

## The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes Part I: Pathophysiology and Clinical Trial Evidence (Risk Factors Through Stable Coronary Artery Disease)

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Fifteen years ago, a panel of experts representing the full spectrum of cardiovascular disease (CVD) research and practice assembled at a workshop to examine the state of knowledge about CVD. The leaders of the workshop generated a hypothesis that framed CVD as a chain of events, initiated by a myriad of related and unrelated risk factors and progressing through numerous physiological pathways and processes to the development of end-stage heart disease (Figure 1).<sup>1</sup> They further hypothesized that intervention anywhere along the chain of events leading to CVD could disrupt the pathophysiological process and confer cardioprotection. The workshop participants endorsed this paradigm but also identified the unresolved issues relating to the concept of a CVD continuum. There was limited availability of clinical trial data and pathobiological evidence at that time, and the experts recognized that critical studies at both the mechanistic level and the clinical level were needed to validate the concept of a chain of events leading to end-stage CVD.

In the intervening 15 years, new evidence for underlying pathophysiological mechanisms, the development of novel therapeutic agents, and the release of additional landmark clinical trial data have confirmed the concept of a CVD continuum and reinforced the notion that intervention at any point along this chain can modify CVD progression. In addition, the accumulated evidence indicates that the events leading to disease progression overlap and intertwine and do not always occur as a sequence of discrete, tandem incidents. Furthermore, although the original concept focused on risk factors for coronary artery disease (CAD) and its sequelae, the CVD continuum has expanded to include other areas such as cerebrovascular disease, peripheral vascular disease, and renal disease. Since its conception 15 years ago, the CVD continuum has become much in need of an update. Accordingly, this 2-part article will present a critical and comprehensive update of the current evidence for a CVD continuum

based on the results of pathophysiological studies and the outcome of a broad range of clinical trials that have been performed in the past 15 years. It is not the intent of the article to include a comprehensive listing of all trials performed as part of the CVD continuum; instead, we have sought to include only those trials that have had the greatest impact. Part I briefly reviews the current understanding of the pathophysiology of CVD and discusses clinical trial data from risk factors for disease through stable CAD. Part II continues the review of clinical trial data beginning with acute coronary syndromes and continuing through extension of the CVD continuum to stroke and renal disease. The article concludes with a discussion of areas in which future research might further clarify our understanding of the CVD continuum.

### New Understanding of a Pathophysiological Continuum

Our understanding of the pathophysiology of CVD has expanded considerably since 1991. A pathophysiological continuum, which underlies the clinical CVD continuum, describes the progressive processes at molecular and cellular levels that manifest as clinical disease (Figure 2).<sup>2</sup> In addition, cardiovascular risk factors, such as elevated cholesterol, hypertension, diabetes mellitus, and cigarette smoking, are now known to promote oxidative stress and to cause endothelial dysfunction, initiating a cascade of events, including alterations in vasoactive mediators, inflammatory responses, and vascular remodeling, that culminates in target-organ pathology (Figure 3).<sup>3</sup> Considerable evidence suggests that these processes begin earlier in life than previously recognized, indicating that CVD arises over decades. Beyond traditional risk factors, the role of biomarkers/biomediators and surrogate markers in CVD continues to be elucidated. In addition, it is now recognized that neurohormones contribute

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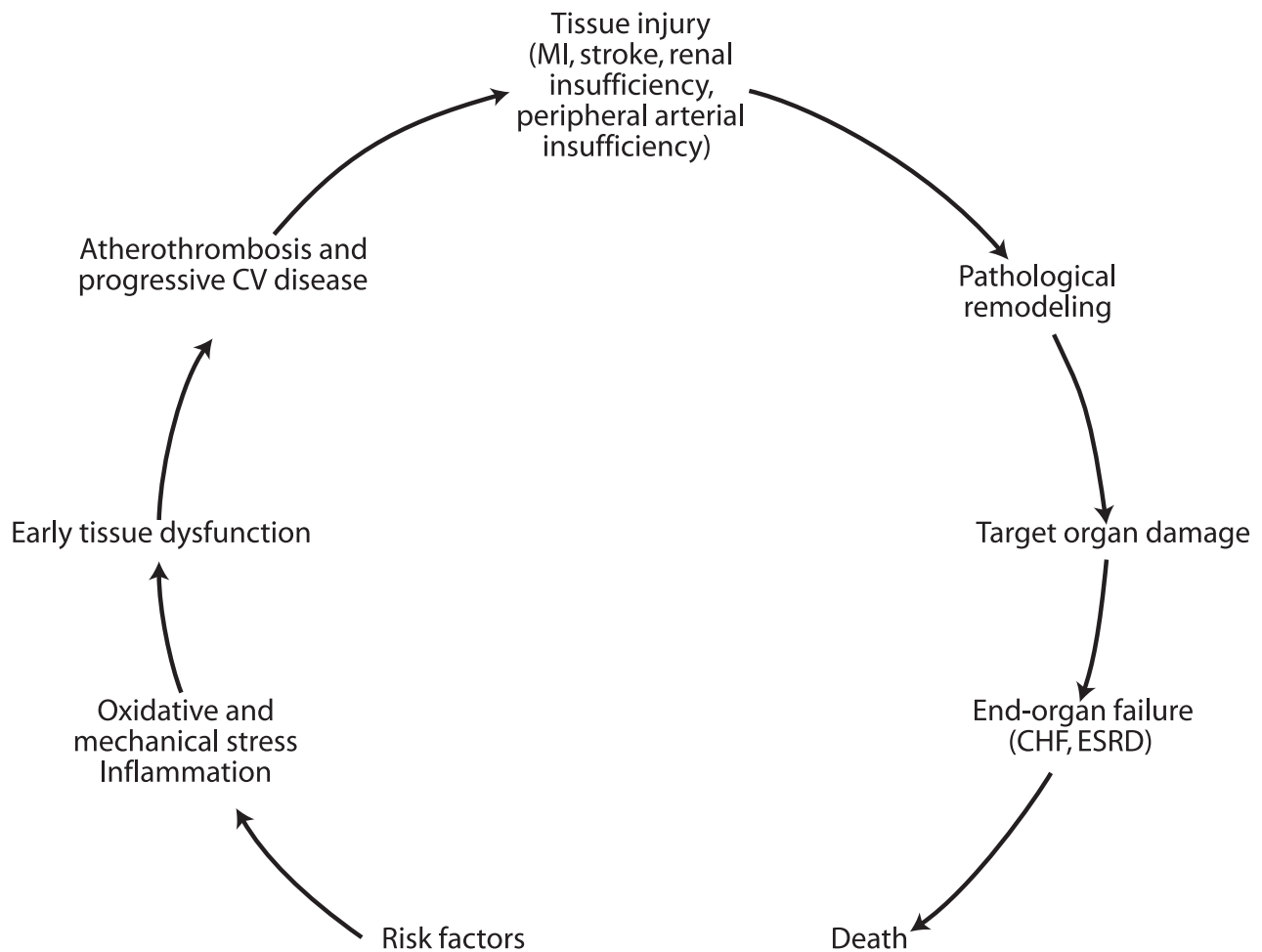
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**Figure 2.** Cardiovascular and renal pathophysiological continuum. CHF indicates congestive heart failure; CV, cardiovascular; ESRD, end-stage renal disease; and MI, myocardial infarction.

expression of cellular adhesion molecules.<sup>6</sup> Higher oxidized LDL content in the lipid core of atherosclerotic plaques may also promote plaque instability.<sup>7</sup> Small, dense LDL particles are highly atherogenic and are associated with increased triglyceride levels. The structure of small, dense LDL particles contributes to their atherogenicity, with increased susceptibility to oxidation, easier penetration into the arterial wall, and altered interactions with the LDL receptor.

