabetes, HF, cerebrovascular accident, and previous MI or history of previous revascularization were optimally treated. The goals of therapy included smoking cessation, intake of cholesterol below 200 mg/d, LDL cholesterol between 60 and 85 mg/dL, HDL above 40 mg/dL, triglycerides below 150 mg/dL, some form of physical activity for 30 to 45 minutes at least 5 days per week, body mass index (BMI) below 25 kg/m^2, BP below 130/85 mm Hg, and a hemoglobin A_{1c} level below 7%. Indeed, medical therapy achieved a BP of 122/70 mm Hg, total cholesterol of 140 mg/dL, LDL cholesterol of 72 mg/dL, HDL cholesterol of 41 mg/dL, triglycerides of 131 mg/dL, and a BMI of 29.5 kg/m^2. About 36% of patients achieved the goal of exercising at least 5 days per week. Medical therapy was similar between the PCI and medical therapy groups. The primary endpoint occurred at a fairly low rate of 4.5% per year in both groups. PCI did not improve outcomes beyond optimal medical therapy. Therefore, intensive, aggressive optimal therapy works.

As a consequence of aggressive optimal medical therapy in high-risk patients, the actual absolute risk has considerably diminished. This reduction has a very desirable effect on patient outcomes, but it also has a substantial impact on outcomes research. Patients recruited for recent trials are much better treated and their risk is much lower, although they may still have comorbidities and risk factors similar to the recruits in previous trials. This shift has bearing on the expected difference in outcomes and the power calculation of prospective randomized trials. It is worthwhile to look at how risk was defined at the end of the century and how it has changed today.

Previous Guidelines

The American Heart Association guidelines defined and calculated

risk in 1999 based on guidelines published and promoted by the American Diabetes Association, ATP III, and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). These guidelines estimated overall risk by adding the categorical risk factors. Estimation was not based on summation of risk factors that have been graded according to severity, although this approach has been advocated by the Framingham investigators.[46,47] Categorical risk factors have the advantage of simplicity but may be lacking some of the accuracy provided by graded risk factors. It is worth mentioning that the Framingham scores estimate risk for persons without clinical manifestations of CHD; therefore, the scores apply only to primary prevention, that is, for persons without established CHD. Patients with established CHD are considered high risk, and the Framingham scores do not apply.

Absolute risk was defined as the risk of developing CHD over a given period of time. The Framingham risk score specified absolute risk for CHD over a 10-year period. Absolute risk scores can be used to evaluate preventive strategies, but they have limitations. First, measures used for the scores were made some years ago and they may no longer be applicable. Second, risk in the Framingham population may not be the same in other populations. Third, there is considerable variability in risk in the Framingham population. And fourth, the Framingham risk factors are not elastic; that is, they may not have the same validity at both ends of the spectrum. The Framingham risk assessment score defined low-risk patients by the following criteria: serum cholesterol level between 160 and 190 mg/dL, LDL cholesterol level of 100 to 129 mg/dL, BP below 120 mm Hg systolic and below 80 mm Hg diastolic, a nonsmoker, and not diabetic. This definition of low risk seems appropriate, and it was validated in the MRFIT cohort of more than 350,000 screenees.[48] Most of the cardiovascular events in that population occurred over a period of 16 years in patients with risk factors above these levels.

In 2001, the European Society of Cardiology identified high-risk patients as those with a risk score predicting a 10-year risk of CHD above 20%. Once this threshold is reached, patients are considered to have established CHD, which requires secondary prevention. Although this approach seems reasonable and offers a bridge between primary and secondary prevention, it has limitations. The old European Society of Cardiology guidelines were based on older Framingham scores that took into account only short-term risk and did not include HDL cholesterol levels in the calculation of risk, and thus underestimate the risk in patients with low HDL cholesterol.

Another limitation of the Framingham risk score is that it does not consider the severity of risk factors in the estimation of absolute risk. The scoring did not adequately account for severe hypertension, severe hypercholesterolemia, or heavy cigarette smoking. In such cases, Framingham scores can underestimate risk, particularly when only 1 of these risk factors is severe. These limitations underscore the need to aggressively control the severe risk factors independently of the risk score estimate of short-term risk.

