Diabetes Mellitus, the Renin-Angiotensin-Aldosterone System, and the Heart

Hoong Sern Lim, MRCP; Robert J. MacFadyen, MD, PhD, FRCP; Gregory Y. H. Lip, MD, FRCP

With diabetes mellitus reaching epidemic proportions, mainly secondary to obesity, the impact of cardiovascular disease due to this combination makes it a dominant public health problem during the first quarter of the 21st century. The complex interaction that results in diabetic heart disease is created by overlapping mechanisms. There is a propensity to develop premature, diffuse atherosclerotic coronary disease, which is associated with adverse short- and long-term morbidity and mortality. There are structural and functional abnormalities of the microvasculature, autonomic dysfunction, and intrinsic failure of myocardial contraction (so-called diabetic cardiomyopathy). These changes are amplified by arterial hypertension and kidney disease. In this review, we consider the role of the renin-angiotensin-aldosterone system and how it is a crucial driver of most of the pathophysiologic mechanisms behind diabetic heart disease and why in the past 5 years blocking this system in diabetic patients has emerged as a critical therapeutic intervention.

The prevalence of diabetes mellitus (DM) is undergoing unprecedented growth. The current prevalence of 150 million affected persons worldwide is projected to increase to 220 million by 2010 and to 300 million by 2025.1 This dramatic effect is largely driven by the linked epidemic of obesity.2 Diabetes mellitus is closely aligned with the occurrence of occlusive coronary artery and other vascular events from population studies. The Framingham study3 showed an increased coronary heart disease risk of 66% in men and 203% in women with DM after controlling for other cardiovascular risk factors, whereas the Multiple Risk Factor Intervention Trial (MRFIT)4 demonstrated the amplified risk attributable to DM. In fact, studies5-8 have confirmed that patients with DM but without coronary heart disease experience an equivalent rate of coronary events as non-diabetic patients with a previous history of myocardial infarction (MI). Whether this finding is simply due to a coalition of conventional factors or more specifically to the complex metabolic effects of pancreatic failure is not clear. What is clear is that the need for specific, proactive management of cardiac and vascular risk is acute in patients with DM whether or not they have overt coronary disease or indeed any cardiac involvement. It should be assumed to dominate their outlook. This review examines the role of the renin-angiotensin-aldosterone system (RAAS) in diabetic heart disease and the evidence base for blocking this system as a key mediator of adverse events in diabetic patients.

THE RAAS

Basic Physiologic and Pharmacologic Processes

Renin is secreted as a prohormone activated to release active renin, which is the rate-limiting enzyme in the control of kidney, sodium, and volume homeostasis. Pro-renin is produced by the juxtaglomerular cells in the kidneys in response to a variety of stimuli, including reduced renal per-
of local, tissue-bound RAAS. Tissue-bound ACE may contribute up to 90% of that found in the body. The activity is widely distributed, with endothelial cells as one important site in the vessel wall. The vessel wall is capable of producing Ang II from circulating and locally produced Ang I and, therefore, of acting as a local "tissue renin-angiotensin system (RAS)."\(^{13,14}\)

Although the circulating RAS is important for systemic cardiovascular regulation, activation of this tissue RAS (with the production of Ang II) alters local function and may, therefore, exert direct autocrine and paracrine effects on endothelium and smooth muscle cells independent of its endocrine effects on systemic hemodynamics. Angiotensin II, acting predominantly via angiotensin type 1 receptors, causes a diverse range of effects, including vascular inflammation and oxidative damage (\textbf{Table 1}).\(^{15-20}\) Increased oxidative stress, in turn, activates cell death pathways (apoptosis),\(^{20}\) whereas vascular inflammation is directly involved in the atherosclerotic process.\(^{20}\) These processes are now implicated in a broad range of cardiovascular disease states, such as acute coronary syndromes and heart failure, and in chronic renal failure.

**DM and the RAAS**

Cellular oxidative metabolic stress and endothelial dysfunction are pivotal in the generalized pathogenesis of cardiovascular disease and are closely linked to circulating and tissue levels of Ang II (\textbf{Figure 1}).\(^{35-38}\) This finding is based on experimental studies and clinical observations demonstrating RAS stimulation and simultaneous activation of nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate oxidase in the arterial wall.\(^{25-27}\) A more specific interaction, however, may link DM and the RAAS.

First, short-term moderate hyperglycemia without glycosuria during the early stages of DM has been linked to an increase in plasma renin activity, mean arterial pressure, and renal vascular resistance.\(^{24}\) with activation of circulating and local (intrarenal) RAS. In the study by Miller,\(^{25}\) for example, mean arterial pressure was significantly higher during

---

### Table 1. Autocrine, Paracrine, and Endocrine Effects of Angiotensin II

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction (particularly coronary and renal)</td>
<td>Direct action Endothelin production Produces superoxide, which reduces nitric oxide bioavailability</td>
</tr>
<tr>
<td>Sodium retention</td>
<td>Direct effect on proximal nephron Aldosterone secretion</td>
</tr>
<tr>
<td>Water retention</td>
<td>Induces thirst Vasopressin release</td>
</tr>
<tr>
<td>Myocyte and smooth muscle cell hypertrophy and fibrosis</td>
<td>Release of growth factors such as TGF-β1, ET-1, and IGF-1 Possible direct action, stimulating matrix metalloproteinases Aldosterone secretion</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Induces expression of IL-6, TNF-α, and adhesion molecules</td>
</tr>
<tr>
<td>Oxidative stress (myocyte necrosis and apoptosis)</td>
<td>Generation of superoxide via NADH/NADPH oxidase</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Increased plasminogen activator inhibitor-1 Increased platelet aggregation and adhesion</td>
</tr>
</tbody>
</table>

**Abbreviations:** ET, endothelin; IGF, insulin-like growth factor; IL, interleukin; NADH/NADPH, nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate; TGF, transforming growth factor; TNF, tumor necrosis factor.

