

The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes

Part II: Clinical Trial Evidence (Acute Coronary Syndromes Through Renal Disease) and Future Directions

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This is the second part of a 2-part article that presents a critical and comprehensive update of the current evidence for a cardiovascular disease (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. In part I, we reviewed the current understanding of CVD pathophysiology and discussed data from clinical trials on subjects ranging from risk factors for disease through stable coronary artery disease (CAD). The present article continues the review of clinical trials, beginning with acute coronary syndromes (ACS) and continuing through extension of the concept of the CVD continuum to include 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.

Acute Coronary Syndromes

ACS represent a spectrum of events ranging from unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). ACS events are frequently the consequence of thrombotic occlusion of a coronary artery. Intervention at this point in the CVD continuum clearly interrupts disease progression by preventing cardiac muscle death, decreasing the risk of a recurrent ischemic event, slowing progression to heart failure, and reducing mortality. Patients presenting with an ACS must receive prompt treatment to prevent ischemic complications; optimal management includes anti-ischemic therapy (eg, supplemental oxygen, nitroglycerin, and β -blocker), antiplatelet agents (eg, aspirin, clopidogrel, or platelet glycoprotein [GP] IIb/IIIa inhibitor), antithrombotic therapy (unfractionated heparin, low-molecular-weight heparin [LMWH]), and the use of invasive reperfusion procedures (ie, percutaneous coronary

intervention [PCI] or coronary artery bypass grafting [CABG]). For STEMI patients, optimal therapy also includes fibrinolytic agents to restore blood flow in the occluded coronary artery.

Treatment of UA/NSTEMI

UA and NSTEMI are considered closely related conditions and may be indistinguishable in their early stages in terms of clinical presentation. UA and NSTEMI encompass a wide range of risk, but NSTEMI is more severe and is considered to have occurred if biochemical biomarkers of myocardial injury have been released.¹

Pharmacological Therapy

Numerous clinical trials involving a variety of agents provide data on the beneficial role of medical therapy in patients with UA/NSTEMI.²⁻³³ These trials are summarized in Table I of the online data supplement.

Aspirin is routinely initiated in ACS patients and continued in the long term to reduce the risk of future events. The addition of clopidogrel to aspirin therapy appears to confer further benefit. Treatment of UA/NSTEMI patients for 3 to 12 months with clopidogrel (plus aspirin) significantly reduced the risk of combined cardiovascular death, nonfatal myocardial infarction (MI), and stroke compared with placebo.⁶ However, the risk of bleeding was increased with clopidogrel, especially in patients undergoing CABG surgery within 5 days of discontinuing clopidogrel therapy.

The role of platelet GP IIb/IIIa receptor inhibitors in ACS patients who did not have persistent ST-segment elevation and who were not scheduled for immediate revascularization was examined in a meta-analysis of 6 randomized trials.³⁴ Compared with placebo or control, GP IIb/IIIa inhibitors were associated with a significant 16% relative risk (RR)

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reduction in death or nonfatal MI at 5 days (95% CI 7% to 23%; $P=0.0003$) and a 9% RR reduction at 30 days (95% CI 2% to 15%; $P=0.015$).³⁴ However, the treatment effect in the average patient is modest.^{1,35} Much stronger evidence exists for the benefit of using GP IIb/IIIa inhibitors as adjunctive therapy during PCI, both in patients with stable CAD, as previously discussed, and in ACS.

Although many patients are treated long term with aspirin after their first hospitalization for UA, the risk of cardiac events remains high.⁴ Recurrent ischemic events in patients with UA appear to be due to ongoing thrombotic stimulus. A combination of aspirin to block platelet activation and moderate-intensity warfarin to suppress activation of the coagulation system, initiated within 12 to 24 hours of hospitalization for chest pain and continued for 3 months, may be superior to aspirin alone in reducing the risk of recurrent ischemic events in UA patients.⁴ However, clinicians are sometimes reluctant to use warfarin in this situation because of concern that patients may need to undergo CABG or a PCI procedure. The addition of intravenous unfractionated heparin to oral aspirin therapy may reduce the 3-month rates of death or MI in patients hospitalized for UA/NSTEMI, although none of the findings of the 6 trials included in a meta-analysis by Oler et al reached statistical significance.³⁶

LMWHs and unfractionated heparin have similar mechanisms of action, but LMWH has important pharmacokinetic advantages; for example, it can be administered subcutaneously rather than intravenously, has a longer half-life, and has a bioavailability approaching 100% (versus about 30%).³⁶ A number of trials have evaluated the use of LMWH in acute and long-term treatment of UA/NSTEMI.^{1,17–25} Most^{18,22–24} but not all²⁵ studies have suggested that short-term treatment with enoxaparin is superior to unfractionated heparin in reducing the risk of death or cardiac ischemic events in patients with UA/NSTEMI, although studies using other LMWH compounds have reported no difference in clinical outcomes and/or increased bleeding with LMWH.^{19,20}

Statin therapy also provides benefit in UA/NSTEMI patients. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study³¹ evaluated the effect of statin therapy initiated shortly after onset of an ACS (ie, UA/NSTEMI) on mortality and nonfatal ischemic events. Results indicated that administration of atorvastatin 80 mg/d within 24 to 96 hours of an ACS reduces the incidence of recurrent ischemic events in the first 4 months compared with placebo, primarily by lowering the risk of symptoms of UA that require hospitalization. Contrasting results were reported by the A to Z trial, which compared early intensive versus delayed simvastatin treatment in 4497 ACS patients.³² Patients were randomized to simvastatin 40 mg/d for 1 month followed by 80 mg/d or to placebo for 4 months followed by simvastatin 20 mg/d for the remainder of the 2-year study. At 4 months, there was no difference in occurrence of the primary outcome (composite of cardiovascular death, nonfatal MI, readmission for ACS, and stroke); however, from 4 months to the end of the study, simvastatin 80 mg/d significantly decreased the RR of the primary outcome by 25% (95% CI 5% to 40%; $P=0.02$) versus simvastatin 20 mg/d.³²

Findings from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial³³ also suggest that ACS patients may derive more benefit from long-term, aggressive lipid-lowering therapy than from more moderate therapy. Patients hospitalized for an ACS and treated with atorvastatin 80 mg/d were significantly less likely to experience a major coronary event in the following 2 years than those who received pravastatin 40 mg/d. These results were correlated with the on-treatment levels of low-density lipoprotein (LDL) cholesterol achieved (62 versus 95 mg/dL for atorvastatin and pravastatin, respectively), providing yet more support for the “lower is better” hypothesis. The clinical benefit of more intensive lipid-lowering therapy became evident as early as 30 days after initiation of treatment.³³

Coronary Revascularization

Patients with UA/NSTEMI who have recurrent symptoms or ischemia despite adequate medical therapy or who have high-risk indicators should be considered for coronary angiography.¹ The decision to undertake a revascularization procedure follows from the results of angiographic evaluation. Numerous clinical trials^{37–62} have evaluated the use of PCI in patients with ACS and are summarized in Table II of the online data supplement. Pretreatment of UA/NSTEMI patients undergoing PCI with clopidogrel and aspirin followed by long-term (up to 12 months) clopidogrel therapy significantly reduces the risk of combined cardiovascular death, MI, or urgent target-vessel revascularization by 30% at 30 days (95% CI 3% to 50%; $P=0.03$) and decreases the risk of cardiovascular death or MI by 25% (95% CI 0% to 44%; $P=0.047$) at a mean follow-up of 8 months.⁵⁵

Numerous trials have shown that platelet GP IIb/IIIa inhibitors reduce the occurrence of early complications in patients with UA/NSTEMI undergoing PCI.¹ For example, the C7E3 Fab Antiplatelet Therapy in Unstable Refractory angina (CAPTURE) trial⁵¹ evaluated the effect of abciximab versus placebo administered 18 to 24 hours before balloon angioplasty and for 1 hour thereafter. All patients had undergone coronary angiography before randomization. The rate of death, MI, or urgent revascularization within 30 days was significantly ($P=0.012$) reduced from 15.9% with placebo to 11.3% with abciximab. At 6 months, death or MI had occurred in 10.6% of the placebo group compared with 9% of the abciximab group; this difference was not significant.⁵¹ Recently announced results of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial⁶² suggest that the direct thrombin inhibitor bivalirudin alone is as effective as either unfractionated heparin/enoxaparin plus GP IIb/IIIa inhibition or bivalirudin plus GP IIb/IIIa inhibition in terms of net clinical benefit and preventing ischemic events in UA/NSTEMI patients undergoing PCI. Furthermore, bivalirudin was associated with fewer major bleeding complications than either therapy that used GP IIb/IIIa inhibition.⁶²