Treatment of cardiovascular risk factors is even more important in patients with established CHD. Evidence from clinical trials supports aggressive risk-reduction therapies for patients with atherosclerotic CVD. Aggressive risk factor management clearly improves patient survival, reduces recurrent events and the need for interventional procedures, and improves the quality of life in patients with known CVD.[49] In 2001, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention for patients with coronary and other vascular disease included the following recommendations: complete smoking cessation, BP of less than 140/90 mm Hg for most patients and less than 130/80 mm Hg in patients with HF or diabetes, LDL cholesterol under 100 mg/dL, non-HDL cholesterol under 130 mg/dL, BMI between 18.5 and 24.9 kg/m^2, hemoglobin A_{1c} less than 7% in diabetic patients, and use of β-blockers and ACE inhibitors in post-MI patients.

Defining CVD Risk in 2007-2008

Numerous new studies demonstrate additional benefit from rigorous risk factor modification. Data from recent lipid-lowering trials have shown that the lower we bring LDL cholesterol, the more we can reduce the risk of adverse cardiac events. Two studies in patients with ACS and another 2 in patients with stable CAD suggest that there is no point at which the benefit of low LDL cholesterol levels plateau. The PROVE IT[42] study has shown that in patients with ACS, reducing LDL cholesterol down to 62 mg/dL is better than reducing it to 95 mg/dL. The benefits included better prevention against recurrent MI, CVD death, stroke, and need for revascularization. The Aggrastat to Zocor (A to Z) trial demonstrated benefit with LDL cholesterol at similar levels.[50] The early initiation of aggressive simvastatin therapy was associated with a favorable trend toward reduction of major cardiovascular events. In patients with

stable CAD, the TNT study[43] has shown that an LDL cholesterol level of 77 mg/dL is better in preventing CVD events than a level of 101 mg/dL. The IDEAL[41] study demonstrated that an average LDL cholesterol of 81 mg/dL is better than a level of 104 mg/dL in preventing CVD events. In this study of patients with previous MI, intensive lowering of LDL cholesterol reduced the risk of nonfatal acute MI and other composite secondary endpoints, including stroke, nonfatal myocardial infarction, any CHD event, and any cardiovascular event. A recent study in patients with CHD and "normal" cholesterol levels showed that treatment to reduce LDL to as low as 40 mg/dL may continue to provide benefit. Studies in high-risk patients with CHD have shown that BP reduction to levels below what is considered normal has additional benefit, including reduction in adverse cardiovascular events.[29]

The 2006 update of the AHA/ACC guidelines for secondary prevention for patients with CAD and other atherosclerotic vascular disease have been modified to reflect changes based on this new information.[49] The update states that "important evidence from clinical trials has emerged that further supports and broadens the merits of aggressive risk reduction therapies for patients with established CAD and other atherosclerotic vascular disease." The growing body of evidence confirms that aggressive comprehensive risk factor management improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life. The findings from additional lipid reduction trials involving more than 50,000 patients resulted in new optional therapeutic targets outlined in the ATP III report. These changes include lower target LDL cholesterol levels for very high-risk patients with CHD, especially those with ACS. Evidence also supports lower target levels for patients with stable CHD. In these patients, it is reasonable to treat LDL cholesterol to below 70 mg/dL. The revised guidelines also recommend use of clopidogrel in post-MI patients, have new recommendations for after coronary stenting, now advise lower-dose aspirin for chronic therapy, and reconfirm the value of ACE inhibitors, ARBs, aldosterone antagonists, and β-blockers. For the first time, the guidelines also added a recommendation for influenza vaccination for patients with chronic CHD to avoid potential complications resulting from influenza.[49]

The 2007 European Guidelines on CVD Prevention in Clinical Practice[51] also adopted more aggressive treatment of cardiovascular risk factors. The earlier guidelines from the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice[52] noted a change from CHD to CVD prevention to reflect the fact that atherosclerosis may affect any part of the vascular tree. A new risk chart, called the Systemic Coronary Risk Evaluation (SCORE), was developed based on 12 European cohort studies and allowed the estimation of 10-year risk of cardiovascular death. Separate charts were produced for high-risk and low-risk regions of Europe. Less emphasis was placed on the terms *primary* and *secondary prevention*, because the risk was considered a continuum (Figure 3).