---

**Figure 1.** Role of angiotensin II (Ang II) and oxidative stress in the pathogenesis of cardiovascular complications.\(^{20}\) NO indicates nitric oxide; ACE, angiotensin-converting enzyme.

---

©2004 American Medical Association. All rights reserved.
hyperglycemic than euglycemic conditions, and arterial pressure responded well to losartan potassium therapy, whereas the response to losartan therapy during euglycemia was minimal. Osei and colleagues also demonstrated an enhanced renal vasodilator response to captopril and eprosartan use during hyperglycemia, suggesting that hyperglycemia leads to an increase in Ang II–mediated renal vascular tone. This may occur through increased responsiveness, which can be direct or indirect depending on the input of other systems, such as the autonomic nervous system and the baroreflex arc, which are also abnormal in DM.

Second, hyperglycemia results in p53 glycosylation, which has been linked to the transcription of angiotensinogen and the subsequent production of Ang II from the local RAS. This finding is supported by the experiment by Fiordaliso and colleagues, who demonstrated a direct correlation among glucose levels, p53 expression, and the quantity of Ang II. Angiotensin II synthesis increased with the degree of glyceria, and this was attenuated by the inhibition of p53 glycosylation. Angiotensin II is recognized to have proapoptotic properties and thus presents a plausible role for the RAS in the pathogenesis of diabetic heart disease. Specific blockade of the RAS with ACEIs and angiotensin receptor blockers (ARBs), for example, may attenuate some of these effects.

Third, recent clinical outcomes studies, such as the Heart Outcomes Prevention Evaluation (HOPE) study, the Captopril Prevention Project (CAPPP), and the more recent Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, have consistently and unexpectedly suggested a reduction in the incidence of new-onset DM. This was not a prespecified primary end point of any of these studies. In the HOPE study, the diagnosis of DM was self-reported by the trial participants and was not verified by glucose measurements, which could undermine any firm conclusions. The CAPPP study had the emergence of a new diagnosis of DM as a secondary end point. In this study, the diagnosis was confirmed according to 1985 World Health Organization criteria. This trial reported an 11% lower risk (337 of 5183 patients in the captopril group vs 380 of 5230 patients in the conventional treatment group) of developing DM in the captopril–treated group. Finally, the LIFE study demonstrated a significant 25% reduction in new-onset DM (P < .001), which, again, was a prespecified secondary end point. This latter study, however, used atenolol (with a known albeit modest adverse metabolic profile) as a comparator. The consistency of the results of these large trials warrants further primary investigation. The hypothesis that specific inhibition of the RAAS, particularly with ACEIs, would reduce the development of new DM is being formally tested in 2 large randomized controlled trials, the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.

**DIABETIC HEART DISEASE**

Large-scale clinical trials during the past 2 decades in particular have led to clinically significant improvements in survival from coronary heart disease in general. However, findings from the World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA)—Augsburg registry show little improvement in the survival of patients with DM after MI, in contrast with nondiabetic patients, despite significant steps forward in management, such as defined clearly in the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial.

The presence of DM doubles the case-fatality rate compared with that in nondiabetic patients. This finding, in part, has often been assumed to be linked to the increased incidence of heart failure symptoms and impaired left ventricular function in diabetic patients. Left ventricular systolic function is a well-known independent predictor of cardiovascular morbidity and mortality. The underlying process may be conventional ischemic heart disease, which can be symptomatic, atypical in symptomatic presentation, or even clinically silent, although this whole area is poorly defined. It is also possible that the incidence of systolic contractile failure might be related to larger infarct size in patients with established coronary disease, but clinical observations suggest otherwise.

The effect of DM on the heart is complex and multifactorial. There are elements of the presentation and timing of symptoms in the diabetic patient, the severity of underlying established risk factors for atherosclerosis (which commonly cluster with DM), and possibly specific features related to DM itself. Although described separately, there is considerable overlap among the proposed pathophysiologic processes described in the following subsections. In most analyses, it has proven impossible to delineate the contributory components of diabetic heart disease.

**Hypertension and Ventricular Hypertrophy**

There is an increased prevalence of hypertension in patients with DM (particularly type 2 DM). Up to 70% of obese type 2 diabetic patients have hypertension (defined as blood pressure [BP] > 140/90 mm Hg), and, in contrast, insulin resistance (defined as an inappropriately high insulin-glucose ratio or more specifically during euglycemic-hyperinsulinemic clamp studies) is estimated to be present in approximately 50% of patients with hypertension. This common association acts synergistically to result in increased cardiovascular event rates and, hence, substantial absolute benefit with rigorous BP reduction.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in the diabetic patients enrolled, each 10-mm Hg decrease in mean systolic BP achieved by treatment reduced the risk of any DM-related complication by 12%, of MI by 11%, and of microvascular complications by 13%. Similar data from ad hoc subgroup analysis of diabetic patients from the Hypertension Optimal Treatment (HOT) trial suggested benefit in BP reduction even into the reference range (BP < 140/85 mm Hg). Furthermore, the Systolic Hypertension in Europe (Syst-Eur) trial showed that patients with DM derived more benefit in terms of cardiovascular morbidity and mortality from BP lowering than...
nondiabetic patients, albeit at the cost of more antihypertensive therapy (Table 2). These and other studies have led to consensus in many national and international guidelines to aim for lower BP targets in patients with DM. This is highlighted by the recent position statement by the American Diabetes Association and the report by the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group report recommending a target BP of less than 130/80 mm Hg.