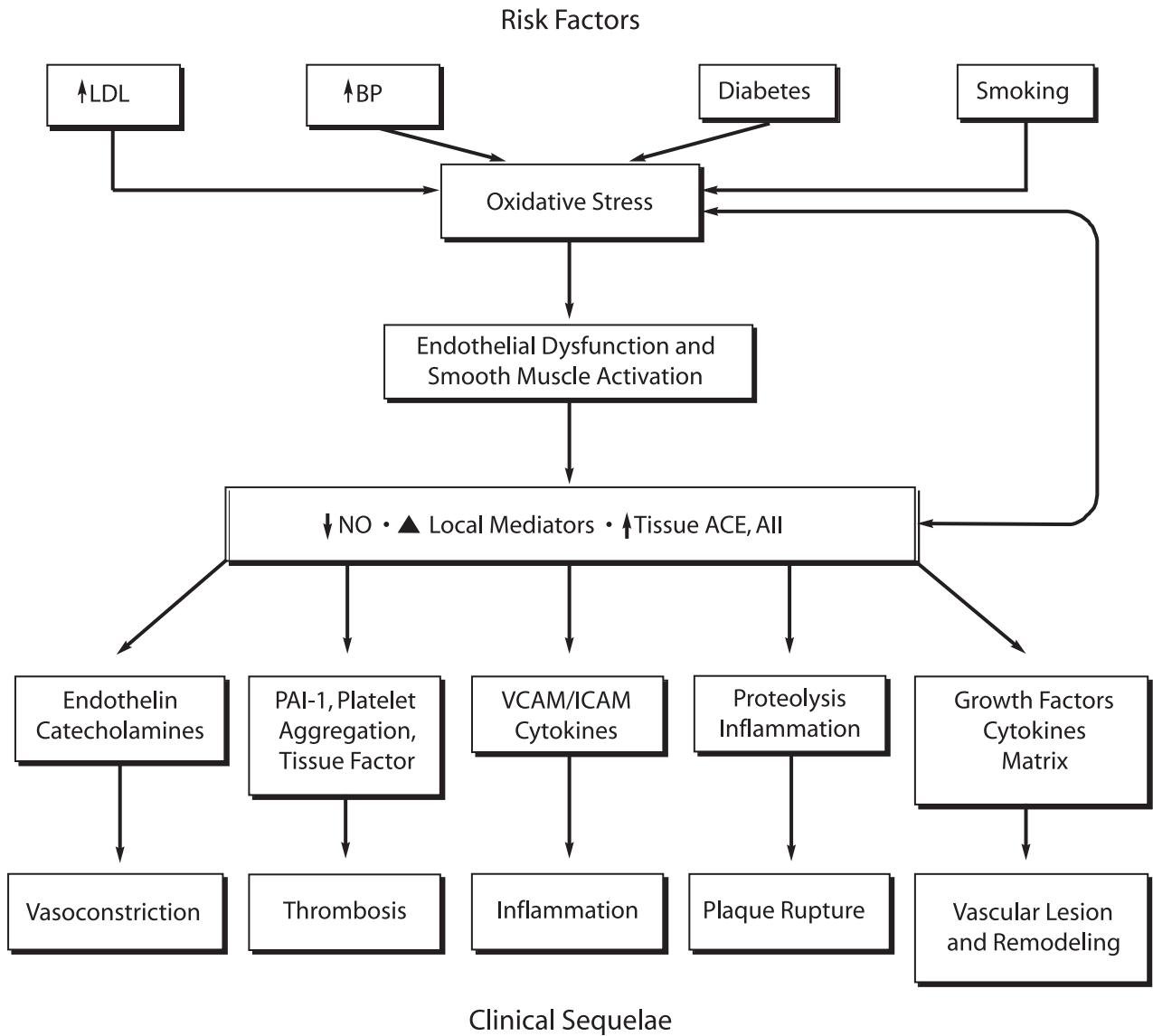
Elevated blood pressure promotes the development of atherosclerotic plaques and increases the risk of CVD complications.<sup>8</sup> Endothelial dysfunction in chronic hypertension is associated with decreased endothelium-dependent relaxation. In hypertensive vessels, increased expression of matrix proteins, matrix proteinases, and growth factors leads to structural changes, such as decreased lumen diameter, increased extracellular matrix, and thickened media.<sup>4</sup> In addition, hypertension is associated with increased production of free radicals and oxidative stress that may promote an inflammatory state and enhance the atherosclerotic process.<sup>8</sup> Indeed, results from the Women's Health Study<sup>9</sup> and other epidemiological studies demonstrate that levels of C-reactive protein, a marker of systemic inflammation, correlate significantly with future risk of developing hypertension.

The metabolic syndrome comprises a group of lipid and nonlipid risk factors, such as insulin resistance and its

associated hyperinsulinemia, atherogenic dyslipidemia, central obesity, and hypertension.<sup>10</sup> Metabolic syndrome is associated with increased CVD risk.<sup>10</sup> Specifically, insulin resistance and subsequent hyperinsulinemia appear to contribute to endothelial dysfunction and impaired NO responses.<sup>11,12</sup> Furthermore, the chronic exposure of vascular smooth muscle to hyperinsulinemia may promote intimal hyperplasia. In addition, the excess adipose tissue characteristic of the metabolic syndrome secretes prothrombotic factors and proinflammatory cytokines, which may contribute to vascular disease.<sup>12,13</sup> Changes in the distribution of adipose tissue, namely, a shift from subcutaneous to visceral locations, may also be associated with a loss of antiinflammatory mediators such as adiponectin.

### Neurohormones

The renin-angiotensin-aldosterone system (RAAS) is now understood to play a significant role in CVD pathophysiology.<sup>3</sup> Interacting with the adrenergic system and various mediators, the RAAS mediates adaptive and maladaptive responses to tissue injury, such as may result from hypertension, ischemic heart disease, cardiomyopathy, other systemic or pulmonary diseases, or the effects of CVD risk factors.<sup>14</sup> The important biologically active component of the RAAS is



**Figure 3.** Integrated model of tissue angiotensin and vascular pathobiology. All indicates angiotensin II; BP, blood pressure; ICAM, intracellular adhesion molecule; PAI-1, plasminogen activator inhibitor-1; and VCAM, vascular cell adhesion molecule. Adapted with permission from Dzau VJ.<sup>3</sup>

angiotensin II. Angiotensin II mediates hemodynamic and renal actions in addition to having direct cardiovascular tissue effects and has been implicated at every stage along the CVD continuum.

The identified pathological effects of angiotensin II are myriad and include, but are not limited to, vasoconstriction, cardiac and vascular remodeling, inflammation, thrombosis, and plaque rupture.<sup>3</sup> Although angiotensin II stimulates 2 major receptors, angiotensin II type 1 (AT<sub>1</sub>) and type 2 (AT<sub>2</sub>), the pathological effects of angiotensin II appear to be mediated through the AT<sub>1</sub> receptor.<sup>15</sup> Evidence suggests that stimulation of the AT<sub>2</sub> receptor mediates more favorable actions, inducing NO and bradykinin release and promoting cGMP-mediated vasodilation.<sup>15</sup> Furthermore, stimulation of AT<sub>2</sub> receptors may promote cell differentiation and apoptosis and inhibit cell proliferation.

Angiotensin II increases the tissue generation of reactive oxygen species, creating an environment of oxidative stress

and decreased NO activity.<sup>3</sup> These changes contribute to inflammatory responses, including the induction of monocytes and smooth muscle cells to release chemoattractant proteins such as monocyte chemoattractant protein-1, as well as other cytokines and adhesion molecules. Angiotensin II promotes vascular remodeling by stimulating expression of growth factors in vascular smooth muscle cells, promoting smooth muscle cell proliferation, inducing the production and release of matrix metalloproteinases, and modulating vascular cell migration.<sup>3</sup>

The RAAS, and specifically angiotensin II, also plays a role in fibrinolytic responses via the endothelium. ACE stimulates plasminogen activator inhibitor-1 production via angiotensin II and also degrades bradykinin. Bradykinin stimulates tissue-type plasminogen activator release from the endothelium.<sup>16,17</sup> Accordingly, the interaction between bradykinin and angiotensin II at the endothelial surface modu-

lates the prothrombotic/fibrinolytic state of the blood vessel.<sup>18,19</sup>

An increase of tissue ACE in atherosclerotic lesions sets up a positive feedback mechanism for angiotensin II production.<sup>3</sup> Increased ACE promotes an inflammatory response via angiotensin II, and inflammatory cells such as monocytes/macrophages, neutrophils, and mast cells release enzymes that generate angiotensin II. The increased level of angiotensin II creates an environment of oxidative stress and induces the release of cytokines, adhesion molecules, and growth factors, which leads to further inflammation and promotes atherogenesis. Tissue ACE and angiotensin II accumulate in the shoulder regions of vulnerable plaques and may contribute to the susceptibility of these plaques to rupture.

Other neurohormones are involved in the pathophysiology of CVD. A-type natriuretic peptide (also called atrial natriuretic peptide) and B-type natriuretic peptide (also called brain natriuretic peptide) are smooth muscle relaxants that cause vasodilation and lower blood pressure. B- and A-type natriuretic peptide are released in response to myocyte stretch.<sup>20</sup> A-type natriuretic peptide also inhibits the RAAS by blocking secretion of renin and aldosterone, and B-type natriuretic peptide appears to have direct relaxant effects on the myocardium. In addition, both A- and B-type natriuretic peptide inhibit sympathetic nervous system activity in the heart. Both B- and A-type natriuretic peptide generally act to oppose the actions of angiotensin II.<sup>21</sup> Arginine vasopressin has been implicated in hyponatremia in heart failure patients.<sup>22</sup> Arginine vasopressin acts on the V<sub>2</sub> vasopressin receptor, which causes antidiuresis activity in the collecting duct of the kidney. In addition, arginine vasopressin binds to vasopressin V<sub>1</sub> receptors on vascular smooth muscle, which may increase vascular resistance.

