DIABETES AND CARDIOVASCULAR DISEASE: The emerging role of the endothelium and implications for treatment

Highlights of a Vascular Biology Working Group Special Adjunct Faculty Meeting presented at the American Diabetes Association 60th Scientific Sessions in San Antonio, Texas

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**Educational Objectives**

On successful completion of this program, you should be able to complete the following objectives:

- Describe the pathophysiologic mechanisms in diabetes and hypertension and how they impair endothelial function and increase the risk of coronary heart disease.
- Discuss the role of tissue ACE inhibition in improving endothelial function and enhancing cardiovascular outcomes in hypertensive diabetic patients.
- Employ therapeutic options for improving endothelial function and decreasing the risk of cardiovascular disease in hypertensive diabetic patients.

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The emerging role of the endothelium and implications for treatment

**OPTIMAL MANAGEMENT OF DIABETIC HYPERTENSIVE PATIENTS**

James R. Sowers, MD  
*Professor of Medicine and Cell Biology  
Chief, Endocrinology, Diabetes,  
and Hypertension  
SUNY Health Sciences Center at Brooklyn  
Brooklyn, New York*

**NEW INSIGHTS INTO ATHEROSCLEROSIS: OPTIONS FOR INTERVENTION**

Jorge Plutzky, MD  
*Director, Vascular Disease  
Prevention Program  
Brigham and Women’s Hospital  
Boston, Massachusetts*

**RAS AND THE FIBRINOLYTIC SYSTEM: MECHANISTIC INSIGHTS FOR DIABETES CONTROL**

Douglas E. Vaughan, MD  
*Professor of Medicine and Pharmacology  
Vanderbilt University School of Medicine  
Chief, Division of Cardiovascular Medicine  
Vanderbilt University Medical Center  
Nashville, Tennessee*

Beecham, Merck & Co., and Bristol-Myers Squibb, and serves on the Speakers’ Bureaus for SmithKline Beecham, Merck & Co., and Pfizer Inc.  
Dr. Plutzky has received grant/research support for clinical trials from Fournier, Abbott, and Merck & Co. He serves on the Speakers’ Bureaus for Merck & Co., Bristol-Myers Squibb, Pfizer Inc, SmithKline Beecham, Bayer Corporation, Takeda, KOS, and Abbott.

Dr. Sowers reports no conflicts of interest.  
Dr. Vaughan has received grant/research support from Pfizer Inc and Merck & Co. He serves as a consultant to Pfizer Inc and Wyeth-Ayerst, and on the Speakers’ Bureau for Pfizer Inc.  
Dr. Weintraub has received grant/research support from Pfizer Inc and serves on the Speakers’ Bureaus for Bristol-Myers Squibb, Merck & Co., AstraZeneca, and Pfizer Inc.
The beneficial effects of tissue ACE inhibition in patients with coronary artery disease (CAD) and normal left ventricular (LV) function have been demonstrated in recent tissue ACE trials, including TREND, BANFF, QUO VADIS, QUIET, and HOPE (Table 1). The findings of these trials suggest a broader role for ACE inhibition in the treatment and prevention of ischemic disease.

TREND (TRIAL ON REVERSING ENDOTHELIAL DYSFUNCTION)

In the TREND trial, 6 months of therapy with quinapril 40 mg significantly improved vasodilation in normotensive patients with CAD and preserved LV function. TREND substudies showed 1) that endothelial dysfunction was accelerated in smokers, but not in smokers treated with quinapril; and 2) that quinapril-treated patients with higher LDL-C levels (>130 mg/dL) had far more improvement in endothelial function than a group with lower LDL-C levels.

BANFF (BRACHIAL ARTERY ULTRASOUND NORMALIZATION OF FOREARM FLOW)