The Fourth Joint Task Force has taken note of several new areas, and has updated recommendations to include: 1) increased input from general practice and cardiovascular nursing; 2) increased emphasis on exercise, weight, and lifestyle changes; 3) more detailed discussion on the limitations of the present system of grading evidence; 4) redefined priorities and objectives; 5) revised approach to risk in the young; 6) total events as well as mortality; 7) more information from the score on total events, diabetes, HDL cholesterol, and BMI; and 8) consideration of sex, heart rate, BMI/waist circumference, other manifestations of CVD, and renal impairment.

It also adopted the use of the SCORE risk chart for the reasons listed in Table 4. It proposed the use of expedited methods to identify high-risk patients requiring aggressive therapy (patients with known CVD, those with type 2 diabetes or type 1 diabetes and microalbuminuria, or those with a multitude of individual risk factors). For all others, the SCORE risk chart can be used to estimate total risk. This difference is critically important because many individuals with mild elevations of several risk factors in combination may have a high level of total CVD risk.

In brief, the objective of CVD prevention is to help low-risk patients remain at low risk, to help moderate- to high-risk patients achieve the characteristics of patients who tend to stay healthy (low-risk patients), to achieve rigorous control of risk factors in high-risk patients with CVD, and to use potentially cardioprotective therapy in high-risk patients, especially those with established CHD.

Ongoing Clinical Trials

Appropriate ways to assess total risk will continue to be the focus of discussion as data from ongoing trials become available. Some trials currently in progress will provide information on how much more we can affect outcomes in high-risk patients receiving modern therapy. Some of the most important ongoing studies include Nateglinide And Valsartan