Early Medical Therapy Versus Early Invasive Procedures

Clinical trials have assessed the relative benefits of early conservative treatment (ie, medical management, with angiography and revascularization reserved for patients with recurrent ischemia and a strongly positive stress test) versus

early invasive treatment (ie, routine use of angiography and revascularization).^{37,38,57,58} The Veterans Affairs Non-Q-Wave Infarction Strategy In-Hospital (VANQWISH) trial⁵⁷ evaluated the effect of routine early coronary angiography or a conservative treatment strategy on death or recurrent nonfatal MI in patients who developed non-Q-wave MI after fibrinolytic therapy. Outcomes were similar with either strategy. However, subsequent findings from the FRagmin and Fast Revascularization during Instability in Coronary artery disease (FRISC II)⁵⁸ and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18)³⁷ trials are more relevant in the current clinical environment. Both of these trials made use of modern antiplatelet and antithrombotic therapies, and both demonstrated a reduced risk of the combined end point of death, MI, and rehospitalization with an early invasive strategy.

Findings from the third Randomized Intervention Trial of Unstable Angina (RITA-3)³⁸ showed that UA/NSTEMI patients treated with an invasive strategy had significantly reduced rates of refractory or severe angina at 4 months and at 1 year compared with those treated with a conservative strategy. There was no difference in the combined occurrence of death or nonfatal MI at 1 year; however, after 5 years, early interventional treatment decreased the RR of this composite outcome by 22% (95% CI 1% to 39%; $P=0.044$) and of all-cause mortality by 24% (95% CI 0% to 42%; $P=0.054$).⁵⁹ Different results were reported by the Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial⁶⁰ in ACS patients without ST-segment elevation. The overall rates of combined death, nonfatal MI, or rehospitalization for anginal symptoms did not differ between the 2 groups. Some notable features of the ICTUS trial included the use of a loading dose of clopidogrel (in combination with aspirin) after this agent received an indication for treatment of ACS in 2002, the recommendation that atorvastatin 80 mg be started as soon as possible after randomization, and the high rate of in-hospital revascularizations (40%) in patients assigned to conservative therapy.⁶⁰

Antithrombotic pretreatment for 3 to 5 days before PCI had no clinical advantage compared with immediate (<6 hours) coronary intervention in the Intracoronary Stenting with Antithrombotic Regimen Cooling-Off (ISAR-COOL) study.⁶¹ The 30-day risk of the composite end point of all-cause mortality or large, nonfatal MI was almost doubled (RR 1.96, 95% CI 1.01 to 3.82; $P=0.04$) in patients receiving pretreatment, primarily due to events that occurred before catheterization.

Treatment of STEMI

The primary goal of therapy for STEMI is timely restoration of coronary blood flow. Both pharmacological and mechanical reperfusion strategies have shown benefit in patients with STEMI. The benefits of myocardial reperfusion are amplified when vessel patency can be achieved quickly after the onset of symptoms.

Pharmacological Therapy

Pharmacological therapy in STEMI patients has been evaluated in a great many clinical trials,^{63–98} as summarized in

Table III of the online data supplement. Reperfusion therapy is a cornerstone of the treatment of STEMI patients. Large randomized trials have shown that fibrinolytic therapy confers an overall survival benefit in patients with STEMI, regardless of age, sex, blood pressure, heart rate, or previous history of MI or diabetes mellitus.⁹⁹ Since publication in the 1980s of large trials of streptokinase (with or without aspirin) that showed improvement in mortality rates,^{100,101} numerous studies have evaluated the efficacy of modified dosing regimens, combinations of adjunctive treatments, and newer types of fibrinolytic agents. A greater understanding of the biochemical mechanisms regulating physiological fibrinolysis led to the concept of fibrin-specific agents and to the development of recombinant tissue-type plasminogen activator (recombinant tPA; alteplase, reteplase). Molecular modification of recombinant tissue-type plasminogen activator has resulted in agents such as reteplase and tenecteplase, which have longer plasma half-lives and regimens of single- or double-bolus dosing.

Two mega-trials—the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-2)¹⁰² and the third International Study of Infarct Survival (ISIS-3)⁶³—failed to show a survival benefit of standard-dose recombinant tPA over streptokinase. However, the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I trial⁶⁴ demonstrated a positive effect of tPA when given with intravenous heparin. In GUSTO I, accelerated infusion of tPA combined with intravenous heparin was superior to streptokinase plus heparin in decreasing 30-day mortality rates. The addition of LMWH to other types of therapy may improve outcomes. For example, a meta-analysis of 14 trials that involved >25 000 patients with STEMI examined the use of unfractionated heparin and LMWH when added to aspirin and fibrinolytic therapy.¹⁰³ Intravenous unfractionated heparin during hospitalization did not prevent reinfarction or death; however, LMWH given for 4 to 8 days reduced reinfarction by ≈25% and death by ≈10% compared with placebo and reduced reinfarction by almost one half when directly compared with unfractionated heparin.¹⁰³

The potential benefit of combination therapy with platelet GP IIb/IIIa inhibitors and fibrinolytics has been evaluated in STEMI patients both in angiographic trials^{81–84} and in trials with “hard” clinical events as the primary outcome.⁸⁶ Although mortality trials using a reduced dose of reteplase (GUSTO-V)⁸⁶ or tenecteplase (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen [ASSENT-3])⁷⁴ showed that combined use of a GP IIb/IIIa inhibitor with a reduced-dose fibrinolytic enhanced coronary artery patency versus full-dose fibrinolytic therapy alone, combination therapy with these agents plus abciximab failed to show any early or late survival benefit over full-dose fibrinolytics alone or any reduction in the risk of intracranial hemorrhage.

Aspirin is part of the early management of all patients with suspected STEMI and is continued chronically after STEMI. The addition of low-intensity anticoagulation therapy (warfarin, median international normalized ratio 1.8 IU) to aspirin does not provide any clinical advantage over aspirin monotherapy.⁸⁸ However, moderate- to high-intensity anticoagulant treatment (median international normalized ratio >2.0

IU) as an adjunct to aspirin has demonstrated a positive effect on reocclusion rates⁸⁹ and risk of recurrent cardiovascular events or death.⁹⁰

The efficacy and safety of the combination of aspirin plus clopidogrel in patients with STEMI was investigated in the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 (CLARITY–TIMI 28) trial,⁹¹ in which patients received clopidogrel or placebo in addition to aspirin and a fibrinolytic agent. Treatment with clopidogrel resulted in a 36% RR reduction (95% CI 24% to 47%; $P<0.001$) in the primary efficacy end point—an occluded infarct-related artery, death, or recurrent MI by the time of angiography. The rates of major bleeding and intracranial hemorrhage were similar in the clopidogrel and placebo groups.⁹¹ Another trial that evaluated the combination of aspirin plus clopidogrel was the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT),^{92,98} which used a 2×2 factorial design to assess the effects of early addition of clopidogrel or the β -blocker metoprolol (each compared with placebo) in STEMI patients also receiving aspirin therapy. In the clopidogrel arm of the study, the incidence of death, reinfarction, and stroke (primary composite end point) was significantly lower in the clopidogrel group than with placebo.⁹² The use of concomitant fibrinolytic therapy did not influence the risk reduction in the primary end point.