BANFF assessed the effects of the ACE inhibitors quinapril and enalapril, the angiotensin II type 1 receptor antagonist losartan, and the calcium antagonist amlodipine on endothelial function in patients with CAD. These drugs were given in doses to cause similar reductions in blood pressure. In 8-week trials of each drug, only quinapril improved endothelial function significantly, suggesting that ACE inhibitors and other vasoactive agents vary in their ability to enhance endothelial function. No improvement was seen in patients with the DD ACE genotype, which increases ACE activity, indicating that ACE genotype influences the response to quinapril.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Major result</th>
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</thead>
<tbody>
<tr>
<td>TREND</td>
<td>129</td>
<td>Quinapril</td>
<td>↑ Coronary dilation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Endothelial function in smokers and those with higher LDL-C</td>
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<tr>
<td>BANFF</td>
<td>56</td>
<td>Quinapril</td>
<td>↑ Endothelial function</td>
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<td></td>
<td>55</td>
<td>Enalapril</td>
<td>NS</td>
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<td></td>
<td>38</td>
<td>Losartan</td>
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<td></td>
<td>45</td>
<td>Amlodipine</td>
<td>NS</td>
</tr>
<tr>
<td>QUO VADIS-I</td>
<td>187</td>
<td>Quinapril</td>
<td>Blocks Ang I conversion to Ang II in vascular preparations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Captopril</td>
<td>NS</td>
</tr>
<tr>
<td>QUO VADIS-II</td>
<td>149</td>
<td>Quinapril</td>
<td>↓ 80% in ischemic events</td>
</tr>
<tr>
<td>QUIET</td>
<td>1750</td>
<td>Quinapril</td>
<td>Trend towards ↓ nonfatal ischemic events</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Atherosclerosis progression with ↑ LDL-C</td>
</tr>
<tr>
<td>HOPE</td>
<td>9297</td>
<td>Ramipril</td>
<td>↓ 22% risk for MI, CVD death, stroke</td>
</tr>
</tbody>
</table>

Table 1. Tissue ACE trials in CAD patients with preserved LV function.
QUO VADIS (Effects of Quinapril on Vascular ACE and Determinants of Ischemia)

QUO VADIS compared the effects on ischemia of the tissue-avid ACE inhibitor quinapril and the non-tissue avid agent captopril in patients undergoing coronary artery bypass grafting. Studies in artery segments removed at surgery showed that 1-month preoperative treatment with quinapril, but not with captopril, significantly reduced vascular angiotensin II formation compared with placebo. These observations suggest that there are functional differences at the vascular tissue level between the two drugs when given in doses that cause similar reductions in blood pressure. In addition, patients who took quinapril for 1 year had an 80% reduction in ischemic events compared with placebo.

“The benefits of ACE inhibition probably relate to an improvement in endothelial function . . .”

QUIET (Quinapril Ischemic Events Trial)

QUIET investigated the effects of long-term tissue ACE inhibition on atherosclerosis progression in 1750 low-risk patients with CAD and normal LV function. Participants were enrolled shortly after successful percutaneous coronary revascularization and randomly assigned to treatment with quinapril 20 mg/day or placebo. After 3 years, the quinapril group showed a trend toward a greater reduction in cardiac deaths, myocardial infarction (MI), and resuscitated cardiac arrest, but the difference between groups was not significant. Angiographic changes also were similar in a 3-year follow up of randomly selected cohort patients. Several factors may have confounded the outcome, including use of too low a drug dose, too low a patient risk group, too brief a duration of treatment, or too few patients. As seen in the TREND study, a subgroup analysis showed that the benefits of quinapril may be related to LDL-C level. In patients with high LDL-C levels (≥130 mg/dL), atherosclerosis did not progress in the quinapril group, but was accelerated in the placebo group.

HOPE (Heart Outcomes Prevention Evaluation)

HOPE investigated the preventive use of the tissue ACE inhibitor ramipril 10 mg daily vs placebo in 9297 patients at high risk for cardiovascular events. Treatment with ramipril for 4.5 years reduced the combined rate of MI, death, and stroke by 22%, nonfatal MI by 20%, stroke by 32%, the need for revascularization by 15%, and worsening angina by 11%. New onset diabetes declined by 34% and diabetic complications by 16%. Results were even more striking in diabetic patients. The combined outcome declined by 25%, stroke by 33%, MI by 22%, and nephropathy by 24%. Treatment benefits were far greater than anticipated from the small blood pressure reduction of 3/2 mm Hg.

A likely mechanism for ACE inhibitor benefits . . .

It is doubtful that blood pressure lowering alone can explain the decrease in ischemic events observed with ACE inhibition. The mechanism for the benefits of ACE inhibition probably involves an improvement in endothelial function. This improvement is likely related to attenuation of the contractile and superoxide-generating effects of angiotensin II and to enhancement of endothelial cell release of nitric oxide secondary to diminished breakdown of bradykinin.

