Hypertension and insulin resistance often coexist in the same individual as part of a well-recognized phenomenon of cardiovascular (CV) risk factor clustering that multiplies the risk of cardiovascular events. Indeed, when diabetes and hypertension occur together, there is a 2- to 3-fold increase in the risk of cardiovascular disease (CVD). Although diabetes is a well-recognized risk factor for hypertension, there is increasing evidence that hypertension also predisposes an individual to diabetes, independently of other common CV risk factors, such as obesity. One prospective
Calcium channel blockers are generally considered to be metabolically neutral, however evidence suggests that third-generation β-blockers may improve insulin sensitivity.30 Some studies have shown that long-lasting (ie, controlled-release) formulations may improve insulin resistance, dyslipidemia, and hypertension.9,12,14-17

Numerous mechanisms have been proposed to explain these observed links, including cellular abnormalities in insulin signaling,10-12 cellular cation imbalance, enhanced sympathetic nervous system activity,11 enhanced tissue renin-angiotensin-aldosterone system (RAAS) activity,12 inflammation, and oxidative stress.12

A practical application of research in this area is the selection of an appropriate antihypertensive therapy because it has become clear that different classes of antihypertensive medications can have contrasting effects on insulin sensitivity in patients with essential hypertension.23,33-27 The effects of antihypertensive agents on the development of diabetes are explored in this review along with the potential links between RAAS inhibition and insulin sensitivity.

ANTIHYPERTENSIVE AGENTS AND DIABETES: EVIDENCE FROM CLINICAL STUDIES

The results of many clinical studies reveal that antihypertensive agents can have detrimental, neutral, or beneficial effects on insulin sensitivity and the propensity to develop DM. For example, both diuretics and β-blockers can accelerate the appearance of new-onset DM2 in patients with hypertension (Table 1).7,15-21,25-28

In contrast, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) have been shown to prevent or delay the emergence of DM2 in patients with essential hypertension.12,30-32 Table 2 presents the results of several trials of patients treated with ACE-Is or ARBs, in terms of the absolute and relative risk of DM2, compared with patients treated with a thiazide diuretic, β-blocker, amlodipine besylate, or placebo.22,31-40

In these trials, reductions in the relative risk of developing new-onset diabetes associated with ACE-Is or ARBs compared with other classes of antihypertensive agents or placebo, ranged between 11% and 88%.22,33-40 A recent meta-analysis, which included the aforementioned trials, observed 2675 new cases of DM2 (7.40%) in the group of 36 167 patients receiving treatment with an ACE-I or ARB, compared with 3842 events (9.63%) in the group of 39 902 controls.41 This correlated with a mean weighted relative risk reduction in new-onset diabetes of 22% associated with RAAS inhibition (P < .00001). Some observers have questioned whether these reported reductions truly are related to the beneficial effects of ACE-Is and ARBs on insulin sensitivity or are more likely a consequence of detrimental effects associated with the comparator agents.7 Although a definitive answer cannot be made at this time, data gathered from several studies showing improvements with ACE-Is or ARBs compared with either placebo or amlodipine besylate therapy (thought to be metabolically neutral) lend support to the former notion that inhibition of the RAAS reduces the risk of developing diabetes.34,35,38,39

Data from several ongoing clinical trials may help confirm these earlier results. For example, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) is assessing the incidence of DM2 as a secondary endpoint in 23 000 patients over a long follow-up period.42 In addition, a number of ongoing trials include specific evaluation of the potential protection induced by inhibition of the RAAS. These trials include the Nateglinide and Valsartan on Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study and the Diabetes Reduction Approaches with Medication (DREAM) study.43,44 Collectively, these studies are expected to clarify the extent to which inhibition of the RAAS can reduce the incidence of new-onset diabetes in patients with impaired glucose tolerance, a group that includes