The nature of the interaction among arterial pressure elevation, vascular resistance, vascular damage, and occulsive vascular events in the hypertensive diabetic patient is complex and is not likely to be directly related to pressure alone. Several small studies and 2 recent large-scale therapeutic clinical trials—the HOPE and LIFE trials—containing a reasonable number of diabetic patients and investigating the effects of ACEI and ARB therapy suggest an important role for the RAAS independent of pressure-lowering effects. The HOPE study investigated the effects of ramipril therapy in “high-risk patients,” with a diabetic subgroup of 3577 patients (analyzed separately in the MICRO-HOPE study). Although uncontrolled hypertension was an exclusion criterion, participants could have treated hypertension. Entry BPs of 141.7/80 mm Hg and 142.3/79.3 mm Hg in the ramipril and placebo groups, respectively, were associated with a modest BP treatment effect (3/2 mm Hg). The substantial benefit (number needed to treat to prevent 1 MI, stroke, cardiovascular death, heart failure hospitalization, revascularization procedure, development of overt nephropathy, laser therapy for retinopathy, and renal dialysis was 15) exceeded what most observers would conceive as attributable to this small BP-lowering effect. However, many researchers believe that the BP impact may have been suboptimally defined and systematically underestimated.

Similarly, the LIFE study, with a diabetic cohort of 1193 patients, demonstrated the superior efficacy of losartan over atenolol in reducing cardiovascular morbidity and mortality (predominantly stroke) rates in patients with DM, hypertension, and left ventricular hypertrophy (primary composite end point: hazard ratio, 0.76; P = .03). Mean BP at the end of the study was 146/79 and 148/79 mm Hg in the losartan and atenolol groups, respectively. As systolic BP was not associated with any change in the primary composite end points, the greater benefit was attributed to specific blockade of Ang II. In both of these studies, the benefits were obtained in patient groups comprising large numbers of diabetic individuals, although the trials were not conducted in diabetic patients only. Although it is not reasonable to deduce additional benefit with specific inhibition of the RAAS in DM, the general hypothesis has been explored for some years and is increasingly tenable.

One issue in diabetic heart disease that merits specific consideration is the prevalence of left ventricular hypertrophy. Blood pressure has a direct graded relationship with the prevalence and severity of left ventricular hypertrophy in individual patients, which, in turn, is an independent population predictor of future cardiovascular morbidity and mor-

Table 2. Hypertension in Diabetes Mellitus

<table>
<thead>
<tr>
<th>Trial†</th>
<th>Patients Total No. (No. With DM)</th>
<th>Agents</th>
<th>Conditions</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPPP</td>
<td>10 985 (572)</td>
<td>Captopril vs conventional†</td>
<td>Hypertension (treated and untreated)</td>
<td>Open trial with blinded end points Reduction in CVD end points in DM cohort receiving captopril 11% Reduction in new-onset DM 3/2-mm Hg BP reduction but 25% reduction in primary end point (P &lt; .001) 16% Reduction to overt nephropathy (P = .04) 34% Reduction in new-onset DM (not prespecified)</td>
</tr>
<tr>
<td>HOPE</td>
<td>9297 (3577)</td>
<td>Ramipril vs placebo</td>
<td>High risk or DM with 1 additional risk factor</td>
<td>Significant reduction in cardiovascular mortality with aggressive BP control in DM cohort (P = .02) &gt;70% of patients with DM require ≥3 drugs to control BP at &lt;85 mm Hg</td>
</tr>
<tr>
<td>HOT</td>
<td>18 790 (1501)</td>
<td>Aggressive (&lt;80 mm Hg) vs less aggressive (&lt;90 mm Hg) BP control (dihydropyridine CCBs)</td>
<td>Hypertension</td>
<td>Similar reduction in systolic BP but risk reduction from CVD was 13% in the non-DM group vs 76% in the DM group Two-thirds of DM patients needed ≥2 antihypertensive agents</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>4695 (492)</td>
<td>BP control with dihydropyridine CCBs as first-line medication</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>UKPDS 38</td>
<td>1148</td>
<td>Tight (n = 758) vs less tight (n = 390) BP control in DM (captopril and atenolol)</td>
<td>DM and hypertension</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CCBs, calcium channel blockers; CVDs, cardiovascular disease; DM, diabetes mellitus.
†CAPPP, Captopril Prevention Project; HOPE, Heart Outcomes Prevention Evaluation trial; HOT, Hypertension Optimal Treatment trial; Syst-Eur, Systolic Hypertension in Europe trial; UKPDS 38, United Kingdom Prospective Diabetes Study report 38.
†Conventional treatment includes β-blockers and diuretics.
‡High-risk patients include those with a history of coronary artery disease, stroke, and peripheral vascular disease.
tality.54 Although any BP-lowering treatment induces some regression of left ventricular hypertrophy, treatments blocking the RAS may be more effective in this respect. However, the changes are small, occur during prolonged periods of treatment, and depend on careful controlled serial echocardiographic measurements. Most of the evidence base for this effect comes from meta-analysis of small studies. There are no specific trials, to our knowledge, suggesting that diabetic left ventricular hypertrophy is more or less susceptible to this effect.