. . . and a new role for tissue ACE inhibition as anti-ischemic therapy

These trials demonstrate that the endothelium is critically important in regulating blood flow and that it can be targeted with ACE inhibition. The importance of tissue ACE implies that differences among agents in tissue-binding capacity might affect clinical response. As these trials suggest, ACE inhibition with highly tissue-avid agents may be particularly advantageous in enhancing vascular function and potentially improving cardiovascular outcomes (Table 2).
Clinical Summary

- The benefits of ACE inhibition are greater than would be expected from blood pressure lowering alone.
- Highly tissue-avid ACE inhibitors might be particularly advantageous in improving endothelial function and decreasing cardiovascular morbidity and mortality.

Selected Readings


The rate of coronary heart disease (CHD) in individuals with diabetes is increased by a factor of 2 to 4 over those without diabetes and their prognosis is serious. Heart disease is the leading cause of diabetes-related death, accounting for up to 80% of deaths. The incidence of coronary events is greater for more severe outcomes, such as myocardial infarction (MI) and sudden death. Within a year after a first cardiac event, 50% of patients with diabetes may die; one half of these deaths occur before they reach a hospital and therefore are categorized as sudden death.

While age-specific cardiovascular disease mortality in general has declined sharply in the last 35 years, this is not the case for people with diabetes. The decline has been much smaller in men with diabetes than in nondiabetic men, and deaths from coronary artery disease have increased markedly in diabetic women. This suggests that diabetes eliminates women’s protection against cardiovascular disease.

“Prediabetic subjects have an atherogenic pattern of cardiovascular risk factors, including dyslipidemia and high blood pressure, and these changes are seen mainly in those with insulin resistance.”

A problem of growing dimensions

The connection between diabetes and CHD is likely to become more acutely important because of the increasing prevalence of diabetes in both high-risk (Mexican Americans, African Americans, and Native Americans) and low-risk populations. In the San Antonio Heart Study, the 7-to-8-year incidence of type 2 diabetes nearly tripled in both Mexican Americans and non-Hispanic whites. The group with the highest fasting plasma glucose level had a nearly 5-fold greater risk of mortality from cardiovascular disease. A population study among nondiabetic and diabetic subjects with and without prior MI confirmed that middle-aged diabetic subjects with no history of MI had a similar risk of infarction as nondiabetic subjects with a prior MI. These findings suggest that all patients with diabetes should be treated as if they already had CHD.

The prediabetic state:
A time to reduce cardiovascular risk

Patients with newly diagnosed type 2 diabetes commonly have dyslipidemia (elevated triglycerides and low HDL-cholesterol) and high blood pressure. In the United Kingdom Prospective Diabetes Study, blood pressure control produced significant reductions in both microvascular and heart disease, whereas glycemic control lowered only the rate of microvascular disease. The existence of a protracted atherogenic state before the onset of diabetes may help explain why glucose control alone will not completely eliminate the excess risk of CHD in patients with type 2 diabetes.
An atherogenic pattern of cardiovascular risk factors, including dyslipidemia and high blood pressure, occurs in prediabetic subjects, mainly those with insulin resistance (Figure). Thus, diabetes prevention with insulin-sensitizing interventions might be more beneficial than those that increase insulin secretion to reduce the risk of CHD. In both diabetic and prediabetic populations, interventions to reduce cardiovascular risks are essential for the primary prevention of CHD in view of the poor prognosis after an initial event.

The sixth report from the Joint National Committee for the Treatment and Prevention of Hypertension (JNC-VI) recommends a target blood pressure below 130/85 mm Hg for patients with diabetes. JNC-VI advises the use of ACE inhibitors as initial therapy, along with diuretics and beta blockers. Current National Cholesterol Education Program and American Diabetes Association guidelines advise lowering LDL-cholesterol to less than 100 mg/dL in diabetic patients. Several large clinical trials have shown that statin therapy reduces the incidence of cardiovascular events in diabetic patients with CHD.

**Clinical Summary**

- Interventions to reduce cardiovascular risk are essential for the primary prevention of CHD in both diabetic and prediabetic populations.
- JNC-VI recommends lowering blood pressure to below 130/85 mm Hg in diabetic patients and advises the use of ACE inhibitors as initial therapy.

