Diabetes, Hypertension, and Renal Insufficiency in Post-Myocardial Infarction Cardiovascular Risk

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The prognosis for patients who suffer myocardial infarctions (MIs) is poor, with 22% of male and 46% of female survivors being disabled by heart failure within 6 years. Many well-established risk factors for increased morbidity and mortality post-MI are closely linked to the metabolic syndrome and associated with over-activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Results from numerous large-scale clinical endpoint trials have shown that blocking the deleterious effects of these systems with either an angiotensin-converting enzyme inhibitor or a ß-adrenoceptor antagonist significantly reduces the risk of mortality and cardiovascular events in post-MI patients. Results from 1 recent study of the ß-blocker, carvedilol, have shown further that these benefits extend to high-risk patients with either diabetes or hypertension.
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Key words: Angiotensin • ß-blocker • Diabetes • Heart failure • Myocardial infarction

Approximately 1.1 million Americans will have a new or recurrent myocardial infarction (MI) in 2003.[1] Most individuals who experience MIs survive these events, but post-MI morbidity and mortality for survivors is high. Results from the Framingham Heart Study showed that 22% of men and 46% of women who survived MIs were disabled by heart failure within

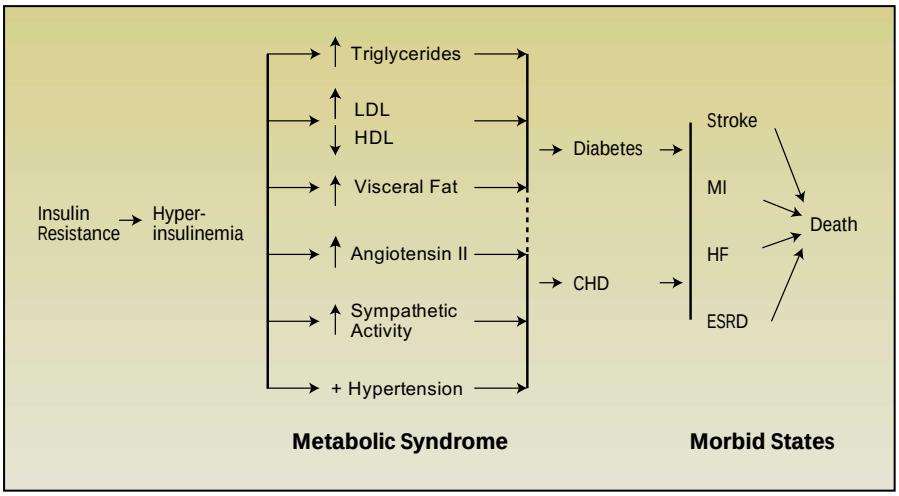

Figure 1. *Insulin, the metabolic syndrome, and the progression of cardiovascular disease . LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure; ESRD, end-stage renal disease. Data from Elliott[8] and Ford.[9]*

6 years.[2] Thus, determining the characteristics of patients at the highest risk post-MI and delineating the best approaches to treating them are important healthcare priorities. This brief review considers both of these issues with emphasis on clustering of cardiovascular risk factors, neurohormonal activation as a key determinant of risk, and interventions that have proved effective in reducing cardiovascular risk post MI.

Risk Factors in Post-MI Patients

Results from a number of studies have identified predictors of mortality in post-MI patients. They include advanced age,[3] low left ventricular ejection fraction,[3] arrhythmia,[3] high creatine kinase MB mass,[4] increased heart rate,[5] elevated blood urea nitrogen,[5] and the presence of hypertension or diabetes.[6,7]

Many of these risk factors and others are associated with metabolic syndrome, which is a key risk factor for the development and progression of cardiovascular disease (Figure 1).[8,9] The progression of metabolic syndrome is thought to be initiated by the development of insulin resistance and hyperinsulinemia, which give rise to multiple abnormalities, including hypertriglyceridemia, elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, increased visceral fat, and activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), as reflected by elevated catecholamines and angiotensin II, respectively. These metabolic abnormalities increase the risk of diabetes, hypertension, and ultimately for cardiovascular disease and its manifestations (eg, stroke, MI, heart failure, end-stage renal disease), and death.[9]

Evaluation of data collected in the third National Health and Nutrition Examination Survey (NHANES III) in light of criteria for metabolic syndrome set forth by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) indicates that about 25% of people in the United States meet the criteria for having metabolic syndrome.[9] It is also important to note that the prevalence of this syndrome increases markedly with age. About 7% of people younger than 30 years have metabolic syndrome versus nearly 45% of those age 60 years or older.[9] Thus, there are a very large number of individuals in the United States who are now at high risk for cardiovascular disease and who would have a poor prognosis post-MI, and this number is likely to increase as the population ages.