Again, more generally, use of the ACEI lisinopril has been shown55-57 to improve myocardial perfusion reserve and maximal coronary flow in patients with hypertension-induced left ventricular hypertrophy, possibly by increasing myocardial capillary density. This effect was not observed with losartan therapy, and it has tempted some researchers to suggest that this is one example of a bradykinin-mediated mechanism.37 The use of ACEIs can also reverse endothelial dysfunction in patients with coronary heart disease, hypertension, and DM and can favorably affect coronary heart disease, hypertension, and DM and can favorably affect the fibrinolytic balance, possibly by increasing myocardial capillary density. This effect was not observed with losartan therapy, and it has tempted some researchers to suggest that this is one example of a bradykinin-mediated mechanism.37 The use of ACEIs can also reverse endothelial dysfunction in patients with coronary heart disease, hypertension, and DM and can favorably affect coronary heart disease, hypertension, and DM and can favorably affect the fibrinolytic balance, possibly by increasing myocardial capillary density. This effect was not observed with losartan therapy, and it has tempted some researchers to suggest that this is one example of a bradykinin-mediated mechanism.37

The ongoing European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) and the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) studies, although again not primary studies of diabetic heart disease, will contain prespecified subgroup analyses and should shed more light on this issue.

**Ischemia**

The effect of acute coronary occlusion, and, hence, myocardial necrosis, on the heart depends on the size of the infarct zone and on the response of the surviving myocardium in maintaining global cardiac function. Noninfarcted myocardium, in the presence of adequate perfusion, usually demonstrates compensatory hyperkinesia to maintain a normal ejection fraction.58 This compensatory response is impaired in patients with DM.59,60 which may simply reflect more diffuse multivessel disease in DM. This finding alone may independently predict an adverse short-term outcome, but, in addition, reduced flow reserve and impaired coronary vasodilation may intensify ischemic damage in the noninfarct segments by a watershed effect.

Coronary vasodilation depends on the structural and functional integrity of the endothelium. Changes in the endothelium are well recognized in type 2 DM and predate the development of microangiopathy.62 Hyperglycemia is widely believed to be an important cause of endothelial dysfunction. Hyperglycemia induces intracellular alterations in the redox state, with activation of diacylglycerol and phosphokinase C and subsequent depletion of the nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate pool. Nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate is required for generating nitric oxide63; a crucial endothelium-derived vasodilator. Furthermore, locally produced endothelial nitric oxide may be inactivated by interactions with advanced glycosylated end products, formed via nonenzymatic interactions between glucose and amino groups of proteins, lipids, and nucleic acids. This reaction is enhanced by hyperglycemia and in the presence of DM.64 In addition, these glycosylated products are commonly found in atherosclerotic lesions65 and can lead to activation of the transcription factor nuclear factor kB,66 modulating gene transcription for endothelin-1, adhesion molecules, tissue factor, and thrombomodulin. These processes result in further oxidative stress, vasoconstriction, and a prothrombotic state,64 facilitating vessel occlusion in DM.

Angiotensin II may directly contribute to oxidative stress by increasing vascular production of superoxide radicals (Table 1),67 which, by reacting with nitric oxide (forming peroxynitrite), reduces levels of free nitric oxide. The free radicals themselves increase leukocyte adhesion to the endothelium, platelet aggregation, and cytokine expression, resulting in macrophage infiltration at the atherosclerotic site and subsequently increasing the likelihood of plaque instability. Angiotensin II may be circulating or may be produced using local or circulating Ang I as substrate. Evidence for this comes from the demonstration of tissue ACE accumulation in the physical area of atherosclerotic plaques.68

Hence, during or after myocardial ischemia, diffuse atherosclerotic disease, structural abnormalities of coronary microvasculature, limited coronary flow reserve, and impaired coronary vasodilation all combine to reduce perfusion of noninfarcted myocardium. This results in limitation of compensatory hyperkinesia, whereas ongoing oxidative stress can add further to myocardial damage in DM.69

**Obesity**

Obesity is reaching epidemic proportions and is closely linked to type 2 DM. Nearly 65% of adults in the United States are either overweight (body mass index [BMI] [calculated as weight in kilograms divided by the square of height in meters] ≥25) or obese—with 31% having a BMI of 30 or greater.70 Kenchaiah and colleagues71 investigated the relation between BMI and the incidence of heart failure in the Framingham Heart Study cohort and demonstrated a graded risk from normal BMI to the obese range with no evidence of a threshold, suggesting a possible causative role. Increased hemodynamic load and activation of the neuroendocrine system have been suggested as 2 possible explanations.72,73

The adipocytes may offer an alternative, or perhaps complementary, mechanism. Angiotensinogen expression, although predominantly found in the liver, has been demonstrated in human adipose tissue. There are also reports of ACE expression and the presence of AT receptors in human visceral adipocytes, supporting the existence of a local RAS in adipose tissue.74 As hepatic production of angiotensinogen remains insulin sensitive in the face of insulin resistance, a state of compensatory hyperinsulinemia such as that found in type 2 DM would increase the renin substrate.
angiotensinogen, leading to increased local and possibly systemic Ang II production. The study by Price and colleagues77 supports this hypothesis by demonstrating a correlation between increased renal plasma flow in response to irbesartan therapy and increasing BMI in 12 obese patients with type 2 DM.