Other hormones that may also be important include vasodilating prostaglandins and the vasoconstrictor endothelin. Prostacyclin and prostaglandin E generally act to counterbalance the vasoconstrictor actions of angiotensin II.<sup>22</sup>

### Inflammatory Processes

An inflammatory state has been associated with atherosclerosis. In the inflammatory response to endothelial injury, release of chemoattractant proteins (chemokines) promotes entry of monocytes into the vessel wall, where they can transform into macrophages. Macrophages then take up modified and oxidized LDL, becoming foam cells.<sup>3</sup> Foam cells contribute to formation of fatty streaks, an early stage of atherosclerotic plaque.<sup>23</sup> Repetitive cycles involving ongoing arterial injury, lipid uptake, and vascular remodeling can result in complicated plaques with large necrotic cores, thin fibrous caps, and accumulation of macrophages in the shoulder regions, where plaque rupture tends to occur. When activated by T cells, macrophages release proteolytic matrix metalloproteinases that degrade the fibrous cap and interstitial collagen, which promotes rupture.<sup>23,24</sup> One important signaling pathway between T lymphocytes and macrophages is the CD40:CD402 system. Macrophage accumulation appears to be associated with increased levels of inflammatory markers, such as fibrinogen and C-reactive protein.<sup>23,25</sup> Thrombosis that results in a clinical event (eg, acute coronary

syndrome) may also be caused by a superficial erosion, rather than intimal rupture, of the atherosclerotic plaque; in either case, the immediate site of plaque rupture or erosion is always marked by an inflammatory process.<sup>26</sup>

C-reactive protein has emerged as a useful predictor of atherosclerotic CVD risk.<sup>27</sup> Data suggest that C-reactive protein may also be a mediator and not just a marker of inflammation. C-reactive protein induces the expression of tissue factor and cell adhesion molecules, binds and activates complement, stimulates monocytes to enter the vessel wall, promotes the production of monocyte chemoattractant protein-1, and mediates macrophage uptake of LDL.<sup>13</sup> The role of C-reactive protein as a biomarker for CVD is discussed further in part II of this article.

### Coagulation Cascade

When a plaque ruptures, the thrombogenic lipid core is exposed to circulating blood, which activates the coagulation cascade that initiates and sustains thrombus formation. During this process, platelets adhere to the site of trauma and contribute to the formation of thrombin, which converts fibrinogen into strands of fibrin. Fibrin strands trap additional platelets, blood cells, and plasma to form a clot that can partly or completely block an artery.

### Vascular Remodeling

Vascular remodeling occurs in response to chronic alterations in hemodynamic conditions that precipitate structural changes in the vessel wall, such as increased ratio of wall to lumen width, changes in luminal dimensions with minimal changes in wall thickness, neointima formation in response to injury, and rarefaction of the microcirculation.<sup>4</sup> Inward remodeling typically occurs in response to reduced blood flow and results in decreased vessel size; conversely, outward remodeling usually is a reaction to increased flow and results in increased vessel size.<sup>28</sup> Locally produced biologically active mediators, such as NO and matrix metalloproteinases, and growth factors, such as platelet-derived growth factor and transforming growth factor- $\beta$ , in addition to hemodynamic stimuli, such as shear stress, interact to promote cell migration, cell growth, cell death, and the production and degradation of extracellular matrix, which results in these structural alterations.<sup>4,28</sup> The pathophysiological changes in vascular structure that result from alterations in endothelial function have clinical implications.<sup>4</sup>

Vascular remodeling in small resistance arteries may be the initial step in the progression from hypertension to target-organ damage.<sup>29</sup> Small resistance arteries that have undergone hyperplastic/hypertrophic remodeling have an enhanced response to vasoconstrictor substances, further reducing vascular reserve. This reduction may contribute to tissue ischemia if surrounding arteries are stenotic. Small-artery remodeling is more common among persons with hypertension than those without, and patients with the highest blood pressures are also the most likely to develop left ventricular hypertrophy (LVH) and have the greatest incidence of small-artery changes.<sup>29</sup>



### Cardiac Remodeling and Target-Organ Damage

Cardiac remodeling is mediated by diverse endocrine, paracrine, and autocrine effects of a number of different hormones that result in hypertrophy.<sup>14</sup> The hormones involved in changing the structure, function, and phenotype of the myocardium include angiotensin II, vasopressin, peptide growth factors, endothelin, natriuretic peptides, cytokines, and NO. Evidence indicates that insulin and insulin-like growth factor may be myocardial growth factors, which suggests that altered glucose and insulin metabolism, such as occurs in diabetes and the metabolic syndrome, further contributes to LVH and accelerated heart failure.<sup>30,31</sup> Oxidative stress also plays an important role in the cardiac remodeling process; in animal studies, inhibition of antioxidant systems disrupts normal cell growth and apoptosis in cardiac myocytes.<sup>14</sup> If uninterrupted, cardiac remodeling results in impaired systolic and diastolic functioning and progresses to heart failure.<sup>32</sup>

Basic science investigations have rendered obsolete the concept that each disease event on the CVD continuum is mediated by a specific and single pathophysiological pathway; rather, common pathophysiological processes participate in multiple steps across the continuum. It is now apparent that common and overlapping mechanisms are involved in disease development across the entire spectrum of CVD. This understanding has therapeutic implications in that many interventions and drugs are effective in treating multiple disease events across the CVD continuum. Clinical trials supporting this conclusion will be discussed next.

### Clinical Trial Evidence for a Clinical Continuum

Validation of the concept of a clinical CVD continuum is based on clinical trial evidence that intervention disrupts the progression of disease. This review will examine interventional efforts at points along the CVD continuum to prevent or delay CVD and its consequences, with primary focus on major clinical trials published since the CVD continuum was first proposed in 1991. Potential trials to include were identified by performing a search of the MEDLINE literature from 1991 to 2005. Search terms used included the well-established risk factors for CVD and major points along the clinical CVD continuum. The resulting trial lists, organized by therapeutic category, were supplemented by a review of major clinical guidelines. Finally, the trial lists were sent to a panel of expert validators, who determined which trials were the most important to be discussed and who suggested additional trials to be included.

### Risk Factors for CVD

Well-known risk factors for CVD include hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, obesity, and physical inactivity.<sup>33</sup> Prevention or control of these risk factors through lifestyle modification (eg, diet, exercise, and smoking cessation) is a key element of preventive cardiology. Many studies investigating lifestyle changes were not designed to quantify benefit on hard clinical end points but instead relied on surrogate end points such as reduced blood pressure and lipid changes and their epidemiological link to decreased CVD risk. Although the present review focuses on specific interventions that have yielded direct benefit on

morbidity and mortality, the authors strongly endorse lifestyle modification as a component of optimizing health and effectively managing CVD.

### Nonpharmacological Interventions

There exists broad consensus based on evidence from a number of clinical trials that lifestyle modifications can lower the risk of developing CVD and can delay the progression of CVD (secondary prevention).<sup>34–42</sup> Trials evaluating the effects of lifestyle modification are summarized in Table I of the online data supplement. For example, reduction or modification of dietary fat intake may be sufficient to reduce cardiovascular events in certain patients.<sup>38,43,44</sup> The often-cited Lyon Diet Heart Study<sup>38</sup> found that post-myocardial infarction (MI) patients who followed a Mediterranean diet rich in polyunsaturated fat and fiber had a lower risk of cardiac death or recurrent MI than those who followed a typical Western diet high in saturated fats and low in fiber. Among seemingly healthy elderly men and women in Healthy Ageing: a Longitudinal study in Europe (HALE),<sup>42</sup> adherence to a Mediterranean diet and healthful lifestyle was associated with a lower rate of all-cause and cause-specific mortality, including death due to coronary heart disease (CHD) and CVD.

Some of the benefit derived from the Mediterranean diet in these studies may have been due to increased consumption of fish. One study that specifically examined the impact of dietary supplementation with fish oil was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione trial,<sup>39</sup> in which patients with recent ( $\leq 3$  months) MI were randomized to receive omega (n)-3 polyunsaturated fatty acids, vitamin E, their combination, or no dietary supplementation. After 3.5 years of follow-up, n-3 fatty acids led to a clinically important and statistically significant ( $P=0.023$ ) benefit on the combined end point of death, nonfatal MI, and stroke. Vitamin E showed no significant benefit.<sup>39</sup> In fact, despite the abundant evidence for a role of oxidative stress in the pathophysiology of atherosclerosis, clinical trials of antioxidants such as vitamin E and beta-carotene have consistently yielded disappointing results.<sup>45,46</sup>

More intense regimens that combine strict lifestyle modifications and pharmacological therapy to aggressively lower LDL cholesterol and triglycerides and increase HDL cholesterol levels may be more effective in reducing events in CAD patients than either dietary changes or lipid-lowering therapy alone.<sup>35,40</sup> Similarly, evidence from the Steno-2 study indicates that a combination of lifestyle and pharmacological interventions targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria also significantly reduces the risk of CVD events in patients with diabetes and other CHD risk factors.<sup>41</sup> Even modest physical activity significantly decreases the risk of developing diabetes. Interestingly, exercise can also lower C-reactive protein levels.