**Selected Readings**


**Figure. Levels of cardiovascular risk factors and insulin resistance status in converters and nonconverters to diabetes.** Adapted from Haffner SM, et al.4
The endothelium is a critical organ that sets the stage for vascular health and disease. Substances released by the endothelium determine the balance between vasoconstriction and vasodilation (Figure). Endothelium-derived nitric oxide (NO) is probably the most important vasodilator involved in local vascular control. Along with other vasodilators released by the endothelium, NO inhibits vascular smooth muscle growth, thrombosis, and inflammation. In addition, NO is an antioxidant. The endothelium also releases vasoconstrictors, the most well known of which is angiotensin II (Ang II). Because angiotensin-converting enzyme (ACE) is present on all endothelial cells, these cells have the capability of converting Ang I to Ang II, and increasing vascular Ang II locally in tissue. Endothelin (ET) is another important vasoconstrictor; Ang II can stimulate ET production, which further mediates the vasoconstrictive effects of Ang II.

**THE RAS AND TISSUE ACE**

The importance of local production of ACE in tissue began to be recognized with the identification of two renin-angiotensin systems (RASs). The circulating RAS has an endocrine effect and regulates acute blood pressure and hemodynamics, while the tissue RAS exerts an autocrine/paracrine effect and influences long-term alterations in vascular structure and function. More than 90% of ACE is generated locally, chiefly in the vascular wall. Appropriate tissue ACE activity helps maintain the balance between vasodilation and vasoconstriction, growth promoters and inhibitors, pro- and anti-inflammatory factors, and thrombotic and fibrinolytic pathways in the vascular wall. In addition to catalyzing the conversion of Ang I to Ang II, ACE initiates the breakdown of bradykinin. Bradykinin stimulates production of NO, prostacyclin, and endothelium-derived hyperpolarizing factor. Too much ACE activity shifts the balance towards processes associated with vascular dysfunction/injury.

Ang II promotes growth and exerts prothrombotic, proinflammatory, and pro-oxidant effects. Ang II also stimulates the conversion of NO to superoxide radicals and the oxidative stress then decreases NO availability. In certain disease conditions, including hypercholesterolemia, atherosclerosis, hypertension, and diabetes, NO production is not altered, but its bioavailability is reduced.

**OXIDATIVE STRESS: COMMON DENOMINATOR OF ENDOTHELIAL DYSFUNCTION**

The mechanisms by which cardiovascular disease risk factors lead to endothelial dysfunction are gradually
being revealed. A common denominator among these risk factors is oxidative stress. Vascular oxidant stress, particularly interactions between NO and oxygen-derived radicals, represents a common pathological mechanism associated with many risk factors for atherosclerosis and endothelial dysfunction. The epidemiologically identified risk factors for atherosclerosis, including diabetes, smoking, hypercholesterolemia, and hypertension clearly alter the balance between vasoconstrictor activity and vasodilator activity. These pathological conditions appear to be associated with increased vascular production of reactive oxygen species. The resulting oxidative stress leads to decreased NO activity, increased local mediators, increased tissue ACE, and promotion of atherosclerosis.

Substantial evidence suggests that vasodilation mediated by endothelium-derived NO is impaired in patients with type 1 and type 2 diabetes. Elevated glucose may contribute to the endothelial dysfunction, although factors other than glucose are also believed to be implicated. The pathogenesis of diabetic vascular disease may involve an abnormality in the availability of endothelium-derived NO that contributes to the development of atherosclerosis.

“In patients with insulin-dependent diabetes, treatment with an ACE inhibitor improves endothelium-dependent vasorelaxation, which suggests that induction of vascular oxidases by Ang II and increased superoxide production might play a role in diabetes.”

PROGRESSION OF GLUCOSE INTOLERANCE PARALLELS PROGRESSION OF CORONARY HEART DISEASE

Coronary heart disease accelerates as glucose intolerance worsens. Prediabetic patients with insulin resistance or hyperinsulinemia and normal glucose tolerance already demonstrate endothelial dysfunction. Patients with insulin resistance and hyperinsulinemia associated with impaired glucose tolerance have endothelial dysfunction and a 2-fold acceleration in coronary heart disease mortality rates. Type 2 diabetes is associated with a 3- to 4-fold increase in the rate of coronary heart disease mortality. Insulin resistance even in the absence of glucose intolerance may be associated with endothelial dysfunction.

Activation of the insulin receptor turns on a pathway that enhances insulin-mediated transport of glucose into skeletal muscle and adipose tissue. Recently, insulin receptor activation of the same pathway has also been shown to mediate endothelial NO production stimulated by insulin. Thus, the state of insulin resistance in addition to being characterized by dyslipidemia, hypertension, and elevated PAI-1 levels, is also associated with endothelial dysfunction and parallel defects in glucose transport and NO production.