Although β -blockers have long been considered an integral part of the treatment of ACS,¹⁰⁴ only a few trials have evaluated early β -blockade in STEMI patients receiving fibrinolytic therapy. The results of the β -blocker arm of the COMMIT trial help to fill this void.¹⁰⁵ COMMIT showed that metoprolol administered for a median of 16 days during hospitalization did not significantly reduce the risk of all-cause mortality or combined death, reinfarction, or cardiac arrest.⁹⁸ There was a significant 18% RR reduction in reinfarction and a 17% reduction in ventricular fibrillation (both $P=0.001$), but these benefits were offset by an increase of 30% ($P<0.00001$) in the risk of cardiogenic shock, chiefly on the first day of hospitalization.⁹⁸ This result suggests that use of β -blockers during acute MI be deferred until patients are hemodynamically stable.¹⁰⁵

PCI-Based Reperfusion

The 1990s saw the increasing use of PCI as a way of opening up thrombosed coronary arteries in STEMI patients. PCI has been used in various treatment settings, including as a primary intervention and after failed fibrinolysis. A review of 23 randomized trials comparing primary PCI with fibrinolytic therapy for the treatment of STEMI suggested that PCI was superior to fibrinolytic therapy in lowering the 4- to 6-week post-MI risk of death, nonfatal reinfarction, and disabling stroke.¹⁰⁶ However, the most recent American College of Cardiology/American Heart Association guidelines for the management of STEMI patients¹⁰⁴ emphasize that timely treatment after the onset of symptoms is the key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI. Accordingly, the goal is to facilitate expeditious recognition and treatment of patients with STEMI, so that initiation of fibrinolytic therapy can be achieved within 30 minutes or

time to PCI (balloon inflation) can be kept under 90 minutes. For patients who have rapid (<90 minutes) access to expert PCI facilities, those with cardiogenic shock, and those with contraindications to fibrinolysis, primary PCI is the preferred reperfusion strategy. For other STEMI patients, prehospital initiation of fibrinolytic therapy is now recommended if the emergency medical service personnel have that capability.¹⁰⁴ If chest pain, hemodynamic instability, or persistent echocardiographic changes persist after fibrinolytic therapy, PCI may be useful in reestablishing normal blood flow and improving outcome (“rescue PCI”).^{107,108}

The use of drug therapy to facilitate the performance of PCI in the setting of STEMI has also been evaluated. In the Plasminogen-activator Angioplasty Compatibility Trial (PACT),⁴⁰ patients were assigned to a 50-mg bolus of recombinant tPA or placebo before angiography with angioplasty. Although patients who received reduced-dose fibrinolytic therapy before PCI had a higher rate of vessel patency, this approach did not improve left ventricular function, as measured by ejection fraction, nor did it reduce the major complications of acute MI, such as 30-day mortality, reinfarction, and major bleeding.⁴⁰ Two trials evaluating the concomitant use of platelet GP IIb/IIIa inhibition during PCI have reported differing results. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC),⁴⁹ the use of abciximab with either balloon angioplasty or bare-metal stenting provided no incremental benefit versus the PCI procedure alone with regard to the 6-month primary composite clinical end point; the Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) trial,⁵⁴ however, found that use of abciximab plus stenting versus placebo plus stenting significantly decreased both the 30-day and 6-month occurrence of the primary composite clinical end point.

The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT)-4 PCI trial⁵⁶ was intended as a large, randomized trial in acute STEMI patients facing very long delays before receiving therapy. This open-label study randomized patients to either full-dose tenecteplase plus PCI (facilitated PCI) or to primary PCI with unfractionated heparin. PCI was performed between 60 and 180 minutes after randomization. The primary end point—death, cardiogenic shock, or congestive heart failure within 90 days—was significantly lower in the PCI-only group than in the facilitated-PCI group, as were the rates of reinfarction and repeat revascularization.⁵⁶ Thus, although it might seem reasonable to initiate fibrinolytic therapy while STEMI patients are waiting for a PCI procedure, this assumption has not been confirmed by clinical trial results. This conclusion was reinforced by a recently published meta-analysis of 17 trials involving >4500 STEMI patients that showed that the facilitated approach resulted in higher rates of mortality, nonfatal reinfarction, and urgent target-vessel revascularizations than primary PCI.¹⁰⁹

Post-MI Patients

Survivors of an acute MI are at high risk for the development of heart failure and for recurrent MI and other CVD events.

Interventions such as therapy with ACE inhibitors^{110–112} and cholesterol modification with statins¹¹³ decrease the risk of subsequent clinical cardiovascular events. Such evidence of target-organ protection, achieved by interruption of the underlying pathophysiology of CVD, further substantiates the existence of a CVD continuum.

Neurohormonal Blockade

Extensive clinical trial evidence demonstrates that neurohormonal blockers, including β -blockers, ACE inhibitors, and angiotensin II type 1 receptor blockers (ARBs), are associated with benefit in post-MI patients.^{110–112,114–122} Representative clinical trials are reported in Table IV of the online data supplement. Overall, clinical trials of renin-angiotensin-aldosterone system (RAAS) inhibition with ACE inhibitors after MI have shown a 25% RR reduction (95% CI 17% to 33%; $P < 0.0001$) in recurrent CVD events.¹²³

Randomized clinical trials conducted in the 1970s and 1980s conclusively demonstrated reductions in morbidity and mortality when β -blockers were used soon after an acute MI and continued chronically.^{124–126} These trials were conducted before the introduction of post-MI interventions such as fibrinolytic therapy and ACE inhibitors. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial¹¹⁴ was designed to test whether carvedilol, begun in the early post-MI period and added to standard therapy that included an ACE inhibitor, would demonstrate benefit in patients with left ventricular dysfunction, with or without clinical heart failure. CAPRICORN showed that long-term treatment with a combined α -/ β -blocker, when added to ACE inhibitors and standard therapy, reduced all-cause mortality and recurrent MI.¹¹⁴

Findings from the COoperative New Scandinavian ENalapril SURvival Study II (CONSENSUS II)¹¹⁵ suggested that administration of an ACE inhibitor within 24 hours of an acute MI provided no survival benefit during the first 6 months after the MI. However, the Survival and Ventricular Enlargement (SAVE) trial¹¹⁶ demonstrated that in post-MI patients with asymptomatic left ventricular dysfunction, long-term treatment (mean 42 months) with an ACE inhibitor initiated within 3 to 16 days of MI significantly reduces the risk of morbidity and mortality due to major CVD events. The Studies Of Left Ventricular Dysfunction (SOLVD) prevention trial¹¹⁰ reported that treatment with enalapril of patients with asymptomatic left ventricular dysfunction during ≈ 3 years of follow-up reduced the incidence of heart failure by 37% compared with placebo (95% CI 28% to 44%; $P < 0.001$). Moreover, a large-scale study¹¹⁷ demonstrated that in patients with acute MI, lisinopril treatment begun within 24 hours of MI symptoms and continued for 6 weeks significantly reduced all-cause mortality and combined mortality and severe ventricular dysfunction during the treatment period.

The Survival of Myocardial Infarction Long-term Evaluation (SMILE) study¹¹⁹ randomized 1556 patients within 24 hours after the onset of symptoms of acute anterior MI to either zofenopril or placebo for 6 weeks. Results showed a 34% reduction in the RR of death or severe congestive heart failure with ACE inhibitor treatment versus placebo (95% CI 8% to 54%; $P = 0.018$). Continued follow-up at 1 year showed

that the mortality rate was still significantly lower in the zofenopril group than in the placebo group (RR reduction 29%, 95% CI 6% to 51%; $P = 0.011$).¹¹⁹ The TRAndolapril Cardiac Evaluation (TRACE) study¹¹¹ evaluated the effects of trandolapril in post-MI patients with left ventricular systolic dysfunction (ejection fraction $\leq 35\%$). Patients were assigned to receive either trandolapril 1 to 4 mg/d ($n = 876$) or placebo ($n = 873$) for an average follow-up of 24 to 50 months. Trandolapril significantly reduced the risk of cardiovascular death by 25% (95% CI 11% to 37%) and of all-cause mortality by 22% (95% CI 9% to 33%) compared with placebo (both $P = 0.001$).¹¹¹