Smoking cessation substantially decreases the risk of clinical cardiovascular events. In fact, 1 year after a person quits smoking, the risk of CHD decreases by  $\approx 50\%$ .<sup>47</sup> A review<sup>48</sup> of 20 studies of smoking cessation found that persons who quit smoking had a 36% reduction in crude

relative risk (RR) for all-cause mortality (95% CI 29% to 42%) compared with those who continued to smoke. The crude RR for nonfatal MI was reduced by 32% (95% CI 18% to 43%) in former smokers versus continued smokers. However, the review was not able to assess how quickly these benefits occurred.<sup>48</sup>

### **Pharmacological Interventions**

Clinical trials of pharmacological therapy have shown unequivocally that risk factor reduction decreases the risk of morbidity and mortality. Evidence accumulated over the past several decades indicates that antihypertensive treatment with several classes of agents, including diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs),  $\beta$ -blockers, and calcium channel blockers, effectively lowers blood pressure in a broad range of patients, while also reducing CVD morbidity and mortality.<sup>49,50</sup> In clinical trials, antihypertensive treatment has been associated with reductions averaging 35% to 40% in stroke, 20% to 25% in MI, and >50% in heart failure.<sup>33</sup> A meta-analysis<sup>51</sup> of 58 randomized trials of cholesterol lowering by any means (fibrates, resins, niacin, statins, or dietary change) showed that for an LDL cholesterol reduction of 1.0 mmol/L (39 mg/dL), the risk of ischemic heart disease events was reduced by 11% the first year, 24% in the second year, 33% in years 3 to 5, and 36% thereafter. After several years, a reduction of 1.8 mmol/L (70 mg/dL) would reduce ischemic events by an estimated 61%.<sup>51</sup> Similar results were reported from a more recent, prospective meta-analysis that examined the efficacy and safety of cholesterol lowering with statins in 14 randomized trials involving >90 000 participants.<sup>52</sup> Each 1-mmol/L reduction in LDL cholesterol was associated with a 23% decrease in RR of first major coronary events and a 21% reduction in major cardiovascular events, largely irrespective of the baseline lipid profile or other presenting patient characteristics.

By interrupting the underlying pathophysiology of CVD, risk factor modification reduces subsequent events, thereby providing substantiating evidence of a CVD continuum.

### **Hypertension**

Evidence from numerous clinical trials<sup>53–65</sup> supports the beneficial effects of various classes of blood pressure-lowering regimens on CVD morbidity and mortality in hypertensive patients with and without evidence of LVH. Only a few of these trials are discussed in this article for the purposes of illustration, but detailed summaries of these and other hypertension trials are provided in Table II of the online data supplement.

Thiazide and thiazide-like diuretics have been the basis of antihypertensive therapy in numerous trials in which 1 or more of the complications of hypertension have been reduced by blood pressure lowering.<sup>33</sup> For example, the Systolic Hypertension in the Elderly Program (SHEP)<sup>53</sup> found that treatment of isolated systolic hypertension with chlorthalidone significantly reduced the 5-year incidence of fatal and nonfatal stroke by 36% (95% CI 18% to 50%) compared with placebo ( $P=0.0003$ ) in patients aged 60 years or older. Isolated systolic hypertension, a condition in which systolic blood pressure is elevated but diastolic blood pressure is <90

or 95 mm Hg, is the most common form of hypertension among older individuals and greatly increases their risk of CVD events.

Similarly, the second Swedish Trial in Old Patients with Hypertension (STOP-Hypertension-2)<sup>60</sup> confirmed the benefits of antihypertensive therapy in subjects 70 to 84 years of age at enrollment. STOP-2 reported that antihypertensive therapy with so-called conventional drugs (eg, atenolol, metoprolol, pindolol, or hydrochlorothiazide plus amiloride) and newer drugs (eg, enalapril, lisinopril, felodipine, or isradipine) similarly lowered blood pressure and prevented CVD mortality or major events to the same degree.<sup>60</sup> Decreases in blood pressure were of major importance in preventing CVD events in this population. More recently, the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT)<sup>66</sup> confirmed the benefits of thiazide-like diuretic therapy. ALLHAT is discussed in detail later, under "Multiple Risk Factors."

Other trials involving newer classes of agents, including calcium channel blockers, ACE inhibitors, and ARBs, have also shown benefit in reducing CVD events. The Hypertension Optimal Treatment (HOT) study<sup>58</sup> provides evidence of an optimal blood pressure level and of the frequent need for more than 1 agent to achieve target levels of blood pressure. HOT randomized >18 000 men and women aged 50 to 80 years with diastolic hypertension (100 to 115 mm Hg) to 1 of 3 target diastolic blood pressure groups:  $\leq 90$  mm Hg,  $\leq 85$  mm Hg, and  $\leq 80$  mm Hg. Felodipine 5 mg was administered to all patients; if adequate blood pressure control was not achieved, investigators followed a 5-step program of dosage increases or addition of further agents. Follow up was conducted for an average of 3.8 years. The investigators calculated that the lowest rate of cardiovascular events occurred with a mean blood pressure of 138.5/82.6 mm Hg.<sup>58</sup>

The Captopril Prevention Project (CAPPP)<sup>59</sup> compared the effects of ACE inhibition (captopril) with conventional therapy (diuretics or  $\beta$ -blockers) on CVD morbidity and mortality in >10 000 hypertensive patients 25 to 66 years of age. At study end, the rates of fatal and nonfatal MI were similar in the 2 treatment groups. Mortality from CVD was lower with captopril than with conventional treatment, but fatal and nonfatal stroke was more common. The difference in stroke risk may have been due to the lower levels of blood pressure obtained initially in previously treated patients randomized to conventional therapy.<sup>59</sup> The Heart Outcomes Prevention Evaluation (HOPE)<sup>67</sup> and other large trials of ACE inhibitor therapy in high-risk patients are discussed later in the section on stable CAD.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study,<sup>63</sup> a randomized trial of a regimen that began with losartan versus one that began with atenolol in patients with hypertension and LVH, showed that the losartan-based regimen was associated with a greater reduction than the atenolol-based regimen in the composite end point of death, MI, and stroke for a similar reduction in blood pressure. Only  $\approx 10\%$  of the subjects enrolled in LIFE received only 1 antihypertensive drug; most were also given hydrochlorothiazide and other agents.<sup>63</sup> Most of the significance in reduction of the composite end point was driven by

a greater reduction in stroke with losartan. The absence of a greater reduction in heart failure events with losartan may be because both atenolol and losartan likely prevented heart failure and did so comparably.<sup>68</sup> Another study of an ARB, the VALsartan Long-term Use Evaluation (VALUE),<sup>69</sup> was conducted in hypertensive patients at high risk for cardiac events and is discussed under “Multiple Risk Factors,” below.

### Dyslipidemia

The largest body of data on lipid-modifying therapy involves 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins. Large-scale, well-controlled primary prevention and secondary prevention clinical trials have demonstrated unequivocally that statin therapy reduces morbidity and mortality from major CVD events across a spectrum of risk.<sup>70–75</sup> Major statin trials are summarized in Table III of the online data supplement. Given this significant advance in knowledge, target lipid levels have been continually redefined by the National Cholesterol Education Program and its guidelines.<sup>10</sup> Treatment with statins is the standard of care and usual first line of therapy. Nevertheless, other agents, such as fibric acid derivatives (fibrates), nicotinic acid (niacin), cholesterol absorption inhibitors, and bile acid sequestrants (resins), may also prove useful in certain patients.<sup>10</sup> For example, treatment with fibrates can reduce cardiovascular end points in both primary and secondary prevention of CHD.<sup>76,77</sup> In the Helsinki Heart Study,<sup>77,78</sup> which included 4081 men with an average LDL cholesterol level of 188 mg/dL, 5 years of treatment with gemfibrozil resulted in a 34% relative reduction in cardiac deaths and fatal and nonfatal MI (95% CI 8.2% to 52.6%;  $P < 0.02$ ). Findings from the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)<sup>76</sup> demonstrated that secondary prevention patients (2531 men) with low HDL and average LDL levels experienced a significant CHD risk reduction with gemfibrozil, which lowers triglycerides, reduces the proportion of small, dense LDL particles, and enhances the clearance of very-low-density lipoprotein. A substantial percentage of the VA-HIT patients had type 2 diabetes mellitus and/or insulin resistance, a common setting in which combination therapy may be useful. Other patients cannot achieve the increasingly lower target LDL cholesterol levels identified as optimal for their risk status or cannot tolerate statin therapy or the dose of statin required to achieve their LDL goal. For all such patients, ezetimibe, either alone or in combination with a statin, has become a commonly used alternative.