**Autonomic Dysfunction**

Autonomic neuropathy is a well-recognized complication of DM and generally occurs overtly in the later stages of poorly controlled disease. However, it may be demonstrable in up to 40% of diabetic patients when appropriately tested either clinically78 or on positron emission tomographic studies to investigate cardiac sympathetic denervation.77

Autonomic dysfunction brings with it an adverse cardiovascular outlook, with increased mortality, left ventricular dysfunction, and risk of sudden death in diabetic patients with or without myocardial ischemia.78-83 There may be several reasons for this finding. First, diabetic patients with autonomic dysfunction have a higher resting heart rate than nondiabetic patients,84 which might logically increase myocardial oxygen requirements, reduce coronary blood flow (shortened diastole), and exacerbate myocardial ischemia. Second, sensory autonomic dysfunction may result in impaired or altered perception of ischemic cardiac chest pain, leading to “silent” infarctions or atypical presentations, potentially delaying access to emergency treatment and increasing the risk of sudden death and complications of MI. This point, although generally accepted,85 remains to be conclusively demonstrated.86 Also, autonomic neuropathy manifests initially as parasympathetic dysfunction, which leads to an autonomic imbalance with a predominance of (particularly nocturnal) sympathetic activity. Increased sympathetic activity is known to be associated with activation of the RAAS, elevated arterial pressure, heart failure, and arrhythmogenesis (and, hence, sudden cardiac death). Findings from experimental studies87 also suggest direct cardiotoxic effects, promoting myocardial hypertrophy. Although this may be a direct effect of catecholamines, concomitant activation of the RAAS, and, hence, the release of Ang II, is likely to play a part.

**Diabetic Cardiomyopathy**

The existence of a specific diabetic cardiomyopathy (a specific failure of systolic cardiac muscle contraction distinct from the effects of coronary flow or infarction) has been an area of intense research and controversy since the 1970s. Early epidemiologic studies87,88 indicated a higher risk of heart failure in patients with DM. This is supported by various pathologic findings, such as myocardial fibrosis, thickening of basement membrane, and capillary microaneurysms.89,90 These changes are not unique to DM, and they resemble the pathologic features of any other idiopathic cardiomyopathy. Also, these changes were not universally described and, when present, did not necessarily correlate with the presence of classic heart failure symptoms.89

Subsequent experimental studies of DM using animal models have demonstrated impaired systolic contractility and diastolic relaxation. The early work of Regan et al91 with alloxan-induced diabetic dogs demonstrated reduced ventricular compliance with accumulation of interstitial glycoprotein and collagen. Jackson et al92, for example, using streptozotocin-induced diabetic rats, showed lower left ventricular pressure and contractility with progressive increase in lipid deposition and deterioration of cardiomyocyte integrity up to 24 weeks. Chemically induced DM in animals, however, bears little resemblance to clinical DM, as these hypoinsulinemic (compared with hyperinsulinemia in type 2 DM) models do not require insulin for survival (unlike type 1 DM). This finding led to the use of spontaneously diabetic rats, such as the Bio-Breed93 and Otsuka Long-Evans Tokushima Fatty94 rat models simulating type 1 and type 2 DM, respectively. Mizushige and colleagues95 investigated serial changes in left ventricular filling dynamics using Doppler echocardiography and histopathologic changes in the hearts of spontaneously diabetic Otsuka Long-Evans Tokushima Fatty rats compared with nondiabetic rats. Some researchers have demonstrated diastolic abnormalities at a prediabetic (or impaired glucose tolerance) stage, which was accompanied by serologic and pathologic changes of cardiomyocyte or interstitial damage (collagen accumulation with no atherosclerotic changes and increased transforming growth factor β1 receptor 2 expression in myocytes and endothelium). Although useful, the inherent limitations of animal experiments prohibit direct extrapolation of these results to humans.

Numerous invasive and noninvasive hemodynamic studies have been performed in an attempt to characterize this potential form of cardiomyopathy in humans. Many of these studies, however, are flawed by the recruitment of patients with mild hypertension (by today’s standards).96-101 lack of distinction between type 1 and type 2 DM,96-101 and, most important, generally inadequate exclusion of possible clinically “silent” coronary disease.102 Some studies102 have found no evidence of such cardiomyopathy in young normotensive diabetic adults free of coronary disease.

Overall, there seems to be a general consensus on the existence of a distinct myopathic state related to DM, which probably manifests initially as subclinical diastolic dysfunction.98-103 However, there is a distinct gap in knowledge here beyond the agreement that it probably does exist.103 Its clinical course is unknown, the response to glycemic control is inconsistently demonstrated in clinical studies,107-109 and treatment for perceived abnormalities of diastolic function remains to be adequately defined.103 In many ways, this may overlap in part with the debate around the existence of heart failure symptoms due to diastolic filling abnormalities in the nondiabetic population. They too are not well defined.