Two major trials have compared an ARB with a proven ACE inhibitor regimen in high-risk post-MI patients. The OPTimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study¹²⁰ compared the effects of losartan 50 mg/d and captopril 50 mg TID on mortality in post-MI patients with left ventricular hypertrophy. Treatment was initiated at hospitalization and continued for a minimum of 6 months. No significant difference between the 2 groups was observed in the primary end point of all-cause mortality, possibly because the dose of losartan was too low to achieve superiority. The Valsartan in Acute Myocardial Infarction (VALIANT) study¹²¹ evaluated the efficacy of valsartan, captopril, or their combination in the treatment of post-MI patients with left ventricular systolic dysfunction or heart failure. Treatments were initiated within 10 days of acute MI. Findings revealed that valsartan was comparable in efficacy to captopril in reducing all-cause mortality and the composite end point of fatal and nonfatal CVD events and had a somewhat better side-effect profile.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)¹²² was conducted in acute MI patients with left ventricular dysfunction and heart failure who were receiving optimal treatment that included ACE inhibitors, ARBs, β -blockers, and diuretics. The addition of the aldosterone antagonist eplerenone for a mean of 16 months significantly reduced all-cause mortality by 15% (95% CI 4% to 25%; $P = 0.008$) and the risk of death or hospitalization due to CVD by 13% (95% CI 5% to 21%; $P = 0.002$). The reduction in cardiovascular mortality was primarily due to the 21% reduction in sudden cardiac death in the eplerenone group compared with controls.¹²²

Other Standard Therapies

In a very wide range of patients with prior occlusive CVD, aspirin reduces the risks of nonfatal MI, nonfatal stroke, and vascular death.¹²⁷ Initiating aspirin therapy within 24 hours after the onset of symptoms of an acute MI also confers conclusive reductions in the risk of nonfatal reinfarction, nonfatal stroke, and total cardiovascular death.¹²⁷ Benefits have also been observed with other anticoagulant/antiplatelet agents.^{128–130} Large, long-term statin clinical trials, such as the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID), that firmly established the survival benefit of cholesterol-lowering therapy in post-MI patients were discussed in part I of this article.

Heart Failure

Systolic hypertension and ischemic heart disease are the main underlying causes of heart failure.¹³¹ Antihypertensive agents and lipid-lowering therapy not only can prevent or delay the progression to heart failure in post-MI patients but also benefit patients who already have heart failure by reducing CVD morbidity and mortality. Although heart failure occurs toward the end of the CVD continuum, the impact of therapy has greatly improved prognosis during the last 15 years. The treatment paradigm has evolved from treatment of severe heart failure to prevention of chronic heart failure with aggressive post-MI therapies and control of risk factors such as hypertension.

Vasodilators and Neurohormonal Blockers

A substantial number of clinical trials have examined the role of vasodilators and neurohormonal blockers in heart failure.^{132–156} The first successful trial was the Vasodilator Heart Failure Trial (V-HeFT),¹³² which showed a survival benefit from combined treatment with hydralazine and isosorbide dinitrate in patients with symptomatic heart failure. This combination is particularly effective in black patients with heart failure,¹³³ and the African-American Heart Failure Trial (A-HeFT)¹³⁴ reported a significant reduction in mortality of black patients with this combination versus placebo (6.2% versus 10.2%; $P=0.02$).

One of the first studies to demonstrate the benefits of ACE inhibitors in heart failure patients was CONSENSUS I.¹³⁵ Patients with severe heart failure (New York Heart Association [NYHA] class IV) were randomized to enalapril 5 to 20 mg BID ($n=127$) or placebo ($n=126$), both added to conventional heart failure therapy that included digitalis and diuretics. After an average follow-up of 188 days, enalapril had significantly reduced all-cause mortality (18% absolute reduction versus placebo; $P=0.002$) and improved heart failure symptoms (ie, improvement in NYHA classification). The beneficial effect on mortality was primarily caused by a reduction in deaths due to the progression of heart failure.¹³⁵

A large number of other clinical trials^{136–139} have confirmed that ACE inhibitor treatment significantly improves survival in patients with overt heart failure; as a result, ACE inhibitors are now considered standard therapy for these patients. Trials of ACE inhibitors and other types of neurohormonal blocking agents in heart failure are summarized in Table V of the online data supplement. The SOLVD treatment trial¹³⁶ demonstrated that in patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$, addition of enalapril to what was conventional heart failure therapy in the mid- to late 1980s led to a significant 16% reduction in risk of all-cause mortality compared with placebo (95% CI 5% to 26%; $P=0.0036$). The risk of combined death or hospitalization for worsening heart failure was also significantly reduced by 26% with enalapril (95% CI 18% to 34%; $P<0.0001$). Higher doses of ACE inhibitors may be necessary to reduce CVD morbidity and mortality in heart failure patients.¹³⁹ The Acute Infarction Ramipril Efficacy (AIRE) study¹³⁷ compared ramipril 1.25 to 5 mg BID ($n=1014$) with placebo ($n=992$) in patients surviving an acute MI who had symptoms of clinical heart failure. After an average follow-up of 15 months,

ramipril significantly reduced the risk of all-cause mortality by 27% (95% CI 11% to 40%; $P=0.002$) versus placebo. After completion of the main AIRE trial, 603 patients in the United Kingdom were enrolled in a 3-year extension (AIREX) to evaluate the long-term effects of continued ACE inhibitor therapy. The benefits of ramipril in heart failure patients were confirmed and, in fact, increased, with a 36% RR reduction for all-cause mortality (95% CI 15% to 52%; $P=0.002$) compared with placebo.¹³⁸

The Evaluation of Losartan in the Elderly (ELITE I) trial¹⁵⁶ reported that although losartan and captopril had similar effects on the primary end point of renal dysfunction, losartan significantly reduced all-cause mortality (a secondary end point). However, the ELITE II study, which was powered for mortality, did not confirm this result.¹⁴⁰ In fact, ELITE II showed no difference in all-cause mortality but did note a nonsignificant trend in favor of captopril compared with losartan for sudden cardiac death or resuscitated cardiac arrests. The Valsartan Heart Failure Trial (Val-HeFT)¹⁴¹ reported that valsartan, when added to standard heart failure treatment, significantly reduced the combined end point of cardiovascular mortality and morbidity by 13% at 23 months (97.5% CI 3% to 23%; $P=0.009$). This benefit was primarily attributed to a 24% reduction in hospitalization for heart failure with valsartan compared with placebo. More recently, the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program^{142–145} examined the role of treatment with candesartan versus placebo in 3 distinct heart failure populations: patients with LVEF $\leq 40\%$ who were taking an ACE inhibitor, those with LVEF $\leq 40\%$ who were not taking an ACE inhibitor, and those with LVEF $>40\%$. In the CHARM-Overall Program,¹⁴² candesartan was associated with a significant 10% decrease in the adjusted risk for all-cause mortality, the primary end point (95% CI 1% to 18%; $P=0.032$). The study also demonstrated reductions of the secondary end points of cardiovascular death and hospitalization for heart failure, primarily among patients with LVEF $\leq 40\%$.

The US Carvedilol Heart Failure study¹⁴⁶ assessed the effect of carvedilol on survival in patients with symptoms of heart failure and LVEF $\leq 35\%$. The significant and large positive effect of carvedilol on survival caused the early termination of the trial. Addition of carvedilol to conventional therapy with digoxin, diuretics, and ACE inhibitors led to a 65% reduction in RR of death compared with placebo (95% CI 39% to 80%; $P<0.001$) during a median follow-up of 6.5 months.¹⁴⁶ More recent evidence from other clinical trials using β -blockers^{148,150,151,153} indicates that the addition of these drugs to conventional therapy with diuretics and an ACE inhibitor or ARB significantly lowers the risk of all-cause mortality, sudden cardiac death, CVD death, and hospitalization in chronic heart failure patients.