### Secondary Prevention With Statins

The Scandinavian Simvastatin Survival Study (4S),<sup>70</sup> which evaluated the effect of cholesterol lowering with simvastatin on morbidity and mortality in CHD patients with elevated cholesterol, was the first major secondary prevention trial to show a significant survival benefit with statin treatment. After  $\approx 5$  years of treatment, the risk of all-cause death was reduced by 30% (95% CI 15% to 42%;  $P < 0.001$ ) and the risk of coronary death was reduced by 42% (95% CI 27% to 54%) in the simvastatin group compared with placebo. Major coronary events and revascularization procedures were also sig-

nificantly reduced.<sup>70</sup> The Cholesterol and Recurrent Events (CARE) trial<sup>71</sup> was designed to determine whether post-MI patients with so-called average cholesterol levels would benefit from long-term statin therapy. Patients with mean total cholesterol levels of 209 mg/dL and mean LDL cholesterol levels of 139 mg/dL were treated with pravastatin or placebo for an average of 5 years. Results showed that the incidence of a fatal coronary event or nonfatal MI was significantly reduced by 24% in the pravastatin group compared with placebo (95% CI 9% to 36%;  $P = 0.003$ ). The incidence rates of both coronary bypass surgery and angioplasty were also significantly reduced with pravastatin.<sup>71</sup> The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study<sup>72</sup> examined the potential benefits of cholesterol-lowering therapy with pravastatin on survival in patients with previous MI or unstable angina pectoris who had a range of moderately elevated total cholesterol levels (155 to 271 mg/dL). After a follow-up of  $\approx 6$  years, pravastatin treatment significantly reduced the RR of death due to CHD by 24% (95% CI 12% to 35%;  $P < 0.001$ ) and of overall mortality by 22% (95% CI 13% to 31%;  $P < 0.001$ ) compared with placebo.<sup>72</sup>

### Primary Prevention With Statins

The establishment of the benefits of statin therapy in secondary prevention was followed by large-scale, well-controlled primary prevention trials that demonstrated that statin therapy also significantly decreases morbidity and mortality from major CVD events in patients without prior CHD. The West of Scotland Coronary Prevention Study (WOSCOPS)<sup>73</sup> demonstrated that pravastatin therapy in patients with elevated total cholesterol (mean 272 mg/dL) with no history of MI is effective in reducing the risk of nonfatal MI and death due to CHD, with no associated increase in death due to noncardiovascular causes. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)<sup>74</sup> showed that cholesterol-lowering therapy with lovastatin 40 mg/d significantly decreased the risk of a first acute coronary event in subjects with no clinically evident CHD and average LDL levels. Of note, AFCAPS/TexCAPS was the first large-scale statin trial to exclude patients on the basis of HDL measurements above predefined levels. After  $\approx 5$  years of treatment, lovastatin was associated with a 37% reduction in risk of first coronary events versus placebo (95% CI 21% to 50%;  $P < 0.001$ ).<sup>74</sup> These findings are particularly relevant to clinical practice because the participants were generally healthy and at lower CHD risk, and benefits were observed in both younger and older age groups.

### Primary/Secondary Prevention

The Heart Protection Study (HPS)<sup>75</sup> provided evidence that the benefits of statin therapy extend to patients not included in previous statin clinical trials. The HPS allowed enrollment of the elderly, women, and patients with hypertension, diabetes mellitus, or peripheral atherosclerosis, which is a patient population more representative of the general population.<sup>75</sup> Additionally, the trial enrolled patients both with and without CHD, so that it can be regarded as a combined primary and secondary prevention trial. The HPS showed that treatment with simvastatin for 5 years in a very large cohort



of  $\approx 20\,000$  patients significantly reduced the risk of all-cause mortality (primary end point) by 13% (95% CI 6% to 19%;  $P=0.0003$ ) and of any vascular death by 17% (95% CI 9% to 25%;  $P<0.0001$ ) compared with placebo. An important finding from HPS was that lipid-modifying therapy with a statin decreased the risk of cardiovascular events by approximately one quarter in subjects with baseline LDL cholesterol levels  $<116$  mg/dL<sup>75</sup>; this result provided support for the “lower is better” hypothesis. The HPS had a  $2\times 2$  factorial design by which patients were also randomized to receive antioxidant vitamin supplementation or matching placebo. Results showed no benefit of antioxidant supplementation on reducing the risk of all-cause mortality or of any cardiovascular deaths and events.<sup>79</sup>

Other major trials that further extended the benefits of statin therapy to a broad range of patients include the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),<sup>80</sup> which is discussed below under “Multiple Risk Factors”; the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial,<sup>81</sup> discussed in the section on stable CAD; and the PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) trial,<sup>82</sup> discussed under “Acute Coronary Syndromes” in part II.

### Diabetes Mellitus

Diabetes mellitus is now considered a “cardiovascular risk equivalent” that confers to diabetic persons a risk of future CVD events equivalent to that of persons who have survived a prior MI.<sup>83</sup> Approximately 50% to 75% of all deaths among patients with diabetes mellitus are CVD related, and type 2 diabetes mellitus increases the risk of death from CHD by 2- to 4-fold.<sup>84</sup> Patients with diabetes are prone to a number of cardiovascular risk factors beyond hyperglycemia, including hypertension and dyslipidemia. Owing to the high risk associated with diabetes, the aggressive control of all risk factors is especially important and includes both lifestyle changes and pharmacological intervention. Clinical trials in diabetes mellitus have examined cardiovascular risk reduction in patients with existing disease and the prevention of new-onset diabetes mellitus in patients with no evidence of diabetes at baseline.<sup>41,59,67,69,85–105</sup> Major trials are summarized in Table IV of the online data supplement.

Achieving and maintaining glycemic control in patients with type 1 and type 2 diabetes mellitus can delay the onset or prevent the progression of microvascular disease and, to a lesser extent, macrovascular disease. For example, intensive glucose control with metformin in the United Kingdom Prospective Diabetes Study (UKPDS) 34 decreased all-cause mortality, primarily due to fewer cardiovascular deaths, particularly deaths due to MI, in a subgroup of overweight subjects with type 2 diabetes mellitus.<sup>85</sup> Despite the relatively disappointing impact on cardiovascular events of tighter blood glucose control in patients with diabetes, the Steno-2 trial showed that aggressive intervention to manage the multiple risk factors present in diabetes does have a favorable impact on outcomes.<sup>41</sup> The effects of the insulin-sensitizing thiazolidinediones on cardiovascular events are being evaluated in several clinical trials. The first to be reported, the

PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) trial,<sup>86</sup> showed a nonsignificant reduction in the primary composite end point; however, pioglitazone significantly reduced the composite secondary end point of all-cause mortality, MI, or stroke.

More aggressive control of hypertension (to a blood pressure level  $<150/85$  mm Hg) in patients with diabetes mellitus, with a  $\beta$ -blocker or an ACE inhibitor as the main treatment, decreases both macrovascular and microvascular event rates compared with less aggressive control ( $<180/105$  mm Hg).<sup>89,90</sup> The STOP Hypertension-2 trial<sup>92</sup> found that treatment of elderly diabetic patients with diuretics,  $\beta$ -blockers, or both was comparable in efficacy to treatment with calcium channel blockers or ACE inhibitors in reducing cardiovascular mortality. In the HOPE study, 37.5% of participants had diabetes at study entry, and ramipril significantly reduced rates of MI, death, or stroke compared with placebo among these high-risk patients.<sup>93</sup> Ramipril also decreased the risk of diabetic complications, such as nephropathy and the need for dialysis.

Inhibition of the RAAS also appears to delay the onset of diabetes in hypertensive patients and in those with congestive heart failure.<sup>106</sup> Findings from the CAPP<sup>102</sup> demonstrated that the risk of developing diabetes was 14% (95% CI 1% to 26%) lower among patients with hypertension treated with captopril than among those treated with diuretics or  $\beta$ -blockers ( $P=0.039$ ). Among subjects in the HOPE study who were not diabetic at study initiation, those who received ramipril were significantly less likely to develop diabetes during the 5-year study than those who received placebo.<sup>67</sup> Among ALLHAT participants who were classified as nondiabetic at baseline, the incidence of diabetes at 4 years was 8.1% in the lisinopril group compared with 9.8% in the amlodipine group and 11.6% in the chlorthalidone group.<sup>66</sup>

Treatment with an ARB also appears to reduce the risk of developing diabetes. Among hypertensive patients with evidence of LVH in the LIFE study,<sup>103</sup> those in the losartan group had a 25% lower risk (95% CI 12% to 37%;  $P=0.001$ ) of developing diabetes than those in the atenolol group. Similar results were reported in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) study,<sup>104</sup> in which candesartan reduced the risk of new-onset diabetes by 22% versus placebo (95% CI 4% to 36%;  $P=0.02$ ) in patients with heart failure. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE)<sup>69</sup> reported a significant 23% (95% CI 14% to 31%) lower rate of new-onset diabetes in the valsartan arm compared with the amlodipine arm ( $P<0.0001$ ). A meta-analysis<sup>106</sup> examined the development of new-onset type 2 diabetes mellitus in 10 randomized controlled trials in which RAAS inhibitors (5 ACE inhibitor trials and 5 ARB trials) were compared with placebo or other antihypertensive agents. Overall, there was a mean weighted RR reduction of 22% (95% CI 18% to 26%;  $P<0.00001$ ) after RAAS inhibition. The beneficial effect was similar with ACE inhibitors and ARBs and in patients with hypertension and in those with heart failure. The type of comparator (placebo or active) did not affect the results.

Statin drugs also reduce the risk of major coronary events in patients with diabetes and impaired fasting glucose.<sup>97,98</sup>

For example, the HPS study<sup>99</sup> reported that diabetic patients treated with simvastatin 40 mg/d experienced a 27% reduction in risk of major coronary events (95% CI 15% to 38%;  $P<0.0001$ ) and a 22% reduction in major vascular events (95% CI 13% to 30%;  $P<0.0001$ ) compared with placebo. The reduction in risk extended to patients with no diagnosed occlusive arterial disease at entry and those with pretreatment LDL cholesterol levels  $<3.0$  mmol/L (116 mg/dL).<sup>99</sup> It is now recommended that patients with diabetes achieve LDL cholesterol levels of  $<100$  mg/dL regardless of their cardiovascular history.