The causes of a specific diabetic cardiomyopathy are similarly elusive, although several mechanisms are easily linked to contractile failure. First, an absolute or relative insulin deficiency results in abnormal substrate metabolism and, hence, contraction. Glucose uptake via glucose transporters and glycocolysis are reduced in the diabetic heart, whereas fatty acid use is in-
creased.\textsuperscript{110} This results in abnormalities of, among others, the sarcolemmal and sarcoplasmic reticulum, vital for calcium handling and, hence, contractile function of the heart.\textsuperscript{110} Second, hyperglycemia, via protein glycation as described earlier or through activation of diacylglycerol and protein kinase C, generates oxidative stress, which is widely implicated in the pathogenesis of diabetic complications.\textsuperscript{111} In an experiment by Wakasaki et al,\textsuperscript{112} overexpression of protein kinase C B2 isoform in the rat myocardium resulted in cardiac hypertrophy, cardiomyocyte injury, and fibrosis, whereas treatment with LY333531, a protein kinase C B isoform inhibitor, prevented most of these changes.

Finally, as described earlier herein, current evidence suggests that DM is associated with an upregulated systemic and local RAS and production of Ang II. This results in the generation of superoxide through stimulation of nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate oxidase, leading to further oxidative stress.\textsuperscript{67} This can directly impair systolic contraction and thus overall may be pivotal in the pathogenesis of cardiac dysfunction in DM (Figure 2).\textsuperscript{110}

**Diabetic Nephropathy**

Diabetes mellitus is the most common single cause of end-stage renal disease in the developed world. Overall, diabetic nephropathy accounts for 40\% of new cases of end-stage renal disease in the United States. With increasing prevalence worldwide and more diabetic patients now accepted for end-stage renal disease programs, this trend is set to continue.\textsuperscript{113}

Diabetic nephropathy, however, has more far-reaching implications. Diabetes mellitus in isolation already confers an unfavorable cardiovascular risk profile, but this risk is accentuated when coupled with renal dysfunction, leading to a 9-fold increase in relative cardiovascular mortality.\textsuperscript{114} In fact, cardiovascular risk has a direct relationship with renal dysfunction, increasing up to 20 times in patients undergoing maintenance hemodialysis.\textsuperscript{115}

What is the role of the RAAS in diabetic nephropathy? Blood pressure and the kidneys are intimately and inextricably linked. Renal diseases are important causes of hypertension, and hypertension causes and accelerates the progression of renal dysfunction. Antihypertensive therapy (and glycemic control) retards the progression of renal dysfunction in type 1 and type 2 DM.\textsuperscript{116,117}

It has been established for some years,\textsuperscript{118} and is continuing to be confirmed by emerging trial results,\textsuperscript{119} that ischemic and nonischemic renal failure are specifically responsive to RAAS blockade. The landmark study by Lewis et al\textsuperscript{120} in 1993 indicated an additional BP-independent renoprotective effect of the short-acting ACEI captopril in type 1 DM (with overt nephropathy). The EUCLID Study Group\textsuperscript{121} extended these findings with lisinopril when they demonstrated a reduction in the progression of renal disease in “normotensive” (target systolic BP <155 mm Hg) type 1 diabetic patients with microalbuminuria. Similar work with ACEIs on type 2 DM emerged recently with the UKPDS (report 39) and the MICRO-HOPE subgroup analysis (see the “Hypertension and Ventricular Hypertrophy” subsection). However, these studies seem to give somewhat conflicting results. In the UKPDS,\textsuperscript{117} BP reduction by using atenolol or the short-acting ACEI captopril reduced the rate of progression of microalbuminuria, without any significant difference between them. MICRO-HOPE,\textsuperscript{31} using the longer-acting, twice-daily ACEI ramipril, suggested an ACEI-specific and BP-independent effect. The role of the RAAS has become a little clearer with further clinical trial results using receptor-blocking drugs (Table 3).\textsuperscript{122-126} This wealth of evidence in support of ARBs has led to the recommendation by the American Diabetes Association\textsuperscript{113} that ARBs be used as the first line of treatment in diabetic nephropathy, although there is little to suggest that the results would be specific for the ARB class rather than any blocker of the RAAS. Indeed, in the cardiac sphere, evidence suggests that the opposite is true and that ACEIs are superior. These studies show that inhibition of the RAAS with ARBs reduces the progression of diabetic nephropathy, an effect likely to be part dependent and part independent of BP and confirming a role for the RAAS in the progression of diabetic nephropathy.

**FUTURE PERSPECTIVES**

There is a complex relationship between generalized atherosclerosis and the separate process of pancreatic failure, whether absolute, as in type 1 DM, or relative, as in type 2 DM. Obesity and its epidemic effects on westernized cultures and dietary habits has a key role to play in arterial pressure and its impact on the vascular tree and heart. Diabetic metabolic changes can directly affect the heart in terms of structure and function and can coalesce with the amplified effects of elevated arterial pressure. Teasing apart the relative importance of each of these elements has proven difficult, but it is very apparent that the
individualized vascular and cardiac risk of the diabetic patient is great whether he or she has symptoms or not. Specific interventions targeting the RAAS seem to have particular efficacy in this group of patients, hence implying a key role for this system in the pathogenesis of diabetic heart and vascular disease. From where will new extensions of this principle come?

