Treatment of Hypertension in Patients With Diabetes

James R. Sowers, MD

At least 17 million people in the United States have diabetes mellitus, and another 50 million have hypertension. These chronic diseases increasingly coexist in our aging population. Both diseases are important predisposing factors for the development of cardiovascular disease (CVD) and renal disease, and the coexistence of these risk factors is a very powerful promoter of CVD and renal disease. There is accumulating evidence that the rigorous treatment of hypertension and other risk factors such as dyslipidemia and hyperglycemia considerably lessens the burden of CVD and renal disease in patients with diabetes mellitus. There is considerable evidence that strategies addressing diet and exercise reduce the development of diabetes and are an important component of treatment in persons who have established diabetes. There are also considerable data suggesting that the treatment strategies that interrupt the renin-angiotensin system have special benefits in patients with diabetes and may prevent the development of clinical diabetes in hypertensive patients with impaired glucose tolerance. Data from a recent study indicate that the control of systolic blood pressure, using a diuretic agent as part of antihypertensive therapy, reduces the risk of stroke and other CVD end points. Recent reports indicate that angiotensin receptor–blocking agents decrease the rate of development of proteinuria and diabetic renal disease. These observations will likely have a significant impact on treatment of hypertension in patients with type 2 diabetes mellitus.

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The prevalence of diabetes, especially type 2 diabetes mellitus, is rapidly increasing throughout the world.1-3 This disease will soon involve more than 20 million people in the United States and 300 million persons worldwide. In the United States, diabetes is now the leading cause of new blindness, end-stage renal disease (ESRD), and nontraumatic amputations.1,2,4 Diabetes is currently the leading cause of ESRD in African Americans as well as others in the United States.3 This increase in the incidence of ESRD, necessitating dialysis and transplantation, is a tremendous burden on our health care resources as well as on families and individuals affected by this medical problem. Nevertheless, cardiovascular disease (CVD) is the major cause of premature mortality in patients with type 2 diabetes6-10 (Figure 1), and hypertension is a major contributor to the development of CVD and renal disease in these patients.11 Accordingly, the pathophysiology of and therapeutic approaches to hypertension in the patient with diabetes are discussed in this review.

HYPERTENSION IN PATIENTS WITH TYPE 1 DIABETES

Patients with type 1 diabetes currently make up about 6% to 8% of the total diabetes population in the United States.1,3 In contrast to patients with type 2 diabetes, those with type 1 diabetes typically develop renal disease before developing hypertension.5,11-13 However, the development of hypertension accelerates the course of microvascular and macrovascular disease in these patients.11-13 Based on clinical trials, antihypertensive therapy in these patients...
should include an angiotensin-converting enzyme inhibitor.\textsuperscript{11,12} Furthermore, \(\beta\)-blockers should not be used as first-line antihypertensive therapy in patients with type 1 diabetes because of their propensity to promote hypoglycemia and reduce the patient's ability to appropriately perceive and manifest hypoglycemic symptoms, as well as their ability to respond physiologically to hypoglycemia.\textsuperscript{11,12} Other aspects of antihypertensive therapy are similar to that for patients with type 2 diabetes, and this is covered in detail in the following sections.

**HYPERTENSION IN PATIENTS WITH TYPE 2 DIABETES**

The prevalence of hypertension in patients with type 2 diabetes is up to 3 times greater than in age- and sex-matched patients with diabetes.\textsuperscript{11,12} Increasing age, obesity, and the onset of renal disease are all factors increasing the likelihood of hypertension in the patients with diabetes.\textsuperscript{5,11,12} Obesity, especially central/visceral obesity, is increasingly an important factor predisposing to the development of diabetes and hypertension.\textsuperscript{5,9,11,14} An increased prevalence of obesity in minority populations contributes to the greater incidence of diabetes and hypertension in these populations.\textsuperscript{5,14}

Persons with hypertension have a high prevalence of insulin resistance\textsuperscript{15} and have a substantially increased risk of developing type 2 diabetes mellitus.\textsuperscript{15,16} Insulin resistance is characterized by reduced ability of insulin to stimulate glucose uptake in insulin-sensitive tissues (especially skeletal muscle tissue)\textsuperscript{15,16} (Figure 2). Skeletal muscle phenotypic characteristics of patients with hypertension that predispose to insulin resistance include:

1. Altered composition of skeletal muscle tissue (less slow-twitch

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**Figure 1.** Seven-year incidence of cardiovascular risk in type 2 diabetes mellitus. CVD indicates cardiovascular disease; MI, myocardial infarction. Adapted from Haffner et al.\textsuperscript{9}

**Figure 2.** Angiotensin II–generated reactive oxygen (\(O_2^+\)) species and Rho-kinase (ROK) activation in impaired glucose utilization in skeletal muscle. Akt indicates protein kinase C; AT\(1\)-R, angiotensin type-1 receptor; GLUT4, glucose transporter 4; IRS, insulin receptor substrate; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; ONOO\(^{-}\), peroxynitrite; PH, pleckstrin homology domain; P13-K, phosphatidylinositol-3-kinase. Reprinted with permission from the American Physiological Society.\textsuperscript{20}
Table 1. Mechanism of Insulin Resistance in Hypertension

<table>
<thead>
<tr>
<th>Insulin Resistance Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Decreased nonoxidative glucose metabolism by skeletal muscle</td>
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<tr>
<td>Postreceptor defect</td>
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<tr>
<td>Decreased insulin-mediated glucose transport</td>
<td></td>
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<tr>
<td>Decreased glycogen synthase activity</td>
<td></td>
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<tr>
<td>Increased oxidative stress</td>
<td></td>
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<tr>
<td>Altered skeletal muscle fiber type</td>
<td></td>
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<tr>
<td>Increased adipose tissue</td>
<td></td>
</tr>
<tr>
<td>Decreased slow-twitch insulin-sensitive skeletal muscle fibers</td>
<td></td>
</tr>
<tr>
<td>Decreased delivery of insulin and glucose to skeletal muscle</td>
<td></td>
</tr>
<tr>
<td>Increased reactive oxygen species</td>
<td></td>
</tr>
<tr>
<td>Reduced generation of nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Vascular rarefaction</td>
<td></td>
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<tr>
<td>Vascular hypertrophy</td>
<td></td>
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<tr>
<td>Increased vasoconstriction</td>
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</tbody>
</table>

Figure 3. United Kingdom Prospective Diabetes Study 38.26 CVD indicates cardiovascular disease.

Insulin-sensitive muscle fibers and increased fat interspersed between skeletal muscle fibers).

2. Decreased blood flow and delivery of insulin and glucose to skeletal muscle tissue due to vascular hypertrophy and rarefaction and vasoconstriction.

3. Postreceptor abnormalities in metabolic signaling responses to insulin in skeletal muscle tissue (Table 1).11,14,16 Both aging and a sedentary lifestyle predisposed to lessening of slow-twitch insulin-sensitive fiber and fat deposition in skeletal muscle.14

Postreceptor abnormalities in metabolic signaling responses to insulin are related, in part, to the overexpression of the renin-angiotensin system in this and other insulin-sensitive tissue11 (Figure 2). Increased tissue angiotensin II has been shown to decrease signaling through the phosphoinositol-3-kinase/protein kinase C signaling pathway in skeletal muscle17,18 and cardiovascular tissue.11,14,19,20 These observations of interference of angiotensin II with insulin signaling may explain why strategies that interrupt the renin-angiotensin system may lessen the development of type 2 diabetes.21-23 On the other hand, certain antihypertensive agents may increase the propensity for hypertensive patients to develop type 2 diabetes mellitus.13,16 In a large prospective cohort study that included 12 550 adults, hypertensive patients who were taking β-blockers had a 28% higher risk of development of diabetes compared with those taking no antihypertensive medications.15 Potential mechanisms by which β-blockers may increase insulin resistance and the predistribution to hypertension have been reviewed16 and include weight gain and decreased blood flow to skeletal muscle tissues.