Diabetes, Hypertension, and Cardiovascular Risk

The presence of either diabetes or hypertension greatly increases cardiovascular risk and may also compound the impacts of other risk factors.

Diabetes

Diabetes is a significant independent risk factor for coronary heart disease, and its presence with other risk factors more than doubles the risk for fatal coronary heart disease.[10] Stamler and colleagues[10] assessed predictors of cardiovascular mortality in 347,978 men aged 35 to 57 years screened as part of the Multiple Risk Factor Intervention Trial (MRFIT). There were 603 cardiovascular deaths among 5163 men who reported taking medication for diabetes over 12 years of follow-up versus 8965 deaths among 342,815 men not taking medication for diabetes. The absolute risk of cardiovascular disease–related death was much higher for men with diabetes at every age stratum, ethnic background, and risk factor level. The absolute risk of cardiovascular death increased more steeply for men with diabetes so

Metabolic syndrome is a key risk factor for the development and progression of cardiovascular disease.

that their absolute excess risk for mortality was higher than that among men without diabetes for each risk factor and combination of factors. Mortality rates increased in men with diabetes more than expected on the basis of simply adding the effects of diabetes and other risk factors. The cardiovascular risk for a diabetic individual with only 1 additional risk factor exceeded that for a non-diabetic patient with 3 risk factors. All of these results are consistent with epidemiologic data collected by the American Heart Association, which show that three quarters of people with diabetes mellitus die of some form of heart or blood vessel disease.[1]

The cardiovascular risk for a diabetic individual with only 1 additional risk factor exceeded that for a non-diabetic patient with 3 risk factors.

The prognosis is also very poor for patients with diabetes who suffer an MI. Patients with diabetes who suffered a prior MI had a marked reduction in their survival over an 8-year follow-up period in the East-West study in Finland.[11] A surprising finding in this study was that patients with diabetes, but without a history of MI, had survival rates similar to those of non-diabetic individuals who had suffered a prior MI. Most importantly in the present context, the 7-year incidence of recurrent MI was 45% for patients with diabetes and a prior MI versus 18.8% for patients with a history of MI but without diabetes.

Hypertension

As noted above, antecedent hypertension is associated with a poor prognosis in post-MI patients. This statement is supported by results from Richards and colleagues[6] who assessed outcomes over a follow-up of 2 years in 1093 consecutive, acute MI patients (436 hypertensive and 657 normotensive). Antecedent hypertension was associated with significantly increased risk of inpatient (8.1% vs 4.4%) and post-discharge mortality (9.5% vs 5.5%), as well as inpatient (33% vs 24%) or subsequent heart failure requiring readmission to the hospital (12.4% vs 5.5%).

Improving Outcomes in High Risk Post-MI Patients

The results summarized in the preceding sections indicate that it is relatively straightforward to identify post-MI patients at high risk for morbidity and mortality. Given this, it is important to ask how best to reduce the risk for these individuals. Results from a number of studies have addressed this issue, and their results are considered in the following sections.

Improving Glycemic Control in Patients with Diabetes

Control over blood glucose is central to the treatment of patients with diabetes, and it is reasonable to believe that it might improve cardiovascular outcomes for individuals with this disease. However, results from the United Kingdom Prospective Diabetes Study (UKPDS 33) indicate that this is not the case.[12] The UKPDS investigators compared the effects of intensive blood-glucose control plus either sulphonylurea or insulin with conventional treatment on the risk of microvascular and macrovascular complications in 3867 patients in whom type 2 diabetes was newly

Deleterious Hemodynamic Effects of Neurohormonal Activation in Heart Failure

Neurohormonal compensation mediated by the sympathetic nervous system (SNS) and renin- angiotensin-aldosterone system (RAAS), occurs in an effort to maintain normal circulation in patients with heart failure, including that associated with myocardial infarction (MI). The RAAS is activated in response to reduced cardiac output (CO). This produces increased levels of plasma renin, angiotensin II, and aldosterone, resulting in both vasoconstriction and sodium retention. Local production of angiotensin II increases arterial tone in peripheral blood vessels and augments the release of norepinephrine from sympathetic nerve terminals in the heart, contributing to ventricular remodeling and increased risk for ventricular arrhythmias. Activation of the SNS nervous system is a homeostatic response aimed at maintaining circulatory stability during decreased CO. Elevated levels of norepinephrine down-regulate cardiac ß-receptors and decrease the heart's response to sympathetic stimulation. This contributes to decreased exercise tolerance in patients with heart failure. Plasma norepinephrine levels are directly correlated with mortality in patients with heart failure. Activation of neurohormonal systems in patients with heart failure increases peripheral resistance, lowers left ventricular ejection fraction, and contributes to a progressive decline in systolic function in these individuals.[1]