An interesting prospect has emerged with the discovery of the thiazolidinediones—peroxisome proliferator–activated receptor (PPAR) activator. The PPAR is a nuclear hormone receptor that after binding to a ligand becomes activated and forms an activated complex with 9-cis-retinoic acid receptor. This complex, in turn, binds to specific peroxisome proliferator response elements, which eventually leads to increased transcription and protein synthesis. In addition to its antihyperglycemic effects, PPAR agonists (PPAR-γ and, to a certain extent, PPAR-α), such as pioglitazone hydrochloride and rosiglitazone maleate, have been shown to alter other "nontraditional" markers of cardiovascular disease. Specifically, they have been shown to decrease serum levels of matrix metalloproteinase 9 (implicated in plaque rupture), C-reactive protein, tumor necrosis factor α, vascular cell adhesion molecule 1 (leukocyte recruitment into atherosclerotic lesions), and tissue factor (thrombogenicity associated with plaque rupture). More important, Ang II has been shown to down-regulate PPAR messenger RNA and protein, thus promoting vascular inflammation and atherosclerosis. Is this a potential link between these 2 seemingly disparate systems? The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROActive), which is currently investigating the relationship of pioglitazone on the primary end points of all-cause mortality and a composite of cardiovascular outcomes, will provide further information on the role of PPAR and its agonists.

Second, there are distinct differences between ACEIs and ARBs, although both are inhibitors of the RAAS and beneficial in diabetic patients. Some of these differences might be attributed to the accumulation of bradykinin with ACEI use (discussed in the "Basic Physiologic and Pharmacologic Processes" subsection), but there are many other systems affected by ACEIs that could equally be considered and that merit evaluation. These alternative pathways are potentially clinically significant in view of the following: (1) chronic treatment with full-dose ACEIs has been associated with Ang II reactivation and elevated aldosterone levels; (2) neuroendocrine activation is related to poor prognosis in states such as symptomatic heart failure; (3) specific inhibition of aldosterone with spironolactone significantly improves morbidity and mortality in severe heart failure; (4) nearly 40% of Ang I may be converted into Ang II via non-ACE pathways, and this may be increased in DM; and (5) although ACEIs are of proven benefit in patients with high cardiovascular risk (HOPE study) and heart failure (CONSENSUS, SOLVD prevention and treatment, AIRE, and SAVE studies), evidence of equivalent benefit using ARBs has proved to be hard to demonstrate (see the Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan [OPTIMAAL] in the following paragraph).

The Evaluation of Losartan in the Elderly (ELITE) study, which was designed to test the superiority of ACEIs compared with ARBs, showed that Losartan (50-100 mg) was superior to lisinopril (H9251) in reducing systolic blood pressure (SBP) and heart rate.

**Table 3. Angiotensin Receptor Blockers in Diabetic Nephropathy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, No.</th>
<th>Study Drug</th>
<th>Results/Primary End Points</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRMA-2</td>
<td>590 With type 2 DM, hypertension, and microalbuminuria</td>
<td>Irbesartan (300 mg) vs placebo‡</td>
<td>Irbesartan (300 mg) most effective in reducing progression to clinical albuminuria</td>
<td>Not powered to show effects on cardiovascular outcome</td>
</tr>
<tr>
<td>IDNT</td>
<td>1715 With type 2 DM, hypertension, and nephropathy</td>
<td>Irbesartan (300 mg) vsamlodipine (10 mg) vs placebo†</td>
<td>Irbesartan significantly slowed the rate of progression of nephropathy but had no significant effect on all-cause mortality</td>
<td>BP significantly lower in the treatment arms vs control &gt;70% Of patients were white</td>
</tr>
<tr>
<td>RENAAL</td>
<td>1513 With type 2 DM and nephropathy (&gt;95% were hypertensive)</td>
<td>Losartan (50-100 mg) vs placebo‡</td>
<td>Losartan significantly reduced the rate of progression of nephropathy and the onset of ESRD but had no significant effect on mortality</td>
<td>Terminated early as evidence emerged that losartan is beneficial in diabetic nephropathy About 48% of patients were white, 16% Asian, 15% black</td>
</tr>
<tr>
<td>MARVAL</td>
<td>332 With type 2 DM and microalbuminuria, 63% vs 67% hypertensive</td>
<td>Valsartan (80 mg) vs placebo†</td>
<td>Valsartan significantly reduced the urinary albumin excretion rate, even in normotensive patients</td>
<td>&gt;85% Of patients were white No difference in BP achieved between groups</td>
</tr>
<tr>
<td>CALM</td>
<td>199 With type 2 DM, hypertension, and microalbuminuria</td>
<td>Lisinopril vs candesartan vs combination</td>
<td>Combination therapy achieved greater BP reduction and significantly reduced albuminuria</td>
<td>Combination therapy was well tolerated Short 12-wk study Effects may be BP related</td>
</tr>
</tbody>
</table>

**Abbreviations:** BP, blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease.

†Any antihypertensive therapy except angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers.
‡Any antihypertensive therapy except angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

©2004 American Medical Association. All rights reserved.
of ARBs (losartan) over ACEIs (captopril), and the Valsartan Heart Failure Trial (Val-HeFT), which was designed to test the superiority of ARBs and ACEIs over ACEIs alone, ARBs alone, or ARBs in combination with ACEIs, did not show any additional mortality benefit, although the ACEI group showed a reduction in the combined end points of mortality and morbidity. Indeed, the most recent ARB trial, OPTIMAAL, comparing losartan with captopril in patients with MI and heart failure, new Q-wave MI, or reinfarction showed a nonsignificant trend in favor of captopril (although losartan was better tolerated). The lack of superiority over ACEIs raises questions about the precise role of the RAAS and ARBs, at least in patients with heart failure. Ongoing studies with ARBs are eagerly awaited and will contain prespecified diabetic subgroups (Table 4).