### Multiple Risk Factors

Cardiovascular risk factors rarely occur in isolation but rather tend to cluster, which confers high risk in individual persons. A well-known example of this phenomenon is the metabolic syndrome, which is characterized by a group of risk factors including central obesity, dyslipidemia, hypertension, and impaired glucose/insulin homeostasis. Intervention in such patients may influence the ultimate development of diabetes, CVD, or both. Although trials have targeted individual components of this syndrome, no end-point trials have specifically targeted the syndrome in its entirety. However, a number of trials have been conducted in patients with  $>1$  risk factor for CVD.<sup>66,69,80,107–109</sup> Results of these trials are summarized in Table V of the online data supplement.

Two large trials of patients with multiple risk factors included both a hypertension arm and a lipid-lowering arm: ALLHAT and ASCOT. ALLHAT is the largest randomized, double-blind, controlled clinical trial with CVD end points in hypertensive patients conducted to date ( $>42$  000 patients originally enrolled). In the hypertension arm, patients were initially randomized to chlorthalidone 12.5 to 25 mg/d, amlodipine 2.5 to 10 mg/d, lisinopril 10 to 40 mg/d, or doxazosin 2 to 8 mg/d.<sup>110</sup> (The doxazosin arm of the trial was terminated early because of an increased risk of congestive heart failure compared with chlorthalidone.<sup>111</sup>) The target blood pressure in ALLHAT was  $<140/90$  mm Hg. Patients who did not achieve the blood pressure goal with the primary double-blinded treatment could receive additional, open-label treatment with other antihypertensive agents.<sup>110</sup> After a mean follow-up of 4.9 years, there was no significant difference between treatments in the primary outcome measure of fatal CHD or nonfatal MI.<sup>66</sup>

The ASCOT study<sup>112</sup> had 2 primary objectives: first, to assess whether combination therapy with newer antihypertensive agents (ie, amlodipine, plus the ACE inhibitor perindopril if needed to achieve goal blood pressure) is more effective in reducing nonfatal MI and fatal CHD (combined primary end point) than traditional combination therapy with a  $\beta$ -blocker (atenolol) followed by a diuretic (bendroflumethiazide), if needed; and second, to assess whether the addition of atorvastatin to these combinations would provide greater benefits in a subgroup of patients with normal to mildly elevated total cholesterol levels ( $\leq 6.5$  mmol/L [ $\leq 251$  mg/dL]). Eligible patients had at least 3 CVD risk factors, such as smoking, LVH, type 2 diabetes mellitus, or peripheral vascular disease.<sup>112</sup>

The ASCOT blood pressure-lowering arm (ASCOT-BPLA)<sup>108</sup> was terminated in December 2004 because of a significantly lower incidence of all-cause mortality with amlodipine-based therapy (11% RR reduction, 95% CI 1% to 19%;  $P=0.025$ ). Although final results showed no significant difference in the primary end point (RR 0.90, 95% CI 0.79 to 1.02;  $P=0.1052$ ) with amlodipine-based treatment versus atenolol-based treatment, significant differences in favor of amlodipine plus perindopril therapy were observed for several secondary end points, including fatal and nonfatal stroke (23% RR reduction, 95% CI 11% to 34%;  $P=0.0003$ ) and total cardiovascular events and procedures (16% RR reduction, 95% CI 10% to 22%;  $P<0.0001$ ). Amlodipine plus perindopril therapy was also associated with a significant 30% reduction in the incidence of new-onset diabetes (95% CI 22% to 37%;  $P<0.0001$ ).<sup>108</sup>

The VALUE trial<sup>69</sup> examined whether regimens based on valsartan or amlodipine would have different effects on cardiovascular outcomes in hypertensive patients at high risk for cardiac events if the same blood pressures were achieved. The unintended unequal reductions in blood pressure in favor of amlodipine, especially early in the study, made it difficult to arrive at definitive conclusions or to prove the primary hypothesis of the trial (that an RAAS-based regimen would be superior to another regimen at reducing cardiac morbidity and mortality, the primary trial end point), because it was assumed that the 2 regimens would achieve equal blood pressure lowering results. Nevertheless, there was no difference in the primary end point between the 2 treatment groups, although there were differences in cause-specific outcomes (eg, significantly [ $P=0.02$ ] lower incidence of MI in the amlodipine arm but a positive trend in favor of valsartan for heart failure).<sup>69</sup> The investigators noted that 79% of the excess MIs in the valsartan group occurred during the first 2 years of the study, when there was a greater discrepancy in blood pressure control between the 2 treatment groups; this emphasizes the importance of early reductions in blood pressure for decreasing the risk of subsequent CVD events.

Numerous trials have examined the role of statins in patients with multiple cardiovascular risk factors. A subset (10 355 patients aged  $\geq 55$  years) of the total ALLHAT cohort was assigned to the open-label, lipid-lowering arm of the trial (ALLHAT-LLT).<sup>109</sup> In addition to the assigned antihypertensive therapy, patients with moderate hypercholesterolemia received pravastatin and a lipid-lowering diet or the lipid-lowering diet plus “usual care” as determined by primary care physicians.<sup>110</sup> In addition to hypertension and moderate hypercholesterolemia, all patients in the lipid-lowering arm had at least 1 additional CHD risk factor. The primary end point was all-cause mortality, and mean follow-up was 4.8 years. Among the subset of patients who had LDL cholesterol levels calculated, pravastatin lowered LDL cholesterol by 28% compared with an 11% reduction in the usual-care group. (During the trial, 32% of usual-care patients with CHD and 29% of those without CHD started taking lipid-lowering drugs.) The differences in reductions in total and LDL cholesterol were not statistically significant. Perhaps because of the lack of a significant difference in cholesterol lowering, all-cause mortality was similar in the 2

treatment groups, as were CHD event rates (fatal CHD or nonfatal MI).<sup>109</sup>

Of the 19 342 patients who were randomized to the antihypertensive treatment arms of ASCOT, 10 305 were also eligible for the lipid-lowering arm and were further assigned to treatment with atorvastatin 10 mg/d or placebo.<sup>80</sup> After a median follow-up of 3.3 years, the primary end point was significantly lowered in the atorvastatin group compared with the placebo group (RR reduction 36%, 95% CI 17% to 50%;  $P=0.0005$ ). The significant benefits of atorvastatin therapy were observed for a number of secondary end points, including total cardiovascular events and revascularization procedures, total coronary events, and nonfatal MI (excluding silent MIs) plus fatal CHD. Atorvastatin also caused a significant 27% RR reduction (95% CI 4% to 44%;  $P=0.024$ ) in fatal and nonfatal strokes.<sup>80</sup>

### Left Ventricular Hypertrophy

LVH is the characteristic pathophysiological mechanism underlying the natural course of heart failure and is a strong predictor of CVD morbidity and mortality. LVH is most commonly caused by elevated blood pressure. Several classes of antihypertensive drugs have been shown to interrupt the progression of LVH. A meta-analysis<sup>113</sup> of 80 double-blind clinical trials that assessed the effects of antihypertensive therapy on left ventricular mass found that ARBs produced the greatest reduction in left ventricular mass, followed by calcium channel blockers, ACE inhibitors, diuretics, and  $\beta$ -blockers. Some evidence also suggests that interventions to reduce left ventricular mass may decrease the risk of events, which provides further support for the existence of a CVD continuum. A meta-analysis was performed of studies that reported left ventricular mass before and during antihypertensive therapy with subsequent assessment of cardiovascular events. Compared with persistence or new development of LVH, regression of LVH was associated with a marked reduction in risk for subsequent cardiovascular events, including heart failure.<sup>114</sup> Evidence from the LIFE trial also supports the premise that interventions targeted to high-risk hypertensive patients with LVH can reduce the risk of cardiovascular events.

### Atherosclerosis and Stable CAD

Atherosclerosis is the major underlying condition in patients who develop myocardial ischemia, CAD, MI, heart failure, peripheral arterial disease, and stroke. A number of trials have used angiography and other imaging techniques to measure changes in the diameter of the arterial lumen.<sup>115–127</sup> Results indicate that aggressive lipid modification may retard progression or cause regression of coronary plaques, decrease the need for revascularization, and reduce the risk of major coronary events. Regression trials that also monitored the effects of intervention on “hard” clinical end points are summarized in Table VI of the online data supplement.

Common treatment options for patients with stable CAD include lifestyle modifications, medical therapy, CABG, and percutaneous coronary intervention (PCI). Risk factor modification and medical therapy (aspirin, antianginal drugs) should be thoroughly explored before revascularization inter-

ventions are considered.<sup>128</sup> The aggressive management of cardiovascular risk factors through lifestyle modification (eg, smoking cessation, exercise, and weight control) and pharmacological therapy is important in controlling symptoms of angina and reducing morbidity and mortality. Advances in pharmacological therapy have made it possible to treat most low-risk angina patients with medical therapy before revascularization interventions such as PCI or surgery are considered. However, revascularization appears to provide superior symptom relief and offers a survival advantage in certain higher-risk patients.