HYPERTENSION AND CVD IN TYPE 2 DIABETES

Hypertension markedly increases the risk for CVD in patients with type 2 diabetes.11 Within the Multiple Risk Factor Intervention Trial (MRFIT),9 more than 5000 patients with diabetes were followed for 12 years and compared with more than 350 000 persons without diabetes. The MRFIT confirmed that hypertension, elevated cholesterol level, and cigarette use were independent CVD risk factors in men with diabetes and that their presence had a greater impact on CVD risk in men with diabetes compared with those without diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), a major risk factor for CVD in type 2 diabetes included systolic blood pressure.13 Blood pressure was also observed to be a strong CVD risk factor in patients with type 2 diabetes in the Prospective Cardiovascular Munster (PROCAM) study.24

There is an increasing body of data from controlled clinical trials indicating that rigorous control of blood pressure to levels below the conventional control levels of less than 140/90 mm Hg markedly reduces CVD and stroke morbidity/mortality as well as development of ESRD in persons with type 2 diabetes mellitus.25-30 For example, in the UKPDS, patients assigned to “tight” blood pressure control (144/82 mm Hg), there were significant reductions in diabetes-related end points, in death-related end points due to diabetes, in strokes, and in microvascular end points, especially diabetic retinopathy.25 (Figure 3). Furthermore, the relative benefit of CVD risk reduction was more powerful for intensive blood pressure reduction than for tight glucose control. The Hypertension Optimal Treatment (HOT) study26 reported that in a diabetic subgroup (n = 1501), major CVD events were reduced by 51% in those randomized to a diastolic blood pressure goal of less than 80 mm Hg compared with a goal of less than 90 mm Hg (Figure 4). In a placebo-controlled trial of treatment of isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) trial,27 the 492 patients with diabetes were reported in a post hoc analysis to have significant reductions in CVD mortality, all CVD events, and stroke with a reduction in mean systolic pressures from 175 to 153 mm Hg. These data from the
Syst-Eur trial are consistent with that of the Systolic Hypertension in the Elderly Program (SHEP) study, in which elderly persons with type 2 diabetes derived more CVD reduction compared with those without diabetes. In general, patients with diabetes in these clinical trials required more antihypertensive agents (1 of 3 medications) to achieve these more aggressive goals.

**STROKE IN PATIENTS WITH TYPE 2 DIABETES AND HYPERTENSION**

Stroke is the third leading cause of death in the United States. There are more than 700,000 strokes annually and more than 4.5 million stroke survivors. Diabetes is a well-documented independent modifiable stroke risk factor of increasing importance as the prevalence of diabetes increases. Indeed, the incidence of stroke among patients is up to 3 times that in the general population with an especially high-risk rate in the southeastern United States. There is an increase in both short- and long-term mortality in patients with diabetes following stroke. High admission glucose levels are one predictor of poor outcomes in these patients.

Since the incidence of stroke is higher and the clinical outcome poorer in patients with diabetes, prevention of this problem is important. Hypertension, heart failure, and cigarette and alcohol use are modifiable risk factors for stroke in patients with and without diabetes. In 8 years of observation in the UKPDS group, increased risk of stroke was strongly associated with systolic hypertension as well as atrial fibrillation. Intervention trials have provided support for rigorous blood pressure control in prevention of stroke in patients with diabetes. In the UKPDS for combined fatal and nonfatal stroke, tight blood pressure control (mean blood pressure achieved, 144/82 mm Hg) resulted in a striking 44% relative risk reduction compared with less aggressive control (mean blood pressure of 154/87 mm Hg). This 44% risk reduction in stroke was even greater than 20% with antihypertensive treatment found in the diabetic cohort in SHEP. Data from the Syst-Eur trial with nitrendipine-based antihypertensive therapy showed that the excess risk of stroke associated with diabetes was abolished by antihypertensive treatment in older patients with type 2 diabetes and isolated hypertension. In the MICRO-HOPE subanalysis of the Heart Outcomes Prevention Evaluation (HOPE) study, 3577 patients with diabetes treated with ramipril showed a reduction of primary combined end points of myocardial infarction, stroke, and CVD death by 25% and a stroke reduction by 33%.