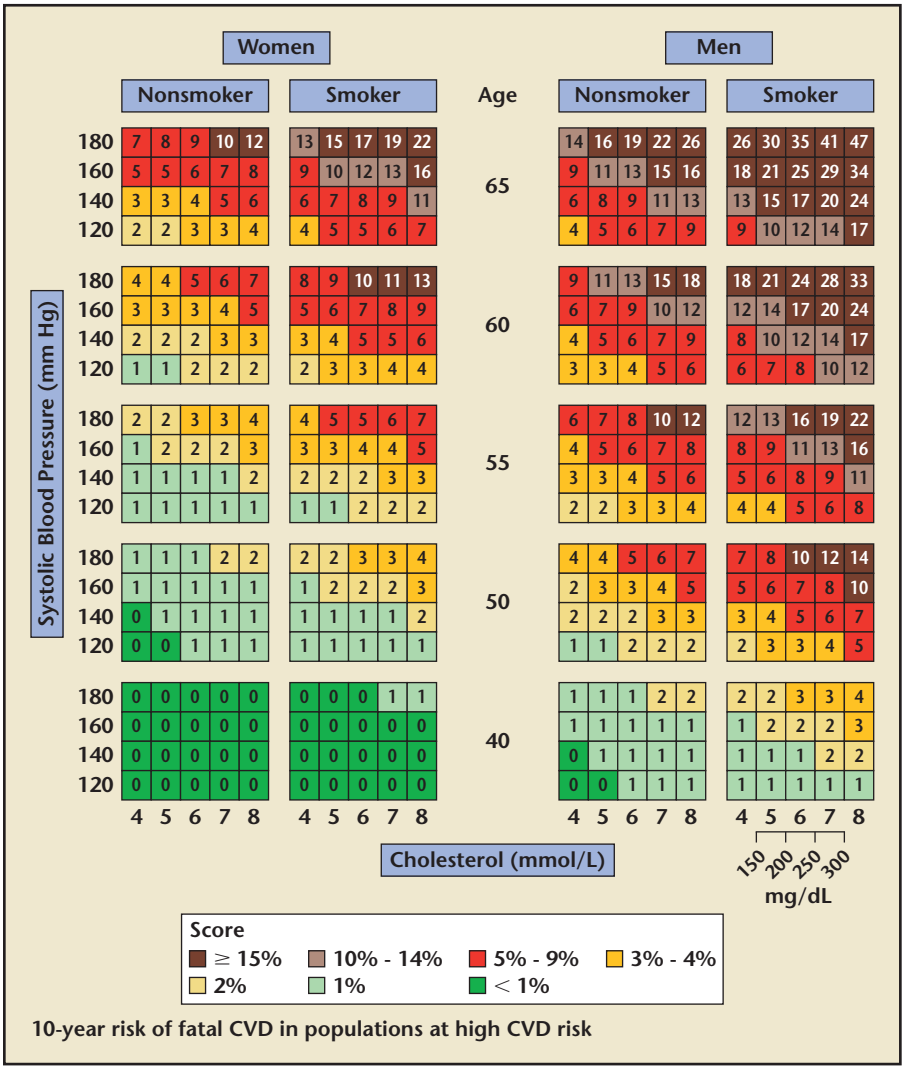

Figure 3. *Systematic coronary risk evaluation. Ten-year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk factors: age, sex, smoking, systolic blood pressure, and total cholesterol. Reprinted from Conroy RM et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.* Eur Heart J. *2003;24:987-1003,*[16] *by permission of the European Society of Cardiology.*
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in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), Prevention Regimen for Effectively Avoiding Second Stroke Trial (PRoFESS), and Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET).

The NAVIGATOR trial is a multicenter, multinational trial. It will be the largest diabetes prevention trial, and it is being conducted in over 30 countries across the world, in North America, South America, Europe, Asia, Australasia, and South Africa. Approximately half of the subjects will be recruited in Europe and approximately one third in the United States. NAVIGATOR recruited about 7500 patients over the age of 50 with impaired glucose tolerance (IGT) and at least 1 other cardiovascular risk factor. The primary objective of NAVIGATOR is to assess the effect of the oral antidiabetic nateglinide or the antihypertensive ARB valsartan in the progression to type 2 diabetes and cardiovascular morbidity and mortality in people with IGT.

Although epidemiologic data indicate that patients recruited for the NAVIGATOR study are high risk (with 3 to 4 times the risk of patients without IGT), aggressive treatment of their comorbidities and other risk factors may indeed reduce the rate of events in this population.

The ACCOMPLISH trial[53] was designed to compare the effects on major cardiovascular events of 2 forms of antihypertensive combination therapy: benazepril plus hydrochlorothiazide and amlodipine plus benazepril in hypertensive patients at high risk for cardiovascular events. The double-blind study enrolled a total of 11,454 high-risk patients with hypertension and prior history of CVD, stroke, or diabetes mellitus. The mean age in the ACCOMPLISH population was 68.4 years; 60% were men, and 12% were black. Patients were overweight, with a mean BMI of 31 kg/m^2. At study entry, 46% of patients had a history of CAD, coronary artery bypass graft, or PCI, 13% had a history of stroke, and 60% were diabetic. Virtually all patients were hypertensive, with 97% receiving medication prior to study entry. BP was fairly well controlled, averaging 145/80 mm Hg; 38% had BP under 140/80 mm Hg and 16% had BP under 130/80 mm Hg. Lipid-lowering medication was administered to 67% of patients and antiplatelet therapy to 63%. Of all study patients, 78% were on ACE inhibitors or ARBs at study entry, and 47% were taking β-blockers. The average LDL cholesterol was 101 mg/dL, and HDL cholesterol was 49 mg/dL. Thus, although patients

Table 4
Advantages of the SCORE Risk Chart

Intuitive, easy-to-use tool
Takes account of the multifactorial nature of CVD
Estimates risk of all atherosclerotic CVD, not just CHD
Allows flexibility in management (if an ideal risk factor level cannot be achieved, total risk can still be decreased by reducing other risk factors)
Allows a more objective assessment of risk over time
Establishes a common language of risk for clinicians
Shows how risk increases with age
Helps illustrate how a young person with a low absolute risk may be at a substantially higher and reducible relative risk

SCORE, Systematic Coronary Risk Evaluation; CVD, cardiovascular disease; CHD, coronary heart disease.

in the ACCOMPLISH study were high risk with a high number of cardiovascular risk factors and comorbidities, they were also well treated. Whether optimal therapy during the study will reduce the rate of events and lower the power to detect differences between groups remains to be seen.