Bales AC, Sorrentino MJ. Causes of congestive heart failure. Prompt diagnosis may affect prognosis. *Postgrad Med.* 1997;101:44-49, 54-56.

diagnosed. Over 10 years of follow-up, intensive therapy that reduced glycosylated hemoglobin (HbA1c) to 7.0% versus 7.9% for the patients who received conventional therapy, significantly decreased the risk of any diabetes-related endpoint, any diabetes-related death, and microvascular disease. However, reductions in risks for MI and all-cause mortality with intensive treatment versus conventional therapy did not reach statistical significance.

Improving Control over Blood Pressure in Patients with Diabetes

In contrast to the results presented immediately above, findings from UKPDS 38[13] showed that achievement of tight blood pressure control in patients with diabetes and hypertension significantly reduced the risk for cardiovascular events. In this trial, 1148 hypertensive patients with type 2 diabetes were treated with captopril or atenolol to achieve systolic blood pressure/diastolic blood pressure < 150/85 mm Hg or < 180/105 mm Hg and were monitored for 8.4 years. Study results showed that tight blood pressure control reduced the risk of MI by 21%, of renal failure by 42%, of stroke by 44%, and of heart failure by 56%. A key aspect of the results from UKPDS 38 was that the backbone of antihypertensive therapy for patients in this study was either an angiotensin-converting enzyme (ACE) inhibitor or a ß-blocker. This is important because these agents interfere with neurohormonal activation, which plays a pivotal role in the onset and progression of cardiovascular disease, including that observed post-MI.

Neurohormonal System, Metabolic Syndrome, and Cardiovascular Risk

The insulin resistance and hyperinsulinemia characteristic of the metabolic syndrome initiate a chain of events that results in activation of both the SNS and the RAAS (Figure 2).[14] Increased activation of each of these systems contributes significantly to cardiovascular risk.

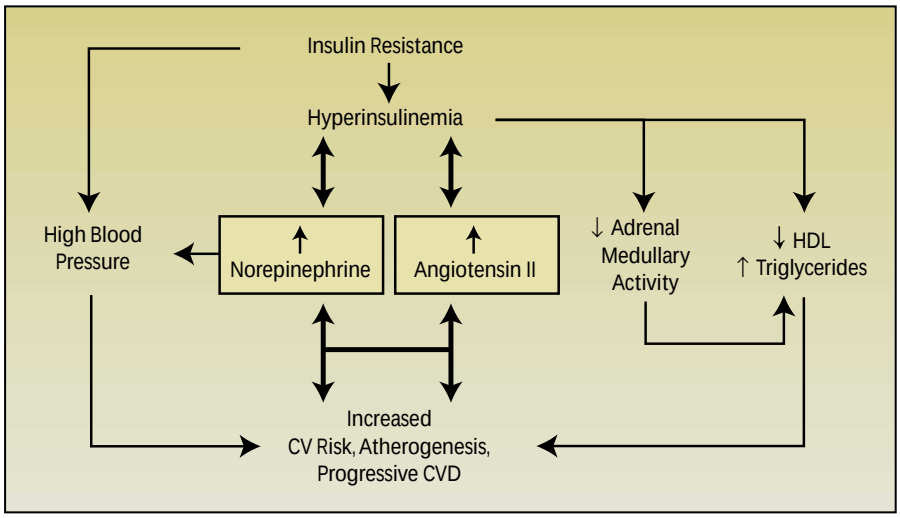

Figure 2. *Role of neurohormonal activation in cardiovascular disease risk and progression. HDL, high-density lipoprotein; CV, cardiovascular; CVD, cardiovascular disease. Adapted with permission from Reaven et al.[14] Copyright © 2003 Massachusetts Medical Society.*

Renin-Angiotensin-Aldosterone System and ACE Inhibitors in the Treatment of Post-MI Patients