Aldosterone-receptor blockade has beneficial effects in patients with heart failure. The Randomized Aldactone Evaluation Study (RALES)¹⁵⁴ evaluated the effects of spironolactone in patients with heart failure (LVEF $\leq 35\%$) who were already taking an ACE inhibitor (if tolerated), a loop diuretic, and, in most cases, digoxin. The trial was discontinued after a mean follow-up of 2 years because of a significant 30%

reduction in mortality with aldosterone blockade (95% CI 18% to 40%; $P < 0.001$). Spironolactone significantly reduced the risk of death due to progressive heart failure and sudden cardiac death. Active treatment also led to a significant improvement in heart failure symptoms.¹⁵⁴

Statins

A retrospective analysis¹¹³ of data from the 4S trial found that secondary prevention patients treated with simvastatin were significantly less likely to develop congestive heart failure during the 5 years of follow-up than patients taking placebo. This effect was attributed to the reduction of coronary events associated with long-term statin treatment. In another study of patients with advanced heart failure, statin therapy was associated with significantly improved survival, without transplantation, over a 2-year period.¹⁵⁷ This effect was independent of heart failure prognostic factors, including age, gender, heart failure cause and functional class, and total cholesterol level. A retrospective and unplanned reanalysis of data from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE)¹⁵⁸ found that 1 year of statin therapy was associated with a 62% (95% CI 35% to 77%; $P < 0.001$) lower risk of death among severe heart failure patients. In a retrospective analysis of 3-year follow-up data from the OPTIMAAL trial,¹⁵⁹ initiation of a statin, with or without a concomitant β -blocker, in patients who developed heart failure or signs of left ventricular dysfunction during hospitalization for acute MI was associated with significant reductions in all-cause mortality of 26% (statin) and 48% (statin plus β -blocker; both $P < 0.001$) after adjustment for other risk factors.

Cardiac Resynchronization Therapy

Approximately one third of patients with chronic heart failure have abnormal, slowed intraventricular conduction, commonly manifested as left bundle-branch block. Activation of the lateral wall of the left ventricle can be markedly delayed, with asynchronous left ventricular contraction such that part of the force generated by septal contraction is absorbed by expansion of the lateral wall. The subsequent contraction of the lateral wall occurs long after maximal septal contraction,¹⁶⁰ so that left ventricular contraction is inefficient. The sequence of left ventricular contraction can often be improved by pacing at the lateral left ventricular wall or simultaneously at the lateral left ventricle and in the right ventricle.^{161–163} Cardiac resynchronization therapy (CRT) has been demonstrated to improve functional capacity and survival.^{161–166} Clinical trials of CRT in patients with heart failure are summarized in Table VI of the online data supplement.

Pacing with CRT is often combined with use of implantable cardioverter defibrillators (ICDs). The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial¹⁶⁵ assessed optimal pharmacological therapy alone or with CRT using either a pacemaker or a combination of pacemaker-defibrillator. Optimal pharmacological therapy in all patients included diuretics (if needed), ACE inhibitors (or ARBs, if ACE inhibitors were not tolerated), β -blockers (unless not tolerated or contraindicated),

and spironolactone (unless not tolerated). Over 12 to 16 months, the primary composite end point of all-cause death or any hospitalization was decreased by $\approx 20\%$ with use of either device therapy compared with pharmacological therapy alone. Furthermore, a resynchronization device with defibrillation reduced the risk of death due to any cause (secondary end point) by 36% (95% CI 14% to 52%; $P = 0.003$).¹⁶⁵

The Cardiac Resynchronization–Heart Failure Trial (CARE-HF)¹⁶⁶ compared standard medical therapy alone to medical therapy with resynchronization in patients with NYHA class III and IV heart failure. The primary end point, time to death due to any cause or unplanned hospitalization for a major cardiovascular event, was significantly decreased by the addition of CRT therapy compared with medical therapy alone; importantly, death due to any cause occurred in 20% of the resynchronization group versus 30% of the medical therapy group ($P < 0.002$). Thus, the CARE-HF study demonstrates for the first time a mortality reduction with CRT alone, ie, without defibrillation.¹⁶⁶

Arrhythmias

Arrhythmias are associated with all types of CVD and are markers of adverse prognosis and often a late stage of the CVD continuum. Therapies that slow the progression of CVD also reduce both ventricular arrhythmias and atrial fibrillation.^{167–180} Selected trials of antiarrhythmic drug and device therapy are summarized in Table VII of the online data supplement.

Ventricular Arrhythmias and Sudden Cardiac Death

Antiarrhythmic Drug Therapy

Cardiac arrhythmias are a common cause of sudden death associated with coronary heart disease (CHD) and cardiomyopathies. Ventricular tachycardia degenerating to ventricular fibrillation is probably the most common sequence of events and is often the consequence of myocardial ischemia or MI.¹⁸¹ However, hypertrophy and depressed ventricular function are also associated with a risk of sudden arrhythmic death without acute infarction. Reentry through areas of ventricular infarction or scar is also a common mechanism. The risk of these arrhythmias increases as ventricular function declines.

Drugs that slow the progression of the CVD continuum can reduce the risk of sudden cardiac death. β -Blockers and antagonists of the RAAS decrease the risk of sudden cardiac death after MI and in heart failure.^{111,122,150,154,182} Attempts to develop antiarrhythmic drugs to prevent sudden cardiac death have been disappointing. Class I sodium channel–blocking agents and the potassium channel blocker D-sotalol increase mortality when administered chronically to patients with prior MI.^{183,184} The newer class III drugs dofetilide and azimilide do not increase mortality in patients with depressed ventricular function, provided that they are administered under careful observation with precautions taken to detect and treat QT prolongation and torsade de pointes.^{185,186} Although these drugs reduce atrial fibrillation, they do not improve survival. Trials of amiodarone suggest a neutral or modest benefit on decreasing mortality but also point to a substantial incidence of withdrawal due to toxicity.^{174,187} Ami-

odarone is clearly inferior to ICDs for preventing sudden cardiac death in high-risk patients who have been resuscitated from ventricular tachycardia or ventricular fibrillation.^{167–169} Thus, antiarrhythmic drug therapy for ventricular arrhythmias is now largely reserved for reducing the frequency of symptomatic arrhythmias in patients who have implanted defibrillators.¹⁸⁸

Implantable Cardioverter Defibrillators

Use of ICDs does not modify the progression of heart disease, but these devices do effectively terminate life-threatening ventricular arrhythmias when they occur. Compared with amiodarone therapy, ICDs reduce mortality in patients who have been resuscitated from ventricular fibrillation or ventricular tachycardia.^{167–169}

ICDs placed for primary prevention of arrhythmic death also reduce mortality in patients with depressed ventricular function who have not yet had sudden cardiac death. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)¹⁷⁴ assessed whether a single-chamber ICD or amiodarone would reduce mortality in patients with depressed left ventricular function (LVEF $\leq 35\%$) and symptoms of heart failure (NYHA class II or III) due to CHD or noncoronary heart disease. After 5 years of follow-up, mortality was decreased from 36% in the placebo group to 28% in the ICD group. Amiodarone had no benefit. The effect of ICD placement was consistent in both CAD ($P=0.05$) and non-CAD ($P=0.06$) causes of heart failure, but a benefit was not observed in patients with more advanced heart failure (NYHA class III).¹⁷⁴ Recurrent ventricular arrhythmias in patients with ICDs are a marker for increased mortality, despite the presence of the ICD, and thus are an indicator of progression of CVD.^{189,190}

Two additional trials assessed the use of ICDs specifically in patients with CAD and depressed left ventricular function. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)¹⁷² examined the effect on survival of patients ≥ 30 days after MI with left ventricular dysfunction (LVEF $\leq 30\%$) who were assigned to either conventional medical therapy or an ICD. Both groups could receive ACE inhibitors, β -blockers, or lipid-lowering drugs. Compared with conventional medical therapy, the ICD group had a significant 31% reduction in risk of death during an average follow-up of 20 months (95% CI 7% to 49%; $P=0.016$).¹⁷² This effect was independent of patient and disease characteristics, including sex, age, NYHA class, LVEF, diabetes mellitus, and hypertension. The Multicenter Unsustained Tachycardia Trial (MUSTT)¹⁷¹ used electrophysiological testing to identify a high-risk group of patients with inducible ventricular tachycardia and assessed whether antiarrhythmic treatment with medication and/or an ICD would reduce the risk of cardiac arrest and sudden cardiac death in patients with CAD, depressed left ventricular function (LVEF $\leq 40\%$), and non-sustained ventricular tachycardia. Although ICD and antiarrhythmic drug therapy were not randomized, patients who received an ICD had lower mortality at 5 years. Those who received an antiarrhythmic drug had no improvement in survival compared with patients randomized to no antiarrhythmic drug therapy.¹⁷¹