The PRoFESS study[54] was designed to assess whether the risk of recurrent stroke will be reduced by aspirin plus extended-release dipyridamole compared with clopidogrel or, in individuals with a history of recent stroke, by telmisartan in addition to usual care. The study was a multicenter, randomized, double-blind trial involving 695 centers in 35 countries around the world. It enrolled patients who were 55 years or older and had had a stroke within the previous 90 days or patients who were ages 50 to 54 years and had had a stroke 90 to 120 days prior to enrollment, providing subjects had at least 2 more cardiovascular risk factors. The study enrolled 20,333 high-risk patients; mean age was 66 years and 64% were men. The etiology of stroke was attributed to large-vessel disease in 28.5% of patients, to small-vessel disease in 52.1%, to cardioembolism in 1.8%, to other determined etiologies in 2.0%, and to undetermined etiologies in 15.5%. Many patients in this study were already receiving appropriate treatment; 47% were on statin therapy, 37% on ACE inhibitors, 24% on calcium channel blockers, and 21% on β-blockers. The mean BP at baseline was 144/84 mm Hg, and the mean BMI was 26.8 kg/m^2.

The ONTARGET program is another large, randomized study that enrolled high-risk patients. The program consists of 2 studies: the ONTARGET study and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND). The objectives of the program are to test whether 1) telmisartan combined with ramipril is superior to ramipril alone, 2) telmisartan is noninferior to ramipril, and 3) telmisartan is superior to placebo in ACE-intolerant subjects in preventing cardiovascular morbidity and mortality. The main study ONTARGET consists of 3 groups: a telmisartan treatment group, a ramipril treatment group, and a combination therapy group. The study enrolled 25,620 patients at high risk of cardiovascular complications to be followed for an

Main Points

- Coexistence of multiple risk factors dramatically increases the risk of vascular complications.
- Results from many randomized clinical trials repeatedly demonstrate the benefits of risk factor control in patients with no demonstrable vascular disease (primary prevention), but more importantly in patients with established cardiovascular disease (secondary prevention).
- Implementation of risk factor modification has been cumbersome, but multidisciplinary efforts are bearing fruit. Patients are more involved in their own care, physicians better understand the significant value of risk factor modification, and results are moving in the right direction.
- As mounting data are published documenting the benefits of aggressive reduction of blood pressure and low-density lipoprotein cholesterol, as well as of diabetes control, the target values are being revised downward.
- Patients recruited for recent trials are much better treated and their risk is much lower, although they may still have comorbidities and risk factors similar to the recruits in previous trials. This shift has bearing on the expected difference in outcomes and the power calculation of prospective randomized trials.

average of 3.5 to 5.5 years. The primary composite endpoint of the study is cardiovascular death, MI, stroke, and hospitalization for heart failure. TRANSCEND enrolled 5920 high-risk patients intolerant to ACE inhibitors.

Data presented in New Orleans in 2004 from 31,000 patients recruited for the ONTARGET program indicate that treatment patterns have changed in high-risk patients compared with data collected for the HOPE trial just 10 years ago: 60% of the ONTARGET trial patients have been treated with statins as compared with 29% in the HOPE trial; and 58% of the ONTARGET patients were treated with ACE inhibitors, about 5 times more than baseline treatment in patients enrolled in HOPE.

Conclusion

The last several years have seen significant developments in the treatment of patients with CVD. Large, randomized trials have provided valuable information regarding risk factor modification, treatment of hypertension, management of high-risk patients, and stroke prevention. Subjects in current trials are at lower risk than those in previous ones. In addition, they are more likely to be receiving appropriate treatment upon enrollment. Some previous recommendations regarding risk assessment and disease management may be superseded by data from recent and ongoing trials. ■

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