### Pharmacological Therapy

Long-term medical therapy with a variety of agents has been evaluated in patients with stable CAD.<sup>67,81,129–136</sup> Important clinical trials are summarized in Table VII of the online data supplement. Aspirin decreases the risk of cardiovascular events and is the mainstay of antiplatelet therapy for patients who have chronic stable CAD, with or without prior MI.<sup>137</sup> In the Swedish Angina Pectoris Angina Trial (SAPAT),<sup>130</sup> the first prospective study of aspirin in stable angina, the addition of a low dose of aspirin to sotalol showed significant benefit compared with placebo in decreasing the risk of primary outcome events (MI and sudden cardiac death). The newer antiplatelet agent clopidogrel can be used as an alternative for patients who cannot tolerate aspirin. The combination of aspirin and clopidogrel has also been investigated, and some of the relevant clinical trials are discussed under “Acute Coronary Syndromes” in part II.

The management of dyslipidemia, hypertension, and diabetes mellitus plays a pivotal role in patients with CAD. If lifestyle modifications alone do not control these risk factors, then drug treatment is warranted. As shown by the 4S,<sup>70</sup> CARE,<sup>71</sup> LIPID,<sup>72</sup> and HPS<sup>75</sup> trials discussed earlier, the use of statins in persons with known CAD or at high risk for the development of CAD, including persons with normal or only slightly elevated levels of LDL cholesterol, results in significant decreases in all-cause and cardiovascular mortality and coronary/cardiovascular events. Other trials that have added to the experience of intensive lipid lowering in patients with stable CAD include the Atorvastatin Versus Revascularization Therapy (AVERT)<sup>134</sup> and Treating to New Targets (TNT)<sup>135</sup> trials. In AVERT, patients with stable CAD who had been recommended for PCI were randomized to either atorvastatin 80 mg/d or to angioplasty followed by usual care (which could include lipid-lowering therapy). After 18 months, atorvastatin had decreased the RR of any ischemic event by 36% ( $P=0.048$ ) versus revascularization.<sup>134</sup> This result did not reach the level for statistical significance after adjustment for interim analyses (a probability value of 0.045). The reduction was primarily due to a decreased incidence of revascularization procedures and worsening angina that required hospitalization. Atorvastatin also significantly ( $P=0.03$ ) prolonged the time to first ischemic event.<sup>134</sup>

The hypothesis of the TNT trial was that aggressively lowering LDL cholesterol to levels well below currently recommended treatment targets (ie, 100 mg/dL) with atorvastatin 80 mg/d would reduce the occurrence of major cardiovascular events compared with therapy that achieved lesser



reductions (with atorvastatin 10 mg/d).<sup>135</sup> More than 10 000 patients with clinically evident CHD and LDL cholesterol levels <130 mg/dL were followed up for a mean 4.9 years. The LDL cholesterol levels achieved were 77 mg/dL in the intensive therapy group compared with 101 mg/dL in the more moderate therapy group. The greater LDL cholesterol reduction with atorvastatin 80 mg/d was associated with a 22% RR reduction (95% CI 11% to 31%;  $P<0.001$ ) for the composite end point of CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke.<sup>135</sup> There was no difference between the 2 groups in overall mortality. The incidence of persistent elevations in liver aminotransferase levels was 0.2% in the 10-mg group and 1.2% in the 80-mg group ( $P<0.001$ ).<sup>135</sup>

Another trial of high-dose versus usual-dose statin therapy in patients with stable CHD was the Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study,<sup>81</sup> which compared atorvastatin 80 mg/d with simvastatin 40 mg/d over a median 4.8 years of follow-up. Although the absolute difference in LDL cholesterol levels achieved at 1 year (22.9 mg/dL) was similar to that observed at the end of the TNT trial (24 mg/dL), the 11% (95% CI -1% to 22%) proportional reduction in risk of the primary composite end point (time to first major coronary event) with aggressive therapy was not significantly different from more moderate therapy. Atorvastatin 80 mg/d significantly ( $P=0.02$ ) decreased the RR of nonfatal acute MI compared with simvastatin 40 mg/d (hazard ratio 0.83, 95% CI 0.71 to 0.98), but no difference was observed in cardiovascular or all-cause mortality.<sup>81</sup>

Antihypertensive therapy in patients with CAD also lowers the incidence of subsequent cardiovascular events. In the large-scale HOPE study,<sup>67</sup> treatment with ramipril for a mean of 4.5 years significantly reduced rates of cardiovascular death, MI, or stroke among patients at high risk for or with confirmed CAD but with no left ventricular dysfunction or heart failure. The HOPE study had a 2×2 factorial design and also randomized patients to receive either 400 IU of vitamin E daily or matching placebo. Dietary supplementation with vitamin E had no apparent effect on cardiovascular outcomes.<sup>131</sup> Longer-term (median 7 years) follow-up confirmed the lack of benefit for the prevention of major cardiovascular events and cancer and suggested that vitamin E supplementation may have increased the risk of heart failure.<sup>138</sup>

Two subsequently completed trials in patients with stable CAD but no symptomatic heart failure provide evidence that the benefit of ACE inhibitor therapy may depend on the patient's overall level of risk, thus explaining a "gradient" of results. The European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA),<sup>132</sup> which enrolled patients who were considered at lower risk than those in HOPE, showed significant reductions in a combined primary end point (cardiovascular mortality, MI, or cardiac arrest) with perindopril compared with placebo. By contrast, the Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) trial<sup>133</sup> reported that trandolapril did not significantly reduce the incidence of combined cardiovascular death, MI, or coronary revascularization compared with placebo. The investigators noted that patients enrolled in PEACE had an average baseline

left ventricular ejection fraction of 58% and normal cholesterol concentrations; in addition, the baseline mean blood pressure was equivalent to the on-treatment levels achieved with ACE inhibitor therapy in both the HOPE and EUROPA trials.<sup>133</sup> Moreover, the patients in PEACE also received more intensive management of risk factors than those in HOPE and EUROPA.

### CABG Surgery

Much of the clinical trial information comparing surgery with medical treatment was published before the 1990s. Three major randomized trials of CABG compared with medical therapy were begun in the 1970s and examined survival in patients with mild to moderate angina pectoris: the Veterans Affairs (VA) Cooperative Study, the European Cardiac Society Study (ECSS), and the National Institutes of Health-supported Coronary Artery Surgery Study (CASS).<sup>139–141</sup> Limitations exist in generalizing the results of these trials to current practice, because the risk profile of patients referred for surgery and the available surgical techniques and medical interventions have evolved considerably since the time those studies were conducted. Nonetheless, the basic findings of these and other trials, synthesized in a meta-analysis,<sup>142</sup> continue to influence current practice guidelines.<sup>143</sup> The meta-analysis found that CABG improves long-term survival in a range of patients at moderate to high risk compared with medical therapy. The absolute benefit of CABG is greatest in certain anatomic subsets of patients, such as those with left main disease and 3-vessel CAD.<sup>142</sup>

### Percutaneous Coronary Intervention

PCI, which includes conventional balloon angioplasty, coronary atherectomy, and stent implantation, is performed in more than 2 million patients worldwide annually.<sup>144,145</sup> The large number of clinical trials that have investigated PCI in patients with stable CAD include comparisons of conventional balloon angioplasty and/or stenting with CABG, drug-eluting versus bare-metal stents, and pharmacological therapy to enhance the success of the PCI procedure and to decrease postprocedure complications.<sup>145–190</sup> These trials are summarized in Table VIII of the online data supplement.

In patients with stable CAD, PCI effectively relieves the signs and symptoms of myocardial ischemia due to coronary artery obstructions and improves the quality of life in symptomatic patients. However, some evidence suggests that PCI may be less useful in stable CAD patients than intensive medical therapy for the prevention of new ischemic events, such as death and MI due to plaque rupture in less significant (<50%) coronary stenoses.<sup>134</sup> In contrast to the outcomes with PCI in patients with stable CAD, PCI reduces the frequency of death, recurrent MI, and recurrent ischemia in patients who present with an acute coronary syndrome, including ST-segment elevation MI (compared with fibrinolytic therapy)<sup>191</sup> and non-ST-segment elevation MI.<sup>192,193</sup>

Although the timing of PCI and the intensity of anticoagulation therapy may depend on the clinical presentation, the methods used to perform coronary revascularization are similar regardless of the particular clinical scenario. In addition, in patients with both stable and unstable CAD, PCI should be coupled with aggressive risk factor modification and lipid management to prevent further ischemic events.



### Coronary Stenting

Early types of PCI procedure, that is, conventional balloon angioplasty and coronary atherectomy, were limited by clinical restenosis rates that approached 30% to 40% over the first year after the procedure.<sup>146</sup> Recurrent narrowing within the treated lesion was due to arterial remodeling and vessel constriction rather than intimal hyperplasia.<sup>194</sup> Balloon-expandable coronary stents provided sufficient arterial scaffolding to prevent the unfavorable vessel constriction that occurred after angioplasty. However, varying degrees of intimal hyperplasia developed within the stent struts, which resulted in clinical recurrence in  $\approx$ 20% of patients.<sup>195</sup>

Numerous randomized trials that compared coronary stents with balloon angioplasty have shown a marked benefit with coronary stents on clinical and angiographic recurrence in patients with de novo and restenotic<sup>146</sup> lesions, on the number of total occlusions, and in patients with saphenous vein graft stenoses. An additional benefit of coronary stenting is that coronary stents “tack up” coronary dissections induced by balloon angioplasty that often (in 5% of cases) used to necessitate emergency CABG.<sup>196,197</sup>

Since the introduction of coronary stents in the early and mid-1990s, coronary stenting has become the default therapy for patients with stable CAD undergoing PCI procedures. More experience with coronary stents has demonstrated that recurrence rates after stenting are higher in patients with long lesions, in those with lesions in smaller vessels, and in those with diabetes mellitus.<sup>149</sup> Although the use of  $\gamma$ -radiation<sup>148</sup> and  $\beta$ -radiation<sup>149,150</sup> therapy reduced recurrence rates in patients treated for in-stent restenosis by 30% to 40%, these methods have been limited by the occurrence of edge restenosis and late (up to 2 years) stent thrombosis, which mandates the use of extended antiplatelet therapy, particularly if additional stents are required. Because of the limitations of these alternative therapies, newer stent designs and drug-delivery systems that would provide a more durable result in patients undergoing PCI were developed.