In patients with insulin-dependent diabetes, treatment with an ACE inhibitor improves endothelium-dependent vasorelaxation, which suggests that induction of vascular oxidases by Ang II and increased superoxide production might play a role in diabetes. Current trials are investigating whether diabetic subjects, as well as hyperinsulinemic insulin-resistant subjects and prediabetic subjects, have increased sensitivity to Ang II and whether inhibition of Ang II might protect the vasculature from atherosclerosis.

CLINICAL SUMMARY

• Prediabetic subjects with insulin resistance and hyperinsulinemia who have normal glucose tolerance already demonstrate endothelial dysfunction.

• Smoking, hypercholesterolemia, and hypertension alter the balance between vasoconstriction and vasodilation and are associated with increased vascular production of reactive oxygen species.

SELECTED READINGS:


Hypertension and diabetes commonly coexist. Moreover, type 2 diabetes is almost 2.5 times more likely to occur in hypertensive individuals as in those with normal blood pressure. In the diabetic adult, hypertension accelerates the progression of both atherosclerosis and microvascular disease. Hypertension, increased central obesity, insulin resistance, and dyslipidemia are major risk factors that lead to impaired endothelial dysfunction and atherosclerosis in diabetic individuals.

**The lower the pressure, the lower the risk**

Rigorous control of hypertension is essential to reduce the rate of cardiovascular events in diabetic adults. In the Hypertension Optimal Treatment trial, reduction of diastolic blood pressure to <85 mm Hg lowered the rate of death and major cardiovascular events significantly in diabetic subjects, while reduction in diastolic blood pressure to <80 mm Hg achieved further benefits. The Syst-Eur trial showed that the benefit conferred per mm Hg blood pressure reduction is substantially greater in persons with type 2 diabetes than in those with hypertension but no coexistent diabetes. In the UK Prospective Diabetes Study, compared with less tight control, tight control of blood pressure (a decrease of 10/6 mm Hg) produced a 24% greater reduction in diabetes-related outcomes, 32% in deaths related to diabetes, 44% in stroke, and 37% in microvascular outcomes.

These trials have also shown that most hypertensive diabetics require multiple antihypertensive agents to achieve tight control of blood pressure. An average of 3 drugs is necessary to achieve the currently recommended blood pressure of 130/85 mm Hg. Pharmacologic treatment should be initiated concurrently with lifestyle modifications. In the sixth report of the Joint National Committee on the Prevention and Treatment of Hypertension, ACE inhibitors, β-blockers, low-dose diuretics, and calcium antagonists are recommended as initial therapy for hypertensive diabetic patients. For patients with diabetes and proteinuria, ACE inhibitors are the preferred first-line therapy.

**Unique cardioprotective effects of ACE inhibition**

ACE inhibitors may provide a special advantage in addition to blood pressure control in hypertensive diabetics, including reductions in complications from cardiovascular disease, renal disease, and nephropathy. In the CAPtopril Prevention Project (CAPPP) trial, diabetic subjects had a significantly lower rate of total mortality with captopril than with diuretics or β-blockers, and a 66% lower rate of myocardial infarction (MI) (Figure). In addition, other studies comparing ACE inhibition with calcium channel blockade support the notion that an antihypertensive regimen based on ACE inhibitors is especially suitable for the treatment of diabetic patients with hypertension.

“These studies support the notion that an antihypertensive regimen based on ACE inhibitors is especially suitable for the treatment of diabetic patients with hypertension.”
hypertension. ACE inhibitors may also improve insulin sensitivity and decrease the risk of type 2 diabetes. The CAPPP trial found an 11% reduction in new-onset diabetes in the group treated with captopril (Figure). In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibition with a tissue-avid agent resulted in a 30% reduction in new cases of diabetes in patients with cardiovascular risk factors.

![Figure. CAPPP study: Outcomes in patients with diabetes. Adapted from Hansson L, et al.](image)

Until we have conclusive evidence, it seems prudent to use ACE inhibitors, low-dose diuretics, and probably β-blockers as initial therapies in hypertensive patients with diabetes. Low-dose diuretics in conjunction with ACE inhibitors generally are effective in lowering blood pressure and the combination further minimizes potential metabolic problems. Despite concerns that β-blockers may increase the risk of diabetes, these agents reduce cardiovascular morbidity and mortality in patients with diabetes and have an important therapeutic role in hypertensive diabetic patients.