Recent studies have shown the beneficial effects of an angiotensin receptor blocker (ARB) and an angiotensin-converting enzyme/diuretic combination in reduction of primary and secondary strokes in high-risk patients, including those with diabetes. The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) also showed that treatments using a diuretic and lowering systolic blood pressure were very important strategies to reduce stroke incidence in patients with diabetes. These data support recent guidelines recommending a blood pressure of less than 130/80 mm Hg in patients with diabetes and hypertension.

**LIFESTYLE CHANGES IN TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES**

An integral component of management of hypertension in patients with diabetes is the institution of lifestyle changes. Lifestyle changes emphasizing diet and exercise have been shown to prevent the development of type 2 diabetes in persons with im-
paired glucose tolerance. In addition to improving glycemic control, a diet that is high in fiber and potassium and lower in saturated refined carbohydrates and salt can improve the lipid profile and significantly lower blood pressure. Thus, to address risk factors for CVD in patients with diabetes, institution of lifestyle intervention strategies for reducing risk in this population is important.

**TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETIC NEPHROPATHY**

Diabetic nephropathy has become the leading cause of ESRD in the United States. Approximately 35% of persons with diabetes will develop diabetic nephropathy characterized by proteinuria, decreased glomerular filtration rate, and increased blood pressure. In fact, development of diabetic nephropathy often predates or occurs simultaneously with the evolution of hypertension in patients with type 1 diabetes. Diabetic nephropathy is thus thought to be a powerful promoter of hypertension in patients with type 1 diabetes. In patients with type 2 diabetes, the incidence of nephropathy is approximately 20%. Nevertheless, because up to 95% of diabetic patients have type 2 diabetes, more than half of ESRD cases in diabetes occur in patients with type 2 diabetes. The prevalence and incidence of ESRD are approximately twice what they were 10 years ago. If the trends of the past 2 decades persist, approximately 175,000 new cases of ESRD will be diagnosed in 2010. This is due in part to the expectation that the incidence of type 2 diabetes will double within the next 10 to 15 years and the fact that patients with diabetes are living longer and are thus more likely to develop chronic problems, including ESRD. The cost associated with the management of ESRD is expected to exceed $28 billion by 2010.

A routine urinalysis should be performed in all newly diagnosed patients with type 2 diabetes. If the urinalysis finding is negative for protein, the most utilitarian method is to measure albumin-creatinine ratio in a spot urine collection. Microalbuminuria is present if urine albumin excretion is equivalent to or greater than 30 mg/d (equivalent to 20 µg/min on a timed specimen collection or 20-200 mg/g urinary albumin-creatinine ratio on a random collection). A number of factors can artificially increase urinary albumin excretion, including urinary tract infections, exercise, fever, poor glycemic control, and congestive heart failure. The current recommendations by the American Diabetes Association, as well as the National Kidney Foundation, is to have at least 2 measurements of an elevated albumin-creatinine ratio to affirm microalbuminuria.

Microalbuminuria has been observed to predict the development of CVD and stroke as well as progression of diabetic nephropathy. Indeed, microalbuminuria has been associated with insulin resistance and hyperinsulinemia, atherogenic dyslipidemia, and the absence of a nocturnal drop in systolic and diastolic blood pressure and has been identified as a part of the cardiometabolic syndrome (Table 2). Because microalbuminuria is part of the cardiometabolic syndrome and is related to endothelial dysfunction and increased oxidative stress, it is not surprising that diabetic glomerulosclerosis parallels the process of diabetic atherosclerosis and is a powerful risk factor for CVD and stroke. Thus, even after adjustment for renal function, microalbuminuria remained a strong risk factor for CVD in a sub-analysis of the HOPE trial. In the HOPE trial, the presence of albuminuria doubled the risk for the composite end point of myocardial infarction, stroke, or CVD death and all-cause mortality. The risk of heart failure was 3.7 times greater in type 2 diabetic patients with microalbuminuria compared with those without albuminuria. Furthermore, the risks of the composite end points, all-cause mortality, and heart failure hospitalizations in diabetic patients with microalbuminuria was significantly reduced with treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril.