### Drug-Eluting Stents

Drug-eluting stents include a polymer coating and an anti-proliferative agent that reduces the magnitude of intimal hyperplasia after stent placement. The first clinically available drug-eluting stent was the sirolimus-eluting stent (SES; CYPHER, Cordis Corporation, Warren, NJ), which provided controlled release of sirolimus for 30 days after the procedure using a “Topcoat” durable polymer coating. Several randomized studies have demonstrated dramatic (60% to 80%) reductions in clinical and angiographic restenosis using coated compared with bare-metal stents, resulting from a profound reduction in the magnitude of intimal hyperplasia within the stent.<sup>151–153</sup> Another stent available for clinical use, the paclitaxel-eluting stent (PES; TAXUS, Boston Scientific, Natick, Mass), releases the antimicrotubule agent paclitaxel from the Translute polymer for 30 days after the procedure.<sup>154</sup> In contrast to the SES, 92% of the paclitaxel remains within the polymer after the initial elution. The slow-release formulations of the PES are associated with reduced in-stent neointimal formation and restenosis compared with the bare-

metal stent. These effects have been sustained for up to 2 years after the procedure.<sup>155</sup>

A number of studies have compared the outcomes of patients treated with SES and PES, with varying results depending on the complexity of the lesions treated. In patients with complex coronary disease, such as those with in-stent restenosis, there appears to be an advantage with the SES. For example, the SES and PES were compared with angioplasty in 300 patients with angiographically significant in-stent restenosis.<sup>156</sup> Both stents significantly decreased the rate of restenosis compared with balloon angioplasty and significantly reduced the need for target-vessel revascularization, but a secondary analysis found a trend or a significant difference in favor of the SES for all angiographic parameters and a significant reduction in target-vessel revascularizations versus the PES (8% versus 19%;  $P=0.02$ ). Additional studies have demonstrated a similar effect in patients with long lesions, uncontrolled diabetes,<sup>157</sup> and “all comers.”<sup>158</sup> Importantly, in patients with less complicated CAD, the SES and PES appear to result in similar clinical outcomes.<sup>159</sup>

### Stent Thrombosis

A major limitation of early studies of bare-metal stents was subacute stent thrombosis, which often occurred despite aggressive anticoagulation treatment after patient discharge. The addition of a thienopyridine derivative, such as ticlopidine or clopidogrel, to aspirin results in a dramatic reduction in the occurrence of subacute stent thrombosis.<sup>186</sup> Because of its more favorable side-effect profile, clopidogrel is preferred over ticlopidine, and therapy has been continued for 1 month after bare-metal stent placement to prevent this complication.

More prolonged dual-antiplatelet therapy has been recommended with the SES (3 months) and PES (6 months) owing to delays in endothelialization that may occur with these stents. The rate of occurrence of stent thrombosis appears similar in patients receiving drug-eluting and bare-metal stents provided that the antiplatelet therapy is given for the recommended duration. The importance of antiplatelet therapy was emphasized in a “real world” registry of patients undergoing drug-eluting stenting for complex CAD.<sup>198</sup> This prospective, observational cohort study of 2229 consecutive patients who had successful implantation of SES (1062 patients) or PES (1167 patients) suggested that the rate of stent thrombosis may be higher in actual clinical practice than the rates reported in controlled clinical trials.<sup>198</sup> This study reported a 29% incidence of stent thrombosis if the dual-antiplatelet therapy (aspirin plus clopidogrel or ticlopidine) was discontinued prematurely.

### Angioplasty Versus CABG

Twenty-five years ago, percutaneous balloon angioplasty was reserved for patients with single-vessel CAD. With dramatic technical advances and improved early and late outcomes, it is now used in multivessel disease as well. Numerous randomized clinical trials comparing balloon angioplasty with CABG in patients with both single-vessel and multivessel disease found no significant difference in survival.<sup>162–165,199</sup> The Bypass Angioplasty Revascularization Investigation (BARI),<sup>166</sup> which compared CABG with conventional balloon angioplasty in patients with multivessel CAD, showed that initial angioplasty did not

significantly compromise 5-year survival, although subsequent revascularization was required more often with angioplasty. However, by 7 years of follow-up, CABG conferred a significant survival advantage, primarily owing to a benefit in patients with diabetes.<sup>200</sup> In contrast to the information available on the relative effectiveness of angioplasty versus CABG, more limited data are available on angioplasty compared with medical therapy. It is worth noting that the outcomes of these early PCI studies may not reflect current PCI practice, because none capitalized on the most recent treatment advances with anticoagulation therapy and drug-eluting stents during PCI.

#### *Stenting Versus CABG*

Several trials have compared stent implantation with CABG in patients with single-vessel or multivessel CAD. In general, outcomes have been similar in terms of mortality and morbidity, although the need for repeated revascularization has been greater with stents.<sup>167–174</sup> The largest of these trials, the Arterial Revascularization Therapies Study (ARTS)<sup>168</sup> of 1205 patients with multivessel disease, found no difference at 1 year in the combined rate of death, MI, and stroke between the 2 strategies; however, the need for repeat revascularization was higher with stenting, and this difference was even more pronounced in diabetic patients. Outcomes at 5 years confirmed the higher rate of major adverse cardiac or cerebrovascular events with PCI, driven by the increased need for repeat revascularization (30.3% versus 8.8%;  $P < 0.001$ ).<sup>169</sup> The Stent or Surgery (SoS) trial<sup>173</sup> showed increased mortality in the stent arm, a difference that was not attributable to diabetes. The rate of revascularization was also higher with stenting. Neither of the stent arms of ARTS and SoS used concomitant platelet glycoprotein IIb/IIIa inhibitors, which current treatment guidelines consider a reasonable drug option for patients undergoing elective PCI with stent placement.<sup>201</sup>

#### *Drugs to Improve the Performance and Safety of PCI*

Periprocedural use of platelet inhibitors (eg, aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors) and anticoagulants (eg, unfractionated heparin and direct thrombin inhibitors) decreases the frequency of early ischemic complications after PCI. Long-term synergistic antiplatelet use may also reduce the occurrence of late events. Aspirin is an essential treatment before PCI, whereas the addition of a thienopyridine derivative to aspirin confers additional benefit (see “Stent Thrombosis,” above). The Clopidogrel for the Reduction of Events During Observation (CREDO) trial<sup>188</sup> did not demonstrate an overall benefit at 28 days from administration of a loading dose of clopidogrel (along with aspirin) compared with no loading dose before the PCI procedure. A prespecified subgroup analysis, however, showed that patients pretreated with clopidogrel at least 6 hours before PCI experienced an RR reduction of 38.6% versus placebo (95% CI –1.6% to 62.9%;  $P = 0.051$ ) for the combined end point of death, MI, or target-vessel revascularization at 28 days compared with no risk reduction versus placebo with treatment  $< 6$  hours before the PCI. Long-term use of dual-antiplatelet therapy (aspirin and clopidogrel) in CREDO resulted in a 26.9% (95% CI 3.9% to 44.4%;  $P = 0.02$ )

reduction in combined death, MI, or stroke at 1 year after the procedure.<sup>188</sup>

Treatment with glycoprotein IIb/IIIa inhibitors before stent implantation lowers the incidence of ischemic complications within 48 hours of the procedure and at 1-month follow-up<sup>187</sup> and substantially reduces (by 38%) the risk of death or nonfatal MI at 30-day follow-up.<sup>145</sup> These agents are frequently administered with unfractionated heparin, but the risk of major bleeding with this combination remains a concern.<sup>189</sup> Evidence from the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial suggested that direct thrombin inhibitors, such as bivalirudin, may be used instead of heparin with glycoprotein IIb/IIIa inhibitors in stable CAD patients undergoing elective, but not urgent, PCI.<sup>189</sup> The benefits of bivalirudin were confirmed in unstable angina/non-ST-segment elevation MI patients by the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial,<sup>202</sup> which will be discussed in part II of this article under “Treatment of UA/NSTEMI.”

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### Dedication

This article is dedicated to Eugene Braunwald, MD, my friend and mentor, in recognition of our close work conceiving the CVD continuum 15 years ago.

—Victor J. Dzau, MD.

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KEY WORDS: cardiovascular diseases ■ diabetes mellitus ■ drugs  
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