A TOTAL APPROACH TO PREVENTION

Strategies for reducing macrovascular complications in hypertensive diabetic patients should also include treatment of dyslipidemia and the use of antiplatelet therapy. Aggressive lipid lowering, similar to that recommended for patients with heart disease, is appropriate for diabetic patients, including women, because diabetes abrogates the cardioprotective effects of estrogen. In the Scandinavian Simvastatin Survival Study, simvastatin significantly reduced the rate of cardiovascular events in diabetic subjects. Combined ACE inhibition and statin therapy reduces blood pressure to a greater degree than either agent alone.

**CLINICAL SUMMARY**

- Most adults with diabetes require multiple drugs to reach the blood pressure goal of 130/85 mm Hg or less.
- ACE inhibitors may provide a special advantage in addition to blood pressure control in hypertensive diabetics, including reductions in complications from cardiovascular disease, renal disease, and nephropathy.

**SELECTED READINGS:**

Following a successful percutaneous coronary intervention, cardiologists are faced with the challenge of developing a management plan that must address the risk of future unstable angina or myocardial infarction. For example, consider the following case.

**A 63-YEAR-OLD WOMAN WITHOUT PRIOR CARDIAC HISTORY**

This patient presented with an acute posterior myocardial infarction caused by a total occlusion of the proximal portion of the left circumflex coronary artery. This occlusion was opened with primary angioplasty/stenting, with resolution of the patient’s symptoms. However, there was a lesion with 50% luminal narrowing in the right coronary artery and another with 80% luminal narrowing in the left anterior descending artery.

Although the acute presenting myocardial infarction has now been treated, a key question arises regarding which site presents the highest risk for future cardiac events? Is the intervened site at risk for restenosis, due in part to stent endothelial injury? Or is it one of the other two sites?

In fact, it is most likely the 50% lesion—the lesion that appears less troublesome on the angiogram—will be the site of a future acute event. Advances in stent placement and adjunctive antithrombolytic and antiplatelet therapy have reduced the incidence of in-stent thrombosis to less than 1%. Several studies have shown that myocardial infarctions most frequently occur at sites of less than 50% luminal narrowing, in so-called vulnerable lesions.

**IVUS AND A NEW CONCEPT OF HIGH-RISK LESIONS**

Intravascular ultrasound (IVUS) studies have shown that unstable, high-risk lesions appear less stenotic on the angiogram because much of the atheroma is located in the vessel wall. Outward enlargement of the vessel to accommodate a growing atheroma preserves luminal diameter and renders angiography relatively insensitive for the detection of high-risk lesions. But with the use of IVUS, one can in fact demonstrate that in patients with coronary artery disease, more than 90% of the arteries that appear normal on the angiogram have substantial plaque burden lurking within the vessel wall.

**IMPLICATIONS OF COEXISTING DIABETES**

Data from the NHLBI 1985-1986 Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry show that diabetic patients have more extensive and diffuse disease than nondiabetic patients. Moreover, diabetic patients referred for intervention tend to be older, have more comorbid baseline conditions, and triple- rather than single- or double-vessel disease. In long-term follow-up, diabetics have a higher incidence of mortality and revascularization. Finally, diabetes is an important predictor of restenosis. These findings highlight the adverse effects of diabetes on the endothelium.

**MEETING THE CHALLENGE OF DIABETES**

The survival benefits conferred by statins have been demonstrated in patients with diabetes or impaired fasting glucose levels. There is also evidence that the statin class of lipid-lowering agents may stabilize
plaque by mechanisms beyond LDL-cholesterol (LDL-C) reduction. Several studies have demonstrated dramatic benefit among diabetic patients from statin use that exceeded the benefits in nondiabetic patients. Such findings support the notion of diabetes as a risk equivalent for coronary artery disease and the recommendation that all patients with diabetes be treated to the same LDL-C levels that are advised for secondary prevention. Advances have also occurred in understanding the role of peroxisome proliferator activated receptors (PPARs) in vascular health. Antidiabetic agents such as the thiazolidinediones, which bind to the PPAR gamma receptor subtype, appear to have implications for adipogenesis, glucose control, lipid metabolism, and possibly vascular signaling.