Several studies have provided evidence for unique benefits of antihypertensive agents that interrupt the renin-angiotensin system. The Collaborative Study Group compared the ACE inhibitor captopril with conventional antihypertensive therapy in patients with type 1 diabetes and nephropathy. Captopril treatment reduced the risk of a doubling of serum creatinine level and the combined end points of death and ESRD by approximately one half. The renoprotective effect of captopril was observed to be greater than would be expected from blood pressure reduction alone. Recent studies have addressed renal protection in type 2 diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT) evaluated the effects of irbesartan in 1715 patients with hypertension, type 2 diabetes, and pro-

**Table 2. Cardiovascular Disease Risk Factors Associated With Cardiometabolic Syndrome**

<table>
<thead>
<tr>
<th>1. Hypertension</th>
<th>6. Low high-density lipoprotein cholesterol levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Central obesity</td>
<td>7. High triglyceride levels</td>
</tr>
<tr>
<td>3. Hyperinsulinemia/insulin resistance</td>
<td>8. Small, dense low-density lipoprotein cholesterol particles</td>
</tr>
<tr>
<td>4. Endothelial dysfunction</td>
<td>9. Increased apolipoprotein B levels</td>
</tr>
<tr>
<td>5. Microalbuminuria</td>
<td>10. Increased fibrinogen levels</td>
</tr>
<tr>
<td></td>
<td>11. Increased plasminogen activator inhibitor 1 and decreased plasminogen activator levels</td>
</tr>
<tr>
<td></td>
<td>12. Increased C-reactive protein level and other inflammatory markers</td>
</tr>
<tr>
<td></td>
<td>13. Absent nocturnal dipping of blood pressure and heart rate</td>
</tr>
<tr>
<td></td>
<td>14. Salt sensitivity</td>
</tr>
<tr>
<td></td>
<td>15. Left ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td>16. Premature/excess coronary artery disease, stroke, and peripheral vascular disease</td>
</tr>
</tbody>
</table>

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teinuria, with urinary protein excretion of 900 mg/d or greater. These patients were randomized to the ARB irbesartan, placebo control, or amlodipine group, with an average follow-up of 2.6 years. The time event for composite end point of a doubling of serum creatinine level, ESRD, or death was 28% in the control group vs 19.8% in the irbesartan group (20% reduction, \( P = .02 \)). Amlodipine treatment was associated with a 25.2% reduction in composite end points, which was not different from the control group but less than the irbesartan group (\( P = .006 \) (Table 3)).

In another trial, the Reduction in End Points in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) Study, the ARB losartan, 50 to 100 mg, plus conventional hypertensive therapy was compared with placebo plus conventional hypertensive therapy in 1513 patients. Serum creatinine levels were required to be between 1.3 to 3.0 mg/dL (114.9–265.2 µmol/L) and urine albumin-creatinine ratio had to be greater than 300 mg/g or 25 mg/mmol. The blood pressure goal was less than 140/90 mm Hg, and the patients were followed for 3.4 years. Losartan therapy was associated with a 28% reduction in the risk of ESRD and a 25% reduction in doubling of serum creatinine level (Table 3). Furthermore, there was a 32% reduction in the first hospitalization for congestive heart failure. Moreover, there was a nonsignificant trend toward a reduction in myocardial infarction in the losartan group.

The Irbesartan Microalbuminuria (IRMA)-2 trial examined the possibility that an ARB, irbesartan, could delay or prevent the development of clinical proteinuria in patients with type 2 diabetes, microalbuminuria, and a normal serum creatinine level (1.3 mg/dL [114.9 µmol/L] for men and 1.1 mg/dL [97.2 µmol/L] for women). Patients with type 2 diabetes whose overnight albumin excretion rate (UAER) was 20 to 200 µg/min on 2 of 3 consecutive samples were randomized to receive placebo or irbesartan, 150 to 300 mg/d. The blood pressure goal was under 135/85 mm Hg 3 months after randomization;