Furthermore, there is still a lack of evidence of specific efficacy for blocking the RAAS in DM among nonwhite ethnic groups despite observational studies suggesting a higher incidence of type 2 DM and risk of cardiovascular morbidity and mortality. In this regard, 2 recent studies, the African American Study of Kidney Disease and Hypertension (AASK) and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), both with significant numbers of African Americans patients, provide further insight into possible differences and indeed similarities among ethnic groups. The AASK, which excluded diabetic patients, demonstrated greater renoprotective effects with ramipril use over amlodipine use in hypertensive renal disease. However, the ALLHAT, in which approximately 36% of all patients were African American, suggested less BP-lowering effect with ACEI monotherapy. Taking these and other studies into consideration, the Hypertension in African Americans Working Group (1) acknowledged that combination therapy may frequently be required to achieve BP targets, (2) recommended a similar BP goal of less than 130/80 mm Hg in patients at high cardiovascular risk (particularly those with type 2 DM), and (3) stated that any indications for ACEI therapy should be equally applied to African American patients. These are important steps forward, but there remain significant gaps in our knowledge. Although it may seem reasonable to assume efficacy in other ethnic minorities, such assumptions will nonetheless need similar confirmation. This need is now of more urgency, with DM currently undergoing a worldwide epidemic (and its associated cardiovascular burden following this same trend), particularly in China and the Indian subcontinent.1

Finally, there is a real need to evaluate existing treatment strategies with outcome trials specifically in DM. Many trials leave diabetic outcomes as a subgroup analysis or have used surrogate end points such as glycemic control, BP control, and albuminuria. Although it is reasonable to assume that these surrogate end points will

### Table 4. Ongoing Trials With Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>Trial* (Drug)</th>
<th>Patients, No.</th>
<th>End Points</th>
<th>Completion Date/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALUE (Valsartan)</td>
<td>14 400</td>
<td>Cardiovascular mortality</td>
<td>2004</td>
</tr>
<tr>
<td>DONTARGET (Telmisartan)</td>
<td>23 400</td>
<td>Myocardial infarction, stroke, heart failure</td>
<td>2008</td>
</tr>
<tr>
<td>CHARM (Candesartan)</td>
<td>1700</td>
<td>Cardiovascular death, heart failure hospitalization, and all-cause mortality</td>
<td>2002</td>
</tr>
<tr>
<td>VALIANT (Valsartan)</td>
<td>14 500</td>
<td>All-cause mortality</td>
<td>2005</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction.

*VALUE, Valsartan Antihypertensive Long-term Use Evaluation; DONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; VALIANT, Valsartan in Acute Myocardial Infarction Trial.

### Figure 3. Diabetic heart disease.

### Table 5. Myths Regarding Angiotensin-converting Enzyme Inhibitor Use in Diabetes Mellitus

- Fear of azotemia with or without preexisting renal disease
- Fear of precipitating hemodynamic instability, particularly in patients with suspected autonomic neuropathy
- Fear of hyperkalemia because of diabetes mellitus–associated type 4 renal tubular acidosis
- Fear of precipitating renal failure due to exacerbation of bilateral renal artery stenosis, which is more common in diabetes mellitus
lead to clinically significant improvements in outcome, including mortality, it is paradoxical that no mortality data are compiled, particularly where the death rate is so high. In addition, many past experiences in clinical trials have shown that such extrapolation may not always be sound, for example, the Cardiac Arrhythmia Suppression Trial (CAST). Similarly, diabetic nephropathy studies with ARBs have also shown that reduction in albuminuria cannot automatically be assumed to translate into improved overall survival, despite the fact that worsening renal function is associated with progressively higher cardiovascular risk.

CONCLUSIONS

Diabetic heart disease is a complex interplay among hypertension, vascular damage, conventional risk factors for atherosclerosis, autonomic neuropathy, and nephropathy, all of which cluster in DM. Thrombosis, endothelial dysfunction, vascular damage, and inflammation are important effector mechanisms and are powerfully affected by the metabolic changes of overt and subclinical DM (Figure 3).

The morbidity and mortality from the impact of DM on the heart remain considerable despite recent progress in the treatment of cardiovascular diseases. Although diabetic heart disease is not solely mediated by the RAAS, the improved understanding of pathogenesis and the results of very large general clinical trials where diabetic patients form a substantial subgroup has helped show the way forward. More and specific outcome trials in DM would be helpful to this subgroup to address more general aspects of vascular pathology, especially in the more susceptible ethnic groups, and to dispel the myths surrounding ACEIs, which seem to chronically limit their widespread use in these patients (Table 5).

Accepted for publication June 30, 2003.

Correspondence: Gregory Y. H. Lip, MD, FRCP, University Department of Medicine, City Hospital, Birmingham B18 7QH, England (e-mail: G.Y.H.LIP@bham.ac.uk).

REFERENCES