FOCUS ON THE POSTINTERVENTION CONTINUUM OF CARE

The key to a successful management plan for the patient following percutaneous coronary intervention is to realize that treatment must occur on the same level as the disease itself—namely, at the molecular level. Percutaneous coronary intervention and bypass surgery provide a safe and durable treatment of flow-limiting epicardial coronary obstructions, but they do not address the underlying disease that is affecting the entire coronary tree. As such, they have little impact on decreasing the risk for future cardiac events. In contrast, lowering LDL-C levels alters plaque formation and progression, and is associated with improved survival (Table). In this sense, statin therapy can be recognized as a molecular therapy, acting at the level in which the disease itself occurs.

### Treatment goal

<table>
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<tr>
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<th>Relieve symptoms</th>
<th>Prevent MI</th>
<th>Prolong life</th>
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<tr>
<td>CABG</td>
<td>+</td>
<td>-</td>
<td>+/-*</td>
</tr>
<tr>
<td>PCI</td>
<td>+</td>
<td></td>
<td>+/-*</td>
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<tr>
<td>Lipid lowering†</td>
<td>+</td>
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*Certain subsets only
†Principally statin plus diet
CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention

### Clinical Summary

- With current techniques, percutaneous coronary intervention is highly successful in revascularizing obstructed conduit arteries and relieving symptoms, but does not extend survival.
- The management plan following percutaneous coronary intervention is even more challenging in diabetic patients, who are at increased risk for coronary artery disease relative to nondiabetics, as well as more prone to restenosis following the procedure.
- To decrease risk and extend survival, it is also necessary to treat the diffuse disease elsewhere in the coronary tree. This is accomplished through aggressive LDL-C lowering.

### Selected Readings

The fibrinolytic system is an important endogenous counterregulatory mechanism against intravascular thrombosis, with fibrinolytic activity determined by the balance between plasminogen activators (primarily tPA) and plasminogen activator inhibitors (primarily PAI-1).

**ELEVATED PAI-1: A COMPONENT OF THE CARDIOVASCULAR DYSMETABOLIC SYNDROME**

PAI-1 is emerging as an important mediator of cardiovascular risk in patients with insulin resistance or diabetes. Data from the Framingham Study show that levels of PAI-1 are directly related to increasing systolic and diastolic blood pressure levels. Other studies show that PAI-1 levels are also independently related to many of the other components of the cardiovascular dysmetabolic syndrome (CDS), including high body mass index, hyperglycemia, and hyperlipidemia. The greater the number of these risk factors, the higher the PAI-1 levels. These findings have prompted the suggestion that elevated PAI-1 levels be considered a component of the CDS.

**THE LINK TO ATHEROSCLEROSIS**

Both PAI-1 and tPA are synthesized by endothelial cells, and accumulation of PAI-1 in atherosclerotic plaque has been observed. In other studies of directional coronary atherectomy samples obtained from patients with or without diabetes, significantly higher levels of PAI-1 were found in samples from diabetics. A number of mechanisms can be proposed by which PAI-1 might promote the progression and clinical expression of atherosclerosis. tPA converts plasminogen to plasmin, a protease enzyme that degrades fibrin and is also involved in tissue remodeling and smooth muscle cell migration. Thus, in addition to promoting clot formation, elevated PAI-1 levels may also prevent activation of matrix metalloproteinases and inhibit smooth muscle cell and macrophage migration.

**THE LINK TO BRADYKININ AND THE TISSUE RENIN ANGIOTENSIN SYSTEM (RAS)**

Studies in vascular endothelial cells, isolated tissue preparations, and rats suggested that bradykinin may be a potent stimulant of endothelial release. Our group has extended these findings and has shown that bradykinin is a dose-dependent stimulant of endothelial release of tPA in humans. In addition, we and others have shown that angiotensin II (Ang II) increases PAI-1 expression in cultured endothelial cells and in humans. Because ACE converts Ang I to Ang II and bradykinin to inactive peptides, the tissue RAS is strategically poised to regulate vascular fibrinolytic activity (Figure).
BENEFICIAL EFFECT OF TISSUE ACE INHIBITORS ON FIBRINOLYTIC BALANCE

The hypothesis that tissue ACE inhibition favorably affects fibrinolytic balance was tested in a placebo-controlled study that evaluated the effects of the tissue ACE inhibitor ramipril on PAI-1 levels in a post-myocardial infarction population. PAI-1 levels are known to be elevated following myocardial infarction. Tissue ACE inhibition was associated with a 44% reduction in PAI-1 antigen levels and a 22% reduction in PAI-1 activity.