Angiotensin II, the effector hormone of the RAAS, acts both as a circulating hormone and as a locally acting paracrine/autocrine/intracrine factor. Angiotensin II has a multiplicity of adverse effects on the heart, blood vessels, and kidneys. Increased levels of angiotensin II produce elevated resistance to the pumping function of the myocardium, vasospasm, left ventricular remodeling, arrhythmias, alterations in the coagulation-fibrinolysis equilibrium, increased oxidative stress, and pro-inflammatory actions.[15] Angiotensin II also has mitogenic and trophic actions on vascular smooth muscle cells that lead to vascular hypertrophy.[16] The multiple effects of angiotensin II in the kidney have also been well described. It plays a central role in the maintenance of glomerular filtration rate and sodium balance, increases the resistance of efferent arterioles, enhances tubular reabsorption of sodium in proximal tubules, stimulates the release of aldosterone from the adrenal cortex, increases cell growth, and promotes inflammatory responses.[17]

Given the multiple deleterious effects of over-activation of the RAAS on the cardiovascular system and kidney, it should not be surprising that blocking the formation of angiotensin II with an ACE inhibitor has significant positive effects on mortality in patients with heart failure or post-MI left ventricular dysfunction. Garg and Yusuf[18] carried out a meta-analysis of results from large-scale clinical endpoint studies in which an ACE inhibitor was included as part of the therapeutic regimen for patients with heart failure. Their results showed that overall mortality for patients treated with an ACE inhibitor (most often enalapril, captopril, ramipril, quinapril, or lisinopril) was 15.8% versus 21.9% for patients who did not have a drug

Table 1
Endpoint Results from the CAPRICORN Trial

	Carvedilol group (n=975)	Placebo group (n=984)	Hazard ratio (95% CI)	*P* value
Primary endpoints				
All-cause mortality	116 (12%)	151 (15%)	0.77 (0.60-0.98)	0.031
All-cause mortality or cardiovascular-cause hospital admission	340 (35%)	367 (37%)	0.92 (0.80-1.07)	0.296
Secondary endpoints				
Sudden death	51 (5%)	69 (7%)	0.74 (0.51-1.06)	0.098
Hospital admission for heart failure	118 (12%)	138 (14%)	0.86 (0.67-1.09)	0.215
Other endpoints				
Cardiovascular-cause mortality	104 (11%)	139 (14%)	0.75 (0.58-0.96)	0.024
Death due to heart failure	18 (2%)	30 (3%)	0.60 (0.33-1.07)	0.083
Non-fatal myocardial infarction	34 (3%)	57 (6%)	0.59 (0.39-0.90)	0.014
All-cause mortality or non-fatal myocardial infarction	139 (14%)	192 (20%)	0.71 (0.57-0.89)	0.002

Reproduced with permission from Dargie.[24]

from this class included in their therapy. Reduced mortality was noted for patients in all age groups and New York Heart Association classes.

Sympathetic Nervous System and Use of ß-Blockers to Treat Post-MI Patients

As for the RAAS, excessive activation of the sympathetic nervous system produces a variety of deleterious cardiovascular effects. Injury to the heart, such as an MI, results in activation of the sympathetic nervous system. This activation produces a variety of negative effects in the heart, vasculature, and kidneys. In the heart, sympathetic activation promotes ongoing cardiac injury, hypertrophy, and adverse remodeling, and increases the risk for life-threatening arrhythmias. Sympathetic nervous system activation also produces arterial and venous vasoconstriction, increasing cardiac preload and afterload. Renal effects of sympathetic nervous system activation include vasoconstriction, salt and water retention, and increased renin release, which elevates the activity of the RAAS (see above). Sympathetic activation can also increase hematocrit and precipitate a procoagulant state. All of these actions contribute to the progression of cardiovascular disease.[14,19,20]

Effects of ß-Blockers on Cardiovascular Morbidity and Mortality

The findings briefly summarized in the preceding paragraph lead to the expectation that blocking the deleterious actions of the sympathetic nervous system has the potential to significantly improve outcomes for post-MI patients. Results from clinical trials have demonstrated that this is, indeed, the case. Freemantle and colleagues[21] carried out a meta-regression analysis of outcomes from clinical trials in which post-MI patients were treated with a ß-blocker. Analysis of results from 82 randomized short- or long-term trials that compared ß-blockers with control therapy and included a total of 54,234 patients indicated that long-term treatment with a ß-blocker significantly reduced the risk of mortality by 23% versus control therapy. The risk reduction with short-term ß-blocker therapy was only 4%. Meta-regression analysis of results from the long-term studies did not

demonstrate significantly reduced effectiveness for drugs with cardioselectivity, but it did indicate a trend toward decreased benefit for ß-blockers with intrinsic sympathomimetic activity.