The benefit of ICDs in patients with CAD does not extend to patients with recent MI. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)¹⁷³ compared implantation of an ICD versus no ICD in 674 patients who had had an acute MI 6 to 40 days before randomization with LVEF $\leq 35\%$ and who were at high risk for ventricular arrhythmias. All-cause mortality (the primary study end point) did not differ significantly between the 2 groups. Although an ICD significantly decreased the RR of death due to cardiac arrhythmia compared with no ICD, it also was associated with a significant increase in nonarrhythmic death.¹⁷³

Atrial Arrhythmias

Atrial fibrillation is often a late manifestation in the CVD continuum. The incidence increases with age and with the severity of underlying heart disease.^{191,192} In animal models, atrial fibrillation is associated with development of fibrosis and electrical remodeling in the atria that can be diminished by ACE inhibitors and ARBs, and the reduced incidence of atrial fibrillation observed during therapy with these RAAS-blocking agents in post hoc analyses of post-MI and heart failure trials supports a potential effect of these therapies on development of the arrhythmia substrate in humans.^{193–195} The irregular and increased ventricular rate in atrial fibrillation can further depress ventricular function.¹⁹⁶ The strategy of using antiarrhythmic drugs to maintain sinus rhythm in patients with atrial fibrillation does not improve survival compared with simply controlling the ventricular rate and employing anticoagulation to reduce the risk of thromboembolism.^{175,176} Patients who maintain sinus rhythm have improved survival, but whether atrial fibrillation is merely a marker of disease severity or actually contributes to increased mortality through hemodynamic and thromboembolic adverse effects is not yet established.¹⁹⁷

Dual-Chamber Versus Single-Chamber Pacing

Dual-chamber cardiac pacing maintains atrioventricular synchrony and may better preserve normal physiological function compared with single-chamber ventricular pacing, but dual-chamber pacemakers are more expensive, are more complex to implant and program, and have a higher rate of complications.¹⁸⁰ Therefore, the effect of pacing mode on morbidity and mortality has been an area of intense interest. A number of trials have been completed.^{177–180} All trials have been relatively consistent in demonstrating a lower incidence of atrial fibrillation during follow-up in patients who receive physiological pacing modes (ie, atrial [AAI] or dual-chamber [DDD] pacing), as opposed to those receiving single-chamber ventricular (VVI) pacing. However, only the Danish pacing trial¹⁷⁷ demonstrated a lower mortality rate with physiological (atrial) pacing. This trial in patients with sick sinus syndrome also showed a lower incidence of severe congestive heart failure with physiological pacing.

In the Canadian Trial of Physiological Pacing (CTOPP),¹⁷⁸ dual-chamber pacing had little benefit over ventricular pacing in preventing stroke and cardiovascular death in patients with no chronic atrial fibrillation who were scheduled for pacemaker implantation for symptomatic bradycardia, although the annual rate of atrial fibrillation was significantly reduced

in the dual-chamber therapy group. Similar results were reported in 2010 patients with sinus-node dysfunction enrolled in the Mode Selection Trial in Sinus-Node Dysfunction (MOST),¹⁸⁰ which also reported that dual-chamber pacing resulted in a small but measurable improvement in the quality of life compared with ventricular pacing.

The potential long-term effect of right ventricular apical pacing was also investigated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial.¹⁷⁹ In this single-blind, randomized trial among patients meeting requirements for defibrillator implantation but with no need for antibradycardia pacing, dual-chamber pacing had no clinical advantage over ventricular backup pacing and may in fact have increased the risk of death or hospitalization for heart failure. This result may have been due to desynchronization that resulted from right ventricular stimulation in patients with existing significant ventricular dysfunction.¹⁷⁹

Target-Organ Damage Beyond the Heart: Brain and Kidneys

On the basis of accumulated evidence from clinical trials, the CVD continuum has been broadened to include implications for other organs beyond the heart, particularly the brain and kidneys. Again, interventions that interrupt the underlying pathophysiology of CVD have “downstream” benefits in preventing target-organ damage. For example, certain antihypertensive agents and statins decrease the risk of stroke, and trials of RAAS inhibition have shown renoprotective effects.

Stroke

Numerous types of intervention have proven useful in the prevention of stroke.^{198–219} Clinical trials of both primary and secondary prevention of stroke events are summarized in Table VIII of the online data supplement, and representative trials are briefly discussed below.

Antiplatelets

Aspirin and other antiplatelet agents have proven effective in secondary prevention of stroke, although clinical trials of aspirin for primary stroke prevention have generally yielded inconclusive results.²⁰⁷ The use of aspirin in acute ischemic stroke was evaluated in 2 megatrials, the Chinese Acute Stroke Trial (CAST)²⁰⁵ and the International Stroke Trial (IST).²⁰⁶ In both studies, aspirin was administered within 48 hours of symptom onset. Results of these trials indicate that aspirin produces a small but real reduction of $\approx 1\%$ in deaths or recurrent strokes in the first 2 to 4 weeks. A meta-analysis of 287 studies involving >200 000 patients suggests that the continuation of antiplatelet therapy in high-risk patients with a past history of stroke, transient ischemic attack, or MI also confers protection against recurrent stroke and other vascular events in the longer term (up to 2 years).²²⁰ Results from the Women’s Health Study in 39 876 initially healthy women ≥ 45 years of age who were followed up for 10 years showed that low-dose aspirin significantly reduced the risk of first stroke compared with placebo (17% RR reduction, 95% CI 1% to 31%; $P=0.04$). In that study, aspirin also significantly decreased the risk of major cardiovascular events and MI in women ≥ 65 years of age.²⁰⁷

Fibrinolytics

The efficacy of fibrinolytic therapy for acute ischemic stroke was shown in a randomized, double-blind trial of intravenous tPA conducted by the National Institute of Neurological Disorders and Stroke.²⁰⁸ Although tPA was associated with an increase in the incidence of intracerebral hemorrhage compared with placebo, fibrinolytic treatment with tPA within 3 hours of onset of stroke improved clinical outcome at 3 months.

Antihypertensive Drugs

The benefits of blood pressure lowering in preventing first or recurrent stroke are well established. For example, the Systolic Hypertension in Europe (Syst-Eur) trial²¹⁰ showed significant reductions over 2 years in stroke and CVD events and a trend toward a reduction in cardiovascular mortality with the moderately long-acting dihydropyridine calcium channel blocker nitrendipine compared with placebo. More recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)²¹¹ evaluated the benefits of treatment with an ACE inhibitor with or without a concomitant diuretic in hypertensive and normotensive patients with a history of stroke or transient ischemic attack. After ≈ 4 years of follow-up, ACE inhibitor treatment alone did not significantly reduce the risk of recurrent stroke or major vascular events compared with placebo; however, in combination with the diuretic (indapamide), perindopril did significantly reduce strokes and major vascular events.²¹¹ In PROGRESS, the ACE inhibitor alone lowered blood pressure by $\approx 5/3$ mm Hg compared with placebo, whereas the combination of perindopril and indapamide lowered blood pressure by 12/5 mm Hg; this increased blood pressure reduction may explain the difference in stroke outcomes. The Losartan Intervention For End point reduction in hypertension (LIFE) trial²¹² found that treatment with losartan produced a 25% greater reduction in risk of fatal or nonfatal stroke than atenolol (95% CI 11% to 37%; $P<0.001$).

Statins

Analysis of data from major statin clinical trials demonstrates that treatment with statins significantly decreases the risk of all strokes, primarily due to reductions in ischemic stroke. A post hoc analysis of data from the 4S trial found a significant 30% reduction in stroke over a median follow-up of 5 years (95% CI 4% to 48%; $P=0.024$).²¹⁵ Both the CARE trial and LIPID specified stroke as a prospective secondary end point. In CARE, the risk of stroke was significantly reduced by 32% with pravastatin (95% CI 4% to 52%; $P=0.03$). The Kaplan-Meier curves for estimates of all-cause stroke incidence began to diverge after ≈ 1 year of follow-up.²¹⁶ In LIPID, pravastatin reduced total stroke risk by 19% (95% CI 0% to 34%; $P=0.05$), with no effect on hemorrhagic stroke.²¹⁷ The Heart Protection Study (HPS),²¹⁸ which enrolled more than 5800 participants >70 years of age, reported that simvastatin significantly reduced the risk of first stroke by 25% (95% CI 15% to 34%; $P<0.0001$) in patients at high risk for CHD. The reduction in risk was primarily attributed to a decrease in the risk of ischemic stroke. An analysis²¹⁹ of pooled data from CARE, LIPID, and the West of Scotland Coronary Preven-

tion Study (WOSCOPS) found a significant reduction in stroke risk across all patient groups treated with pravastatin.