A second study compared the effects of the tissue ACE inhibitor quinapril and the AT₁ receptor blocker losartan on fibrinolytic balance in 25 normotensive subjects who were salt depleted to ensure stimulation of the renin angiotensin and kallikrein kinin systems. Treatment with quinapril decreased PAI-1 antigen and PAI-1 activity. Because tPA frequently circulates as a complex with PAI-1, a slight decrease in circulating tPA levels might have been expected. However, tPA levels were unchanged, which suggested a net increase in tPA synthesis. Treatment with losartan had no effect on PAI-1 but was associated with significantly decreased tPA levels. These findings suggest that the favorable effect of ACE inhibitors on fibrinolytic balance is mediated by increased bradykinin levels as well as by reduction in Ang II levels.

SELECTED READINGS


For more information about the Vascular Biology Working Group, go to vbwg.org.
Self-assessment questions

Please check the appropriate answer for each question on the Answer Key. Instructions for obtaining CME credit are on the back of the Answer Key.

1. What percentage of patients with diabetes die within the first year following a myocardial infarction?
   a) 50%
   b) 75%
   c) 40%
   d) 25%

2. Dyslipidemia and high blood pressure frequently occur in the prediabetic state, chiefly in insulin resistant individuals.
   a) True
   b) False

3. Which of the following changes is not associated with insulin resistance?
   a) Endothelial dysfunction
   b) Defects in glucose transport
   c) Defects in NO production
   d) Decreased PAI-1 levels

4. With regard to evaluating risk in post-intervention patients, which of the following statements is not true?
   a) In patients with CAD >90% of arteries that appear normal on the angiogram have substantial plaque burden as measured by IVUS.
   b) Diabetic patients generally have more extensive and diffuse atherosclerotic disease than nondiabetic patients.
   c) Most MIs occur at sites of <50% stenosis.
   d) Most MIs occur at sites of >75% stenosis.

5. Which of the following strategies improves survival of post-intervention patients?
   a) Providing symptomatic relief
   b) Lowering LDL-C levels

6. Which of the following statements describes the link between the tissue renin angiotensin system and fibrinolytic system?
   a) Insulin resistance and diabetes produce elevations in PAI-1, leading to a prothrombotic state.
   b) Angiotensin II increases PAI-1 expression.
   c) Bradykinin stimulates release of tPA by the endothelium.
   d) All of the above.

7. Levels of PAI-1 are directly related to:
   a) increasing systolic and diastolic blood pressure levels
   b) high body mass index, hyperglycemia, and hyperlipidemia
   c) both a and b

8. Which statement is not a factor in managing hypertensive diabetic patients?
   a) Most diabetic adults require multiple drugs to reach the goal of 130/85 mm Hg blood pressure.
   b) Try lifestyle changes for 6 months before initiating drug therapy.
   c) ACE inhibitors may provide a special advantage in addition to blood pressure control in hypertensive diabetics.
   d) ACE inhibition is the preferred first-line agent for diabetic patients with proteinuria.

9. In the TRENDS and QUIET studies, improved endothelial response with ACE inhibition was related to which LDL-C level?
   a) <130 mg/dL
   b) $\geq 130$ mg/dL
   c) $\geq 190$ mg/dL

10. The FACET and ABCD trials showed a cardioprotective effect of ACE inhibition in patients with diabetes.
   a) True
   b) False

11. In the BANFF trial, which drug produced a significant improvement in endothelial function?
   a) Enalapril
   b) Captopril
   c) Quinapril
   d) Losartan

12. In the HOPE trial, which statement was cited as a possible mechanism for the decline in cardiovascular events with tissue ACE inhibition?
   a) The benefits were completely attributed to the small decline in blood pressure.
   b) An effect of treatment on endothelial function was a possible source for the benefits.
**Program Evaluation**

Your input will help us improve our educational programs. Please rate this monograph in the following areas:

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<tr>
<th>Quality of monograph</th>
<th>Relevance to practice</th>
<th>Value of content</th>
<th>Readability and presentation</th>
<th>Usefulness of illustrations</th>
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To obtain a certificate for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association (AMA) for completing the program Diabetes and Cardiovascular Disease: The emerging role of the endothelium and implications for treatment, please complete the self-assessment questions, fill out the correct answers on the Answer Key, and mail the Program Evaluation and Answer Key with a $15.00 processing fee (checks made payable to University of Florida) to:

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University of Florida College of Medicine
PO Box 100233
Gainesville, FL 32610-0233

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