In addition to reducing post-MI mortality, ß-blocker therapy also significantly decreases mortality in patients with diabetes and coronary artery disease. Jonas and colleagues[22] assessed 3-year mortality in 2723 patients with type 2 diabetes who did (n = 911) or did not (n = 1812) receive ß-blocker therapy in the Bezafibrate Infarction Prevention study. Total mortality and cardiac mortality were reduced by 44% and 42%, respectively, for the patients who received ß-blockers versus those who did not. Three-year survival curves showed significant differences in mortality with increasing divergence.

It is important to note that ß-blockers differ substantially in their effects on insulin sensitivity and thus perhaps also in their overall effects on morbidity and mortality in patients with diabetes. Review of metabolic studies has shown that newer vasodilating ß-blockers, such as dilevalol, carvedilol, and celiprolol, have positive effects on insulin sensitivity, while older agents, including pindolol, atenolol, metoprolol, and propranolol, have negative effects on this cardiovascular risk factor.[23]

The effectiveness of one of these newer ß-blockers, carvedilol, in reducing morbidity and mortality in patients with left ventricular dysfunction after acute MI has been evaluated in the CAPRICORN trial, in which 1959 patients were treated with ß-blocker or placebo in addition to usual therapy and observed until clinical endpoints were reached. Study results showed that carvedilol significantly decreased the risks for all-cause mortality, cardiovascular mortality, non-fatal MI, and all-cause mortality plus non-fatal MI (Table 1).[24]

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Effects of ß-Blockers on Renal Function

While much of the positive effect of ß-blockers on morbidity and mortality in patients with heart disease, including those who have experienced an MI, is probably attributable

Main Points

- The progression of metabolic syndrome may be initiated by the development of insulin resistance and hyperinsulinemia, leading to hypertriglyceridemia, elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, increased visceral fat, and activation of the sympathetic nervous system and renin-angiotensin-aldosterone system.
- Diabetes is a significant independent risk factor for coronary heart disease, and its presence with other risk factors more than doubles the risk for fatal coronary heart disease.
- Antecedent hypertension is associated with significantly increased risk of inpatient and post-discharge mortality as well as inpatient or subsequent heart failure requiring readmission to the hospital.
- According to the findings of the United Kingdom Prospective Diabetes Study, tight blood pressure control in patients with diabetes and hypertension significantly reduces the risk for cardiovascular events.
- Blocking the formation of angiotensin II with an angiotensin-converting enzyme (ACE) inhibitor has significant positive effects on mortality among patients with heart failure or left ventricular dysfunction post myocardial infarction (MI).
- The CAPRICORN trial has evaluated the effectiveness of carvedilol, a newer ß-blocker. Results showed that carvedilol significantly decreased the risks for all-cause mortality, cardiovascular mortality, nonfatal MI, and all-cause mortality plus nonfatal MI. Additional analysis of study results indicated that the benefits of carvedilol were not diminished in patients with either diabetes or hypertension.
- It is important to emphasize that the benefits seen with ACE inhibitors and ß-blockers in post-MI patients and others with heart failure are not achieved with all classes of blood pressure–lowering agents. For example, calcium channel blockers have repeatedly been shown to increase cardiovascular events and/or death in patients with heart failure and diabetes.

to its actions in the myocardium and vascular system, it is also important to note that at least some of these agents have positive effects on indices of renal function. These actions may also improve the prognosis for post-MI patients since elevated blood urea nitrogen is associated with increased risk of mortality in this setting (see above).

Recent results from a pilot study carried out at The Ohio State University Davis Heart & Lung Research Institute in Columbus, OH, indicated that 6 months of treatment with carvedilol, but not with placebo or the $ß_1$-selective adrenoceptor antagonist metoprolol, significantly improved both renal blood flow and glomerular filtration rate in patients with heart failure. These results suggest that the α_1-adrenoceptor antagonist activity possessed by carvedilol may contribute significantly to its positive effects on renal function.

Conclusions

The results summarized in this brief review underscore the point that post-MI patients have very high morbidity and mortality that can be readily predicted from a number of well-defined risk factors. These patients are likely to have metabolic syndrome as well as excessive activation of both the RAAS and SNS. Blocking the activity of either of these systems with an ACE inhibitor or ß-blocker, respectively, has been repeatedly shown to improve outcomes in patients with heart failure, and recent results from CAPRICORN indicate that this benefit extends to very high-risk patients with either diabetes or hypertension. In closing, it is important to emphasize that the benefits seen with ACE inhibitors and ß-blockers in post-MI patients and others with heart failure are not achieved with all classes of blood pressure–lowering agents. For example, calcium channel blockers have been shown repeatedly to increase cardiovascular events and/or death in patients with heart failure and diabetes.[25] ■

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