<table>
<thead>
<tr>
<th>End Point</th>
<th>IDNT (Irbesartan vs Amlodipine)</th>
<th>IDNT (Amlodipine vs Placebo)</th>
<th>RENAAL (Losartan vs Placebo)</th>
<th>IRMA-2 (Irbesartan vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × Creatinine level</td>
<td>37% (( P &lt; .001 ))</td>
<td>−6% (( P = .60 ))</td>
<td>25% (( P = .006 ))</td>
<td>33% (( P = .03 ))</td>
</tr>
<tr>
<td>2 × Creatinine level, ESRD, or death</td>
<td>23% (( P = .006 ))</td>
<td>−4% (( P = .89 ))</td>
<td>16% (( P = .02 ))</td>
<td>20% (( P = .02 ))</td>
</tr>
<tr>
<td>ESRD</td>
<td>23% (( P = .07 ))</td>
<td>0% (( P = .99 ))</td>
<td>28% (( P = .002 ))</td>
<td>23% (( P = .07 ))</td>
</tr>
<tr>
<td>Death</td>
<td>−4% (( P = .8 ))</td>
<td>12% (( P = .4 ))</td>
<td>−2% (( P = .88 ))</td>
<td>8% (( P = .57 ))</td>
</tr>
<tr>
<td>Cardiovascular morbidity and mortality</td>
<td>−3% (( P = .79 ))</td>
<td>12% (( P = .29 ))</td>
<td>10% (( P = .26 ))</td>
<td>9% (( P = .4 ))</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; ESRD, end-stage renal disease; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Irbesartan Microalbuminuria 2 trial; RENAAL, Reduction in End Points in NIDDM With the Angiotensin II Antagonist Losartan study.
agent, which makes interpretation of the findings difficult. After 24 weeks of therapy, diastolic blood pressure was reduced to a greater degree with combination therapy (−16.3 mm Hg) than with either candesartan (−10.4 mm Hg) or lisinopril (−10.7 mm Hg) alone.

CONCLUSIONS

Diabetic nephropathy is a global problem of significant economic consequence. To date, there is not an established means to predictably reduce the primary rate of development of diabetic nephropathy; rather, current practice typically addresses diabetic nephropathy when it is already present, either in the form of microalbuminuria or as the more advanced disease state characterized by macroproteinuria and declining renal function. Important elements of the treatment plan for diabetic nephropathy include meticulous blood pressure control and reduction in urine protein excretion to below 1 g/d. In this regard, ACE inhibitors and/or ARBs are of considerable importance. Currently, in type 1 diabetic nephropathy, ACE inhibitors remain the initial agents of choice, and if this class of drugs is poorly tolerated, ARBs can be substituted. In the instance of type 2 diabetic nephropathy, the available evidence supports the preferential use of ACE inhibitors and ARBs. However, to accomplish blood pressure goals in patients with diabetes and hypertension often requires the use of a low-dose diuretic as part of the treatment regimen. 

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REFERENCES


pared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) random-


23. Dahlöf B, Devereux RB, Kjeldesen SE, et al. Cardiovascular morbidity and mortality in the Losar-
tan Intervention For Endpoint reduction in hyper-

24. Asman G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Pro-


27. Tuomilehto J, Rastenyte D, Birkenhager WH, et al; Systolic Hypertension in Europe Trial Investigators. Effects of calcium-channel blockade in older patients with diabetes and systolic hyper-

28. Curb JD, Pressel SL, Cutler JA, et al; Systolic Hypertension in the Elderly Program Cooperative Re-
search Group. Effect of diuretic-based antihyper-
tensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hy-

betes and hypertension at urban academic medi-


31. Tuomilehto J, Rastenyte D, Diabetes and glu-


33. Sacco RL. Reducing the risk of stroke in dia-
betes: what have we learned that is new? Diabetes Obes Metab. 2002;4(suppl 1):S27-S34.

34. Fagan TC. Sowers J. Type 2 diabetes mellitus: greater cardiovascular risks and greater benefits of therapy. Arch Intern Med. 1999;159:1033-
1034.

35. Davis TM, Millems H, Stratten JM, et al. Risk fac-

36. Haart Outcomes Prevention Evaluation Study Investi-
gators. Effects of ramipril on cardiovascular and microvascular outcomes in people with dia-

37. Dahlöf B, Devereux RB, Kjeldesen SE, Julius S, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For End-