Renal Disease

Recent studies have drawn attention to the relationship between chronic kidney disease and cardiovascular disease.^{221,222} Findings from the VALIANT study suggest that even mild renal disease, as determined by the estimated glomerular filtration rate, should be considered a major risk factor for cardiovascular complications after an MI.²²² Clinical trials have demonstrated that blockade of the RAAS with either ACE inhibitors or ARBs reduces the progression of renal disease.^{223–232} Table IX of the online data supplement summarizes results of these trials. Whether improvements in renal function have a beneficial impact on cardiovascular risk requires further study.

Antihypertensive Drugs

The majority of patients with chronic renal failure have hypertension, and blood pressure must be controlled in these patients to prevent CVD complications and to delay deterioration of renal function.¹³¹ ARBs and ACE inhibitors, in particular, have shown beneficial renal effects in both diabetic and nondiabetic patients. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study²²⁴ showed that inhibition of the RAAS with losartan in patients with type 2 diabetes mellitus and nephropathy reduces the progression of renal disease, independent of blood pressure lowering. In the IRbesartan in patients with type 2 diabetes and MicroAlbuminuria (IRMA-2) study,²²⁵ irbesartan reduced the rate of progression to overt diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus and microalbuminuria during a 2-year period. As in RENAAL, these benefits appeared to be independent of blood pressure lowering. The Irbesartan Diabetic Nephropathy Trial (IDNT),²²⁶ which enrolled patients with more advanced renal disease than those in IRMA-2, showed that irbesartan has a favorable effect on renal function among patients with type 2 diabetes mellitus treated for a mean of 2.6 years. The MicroAlbuminuria Reduction with VALsartan (MARVAL) trial²²⁷ was designed to assess the blood pressure-independent effects of valsartan compared with amlodipine on urinary albumin excretion rates in patients with type 2 diabetes mellitus and microalbuminuria. Valsartan lowered urinary albumin excretion rates more effectively than did amlodipine.

Importantly, the African American Study of Kidney Disease and Hypertension (AASK)²³⁰ demonstrated that ACE inhibitor treatment not only reduces blood pressure but also has a significant renoprotective effect in this population. Treatment of hypertensive renal disease patients with ramipril significantly slowed the decline in glomerular filtration rate over 4 years of follow-up, and to a greater degree than with metoprolol or amlodipine.²³¹

Statins

Some evidence suggests that end-stage renal disease patients treated with statins may experience reduced total and CVD mortality.²³³ However, only a fraction (<10%) of patients with end-stage renal disease are prescribed statins. Further

research is needed to determine the role of statins in end-stage renal disease.

Summary of Clinical Trial Evidence

A review of evidence from clinical trials of different modalities, including lifestyle/behavioral changes, pharmacological therapies, and interventional procedures, demonstrates that interruption of pathophysiological processes leads to prevention of events across the entire CVD continuum. For example, inhibition of the RAAS not only prevents stroke and decreases the risk of CHD morbidity and mortality but also delays the progression of heart failure, diabetes, and renal disease. Modification of lipid levels, particularly LDL cholesterol lowering with statin therapy, reduces the risk not only of major coronary events but also of stroke in a wide variety of patients with and without diagnosed CHD and regardless of baseline LDL cholesterol levels. Statin therapy also lowers the risk of CHD in patients with diabetes, and possibly in those with renal disease. Clinical trial findings and results from pathophysiological studies show that any treatment may have application across the CVD continuum. The concept of individual events treated by individual drugs or procedures has evolved to a more comprehensive approach to the treatment of CVD.

Equipped with the knowledge that interruption of the chain of events that compose the CVD continuum confers cardioprotection, clinicians are increasingly charged with the task of considering the relative treatment effect of interventions at various stages of the continuum, as well as the cost-effectiveness of such interventions. In the case of cholesterol-modifying pharmacotherapy, for example, primary prevention measures probably have the greatest societal impact and long-term cardiovascular protective effects. However, the number needed to treat to prevent 1 event is relatively large, and the upfront cost to the healthcare system is high. As the risk for CVD increases, the cost effectiveness of an intervention tends to improve. Treating post-STEMI patients who have left ventricular dysfunction with inhibitors of the RAAS yields a much smaller number needed to treat because of the bigger upfront treatment effect. Another consideration is the burgeoning cost to the healthcare system to deliver expensive new therapies that are potentially life saving—for example, ICDs in patients with LVEF <30%.

The question of where to intervene and at what cost will also be influenced by the development of drugs that target the underlying pathophysiological mechanisms of CVD. The trials discussed in the present article were aimed at risk factors (hypertension, dyslipidemia) or at specific clinical events along the continuum (stable CAD, ACS). Some agents, however, have effects that appear to be independent of their primary target of action. For example, in addition to their impact on LDL cholesterol, statins have been associated with improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, and inhibition of inflammatory responses.²³⁴ In the future, drugs may be developed that have as their primary therapeutic targets underlying conditions, such as oxidative stress and decreased nitric oxide activity, that mediate pathological processes such as endothelial dysfunction.

Future Directions

Research into the biological processes underlying CVD has identified additional factors beyond established major risk factors that may indicate underlying disease, predict future events, or provide an assessment of therapeutic progress.²³⁵ For example, elevated levels of certain cytokines are suggestive of underlying atherosclerotic disease, and elevated concentrations of C-reactive protein (CRP) indicate increased risk of CHD events. In addition, evidence implicates certain factors as mediators and not only markers of disease. The purpose of this section is to introduce biomarkers, surrogate markers, genetic markers, and genomic markers to the concept of the CVD continuum. The role of these markers in CVD management is not yet established; however, growing evidence suggests that appropriate use of markers, either individually or in combination, may improve risk assessment and allow earlier and better-targeted interventions to reduce the incidence of CVD morbidity and mortality.²³⁶

Biomarkers

Because $\approx 20\%$ to 25% of all patients experiencing an initial vascular event have only 1 major CHD risk factor, and only half have elevated LDL cholesterol, research has continued into identifying other indicators of disease and predictors of future events.²³⁷ These indicators or predictors may be referred to as biomarkers, which are substances that can be measured in the plasma or the urine. The clinical usefulness of an individual biomarker depends on its ability to satisfy many criteria, including whether the marker identifies or predicts patients at risk, how easily and accurately it can be measured in the clinical setting, and whether therapeutic modification of the marker has a beneficial impact on cardiovascular risk. A causal role for any given biomarker in the pathological process remains a separate issue. Many potential biomarkers are under investigation, and only a select few are discussed here as examples.

Marker of Inflammation: CRP

Numerous prospective epidemiological studies have demonstrated that elevated CRP levels accurately predict sudden cardiac death, MI, and stroke.²³⁸ Other markers of inflammation, particularly plasma fibrinogen, show some potential as biomarkers; however, CRP, especially when measured with a high-sensitivity assay (hs-CRP), may hold the most promise as a marker of CVD risk because it combines the relevant characteristics of predictive value, assay reproducibility, access to the assay, and reasonable cost.²³⁷ The relation between CRP level and risk of future CVD events is independent of other CHD risk factors, including cholesterol, blood pressure, smoking, diabetes mellitus, and age. Furthermore, an analysis²³⁹ of data from the large-scale Women's Health Study found that although both CRP and LDL cholesterol were strongly associated with incidence of CVD events, levels of these markers were minimally correlated, and baseline CRP levels appeared to better predict future events than baseline LDL cholesterol levels. CRP may also add prognostic information to standard lipid measures when one assesses the risk of symptomatic peripheral arterial disease.²⁴⁰ Data from the PROVE IT-TIMI 22 trial also suggested a correlation be-

tween LDL lowering and reductions in CRP levels.³³ The possibility that CRP may be not just a marker but also an actual mediator of disease has been raised but remains unresolved.

Markers of Oxidative Stress

The excessive formation of reactive oxygen species creates an environment of oxidative stress that has been associated with hypertension and atherosclerosis. Markers of oxidative stress, such as oxidized LDL particles, are under investigation as possible biomarkers of CHD risk. Patients with CHD have significantly higher plasma levels of oxidized LDL than controls, regardless of blood pressure level, total cholesterol level, diabetes, or cigarette smoking.²⁴¹ Among patients with chronic heart failure, plasma levels of oxidized LDL were significantly ($P < 0.0001$) higher in patients with severe disease and were predictive of mortality independent of low LVEF and norepinephrine.²⁴² Regression analysis has demonstrated that the addition of oxidized LDL to a multivariate model composed of established CHD risk factors improves the predictive value of the model.²⁴³ However, no prospective studies have evaluated whether increased levels of oxidized LDL are a cause or a result of atherosclerosis, and the usefulness of oxidized LDL as a marker of CVD risk remains unclear.²³⁷ Many other potential markers of oxidative stress are being investigated, including but not limited to plasma or urine levels of F-2 isoprostane, modified tyrosines, and glutathione peroxidase-1. Whether these substances will have any clinical application remains to be determined.

B-Type Natriuretic Peptide

In normal persons, A-type natriuretic peptide concentrations are higher than B-type natriuretic peptide concentrations in the plasma.²⁴⁴ However, after MI or in heart failure patients, the B-type natriuretic peptide concentration is higher than that of A-type natriuretic peptide. High concentrations of B-type natriuretic peptide in heart failure patients have been associated with a greater risk of cardiovascular and overall mortality, including sudden cardiac death.²⁴⁵

Surrogate Markers

Although clinical events are the most valuable end points in a trial assessing efficacy of any given treatment, other measures of treatment effects, sometimes called surrogate markers, can be useful.²⁴⁶ A number of surrogate markers of target-organ damage have been investigated to determine their reliability in the clinical setting and usefulness in risk stratification.²³⁵ Structural surrogate markers reflect abnormalities in the arteries or the heart that result from the CVD process.²⁴⁶ Examples include left ventricular hypertrophy and carotid intima-media thickness. Functional surrogate markers are more complex and include indirect markers of structural changes or contributors to the structural changes themselves, such as proteinuria, endothelial dysfunction, and coronary artery calcification.

Left Ventricular Hypertrophy

A high baseline left ventricular mass value in initially normotensive patients predicts subsequent increases in blood pressure and the development of hypertension, independent

of other risk factors.²⁴⁷ In addition, elevated left ventricular mass is a strong predictor of CVD morbidity and mortality, regardless of blood pressure values or the presence of other CVD risk factors.²⁴⁷⁻²⁴⁹ Studies suggest that reversal of left ventricular hypertrophy as measured by electrocardiography or echocardiography may be useful as a surrogate end point for treatment of hypertension.²⁵⁰

Intima-Media Wall Thickness

Early stages of atherosclerosis may be assessed with B-mode ultrasonography. This noninvasive technique can measure the intima-media thickness of the carotid artery; intima-media thickness correlates with atherosclerosis risk factors and with clinical cardiovascular and cerebrovascular outcomes.²⁵¹ The intima-media thickness of extracranial carotid arteries has been proposed as an independent risk factor for MI and stroke.²⁵² Additional research is needed to determine whether interventions that affect intima-media thickness translate into a reduction in clinical events; however, carotid intima-media thickness appears to be a useful surrogate marker for atherosclerotic disease that may lead to CVD events.²⁵⁰

Proteinuria and Microalbuminuria

Proteinuria and microalbuminuria are independently associated with increased risk of CVD in diabetic and nondiabetic individuals.^{221,253} The underlying mechanisms by which microalbuminuria increases CHD risk are not known; however, endothelial dysfunction may play a role.²⁵³ In addition, microalbuminuria in combination with hyperinsulinemia is a strong predictor of CHD death and events.²⁵⁴ Microalbuminuria may be a marker of inflammatory status and may indicate more severe target-organ damage.²²¹ Both microalbuminuria and proteinuria are recognized surrogates of vascular disease in target organs such as the heart, brain, and kidney.²⁵⁵

Endothelial Dysfunction

Coronary endothelial dysfunction predicts future CVD events and atherosclerotic disease progression.²⁵⁶ Using acetylcholine and cold pressor tests to assess vasoconstrictor responses and intracoronary injections of nitroglycerin to assess vasodilator responses, a prospective study²⁵⁶ in patients at risk for atherosclerosis found that impaired vasodilator responses and increased vasoconstrictor responses were significantly associated with future coronary events, independent of established CHD risk factors. However, direct evidence demonstrating that improvement in endothelial function is associated with improvements in clinical outcomes is lacking.²⁵⁵

Coronary Calcification

Electron-beam computed tomography can provide an accurate assessment of coronary calcium.²⁵⁷ This technique is under investigation as a screening tool for atherosclerosis in asymptomatic individuals.²⁵⁰ The extent of coronary calcium is associated with a higher risk of acute MI or UA.²⁵⁷ Electron-beam computed tomography may be useful in identifying calcification burden and pattern (eg, nodule versus scattered), which is related to higher risk of plaque complication.²⁵⁸ However, it does not rule out the presence of noncalcified plaque, including high-risk or vulnerable plaque. Research is ongoing to refine computed tomography techniques to assess coronary calcification and to determine how

these measurements can be used in risk stratification. As with other investigational screening tools, a key issue is establishing how the results from such a test would change patient management compared with interventions that would be implemented on the basis of results of more standard, and less expensive, evaluation tools.

Genetic Markers

The sequencing and mapping of the human genome may eventually provide researchers with the opportunity to identify genetic variations that lead to CVD.²³⁵ A variant in the DNA code that is associated with a specific disease phenotype may be used as a genetic marker. Researchers have identified a number of genetic markers that are associated with an increased risk of CVD; a review of some of these genetic markers was provided by Gibbons et al.²⁵⁹

CVD is a polygenic disease that develops through interaction among multiple genes, as well as through interaction with environmental and physiological factors.²⁵⁹ Therefore, research is more focused on identification of groups of markers, known as haplotypes, which occur together on 1 chromosome and are passed along together in families or populations, rather than on identification of a single-nucleotide polymorphism (a variant at a single DNA base pair). However, some aspects of CVD are monogenic, such as familial hypercholesterolemia and certain forms of hypertension, and study of these diseases has led to important treatment advances that are beneficial to a broad range of CVD patients.²⁵⁹ Studies of differences in patient responses to pharmacotherapy have also revealed important genetic variants, including polymorphisms that influence the response to statins and ACE inhibitors.

The use of newer methods and techniques, such as real-time reverse-transcription polymerized chain reaction, expressed sequence tag technology, DNA microarrays, and serial analysis of gene expression, will help elucidate the role of marker genes in both the healthy and disease states. In addition, intensive research efforts have begun to extend our understanding and use of genetic markers. The development of genomics has been followed by proteomics and metabolomics, which determine the structure, expression, localization, biochemical activity, interactions, and cellular roles of proteins and metabolites, respectively.^{260,261} As technology advances and research continues, it is reasonable to expect that in the future, clinicians will be able to use these genetic markers to identify individuals at high risk for complications of atherosclerosis, as well as those who will benefit most from specific treatments.²⁵⁹

Cell-Based Therapy

Conditions such as ischemic cardiomyopathy and MI are associated with irreversible loss of cardiac muscle (cardiomyocytes). In patients with end-stage heart disease, even optimal pharmacotherapy and interventional cardiology have limited ability to improve outcomes. The loss of cardiac muscle, however, might be compensated for if muscle cells could be regenerated. The identification of adult stem or progenitor cells has led to widespread interest in the use of cell transplantation for the regeneration and repair of the

myocardium. Numerous experimental studies using a range of cell-based therapies with the objective of improving cardiac repair have provided encouraging data to support this approach.²⁶² Clinical studies performed to date can be distinguished as those conducted in patients with acute MI and those that involve patients with chronic heart failure. The pathophysiological processes targeted in these conditions are fundamentally different, and so are the cell types and modes of delivery used. Although promising, the results of these trials have produced more questions than answers,^{262,263} and much research needs to be performed before cell-based cardiac regeneration becomes a practical treatment option.

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