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Table 1. Generalized Overview of the Effects of Different Classes of Antihypertensive Agents on the Development of Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Agents that increase the risk of type 2 diabetes mellitus (DM2)</th>
<th>Diuretics</th>
<th>β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents that delay or reduce the risk of DM2</td>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Angiotensin II receptor blockers</td>
</tr>
<tr>
<td>Agents that have no effect on risk of DM2</td>
<td>Calcium channel blockers</td>
<td>α-blockers</td>
</tr>
<tr>
<td>Agents that have insufficient or no data on risk of DM2</td>
<td>Vasodilators</td>
<td>Centrally acting agents</td>
</tr>
</tbody>
</table>

*Evidence suggests that third-generation β-blockers may improve insulin sensitivity.12

1 Calcium channel blockers are generally considered to be metabolically neutral, however some studies have shown that long-lasting (ie, controlled-release) formulations may improve insulin sensitivity.21
many of the 65 million Americans currently diagnosed as having essential hypertension.32

**Differential Effect of Antihypertensive Agents on New-Onset Diabetes**

Although observations from large-scale clinical studies strongly support the hypothesis that different classes of antihypertensive agents have differential effects on the onset of DM2, explanations for these observations have mainly come from numerous smaller studies in humans and animals that have looked specifically at disease mechanisms.

**Antihypertensive Agents Associated With Increased Risk of New-Onset Diabetes**

In terms of predisposing at-risk individuals to the onset of new DM2, thiazide diuretics appear to dose-dependently reduce both insulin secretion and peripheral insulin sensitivity.15,18-20 Furthermore, metabolic disturbances, including hypokalemia, appear to be important in increasing risk, an observation supported by the finding that potassium supplementation reduces

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**Table 2. Reduction in Risk of Type 2 Diabetes Mellitus in Cardiovascular Trials of Renin-Angiotensin-Aldosterone System Inhibitors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Duration of Follow-up (yrs)</th>
<th>Active Treatment</th>
<th>Control Treatment</th>
<th>Risk of Developing Diabetes for Active vs Control Treatments (absolute risk) (%)</th>
<th>Relative Risk Reduction for Active vs Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-Converting Enzyme Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPP33</td>
<td>10,985</td>
<td>6.1</td>
<td>Captopril, diuretic</td>
<td>6.5 vs 7.3 [0.8]</td>
<td>11</td>
<td>.039</td>
<td></td>
</tr>
<tr>
<td>HOPE34</td>
<td>9,297</td>
<td>4.5</td>
<td>Ramipril, Placebo</td>
<td>3.6 vs 5.4 [1.8]</td>
<td>34</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>ALLHAT37</td>
<td>33,357</td>
<td>4.9</td>
<td>Lisinopril</td>
<td>8.1 vs 11.6 or 9.8 [3.5 or 1.7]</td>
<td>30 and 17</td>
<td>&lt;.001 and .01</td>
<td></td>
</tr>
<tr>
<td>SOLVD35</td>
<td>291</td>
<td>2.9</td>
<td>Enalapril, Placebo</td>
<td>5.9 vs 22.4 [16.5]</td>
<td>74</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>PEACE36</td>
<td>6,904</td>
<td>4.8</td>
<td>Trandolapril, Placebo</td>
<td>9.8 vs 11.5 [17]</td>
<td>15</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE37</td>
<td>7,998</td>
<td>4.8</td>
<td>Losartan, potassium, Atenolol</td>
<td>6.0 vs 8.0 [25]</td>
<td>25</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>CHARM38</td>
<td>7,599</td>
<td>3.1</td>
<td>Candesartan, Placebo</td>
<td>6.0 vs 7.0 [1]</td>
<td>14</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>ALPINE40</td>
<td>392</td>
<td>1.0</td>
<td>Candesartan, Hydrochlorothiazide</td>
<td>0.5 vs 4.1 [3.6]</td>
<td>88</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>VALUE39</td>
<td>15,425</td>
<td>4.2</td>
<td>Valsartan, Amlodipine besylate</td>
<td>13.1 vs 16.4 [3.3]</td>
<td>20</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Mean, unless otherwise stated.
the occurrence of thiazide-induced glucose intolerance in these patients.45-47 Studies have shown that deterioration in glucose metabolism occurs even with minimal reductions in serum potassium levels.24,48 β-Blockers, the other major class of agents known to have detrimental effects on insulin sensitivity, inhibit both pancreatic insulin secretion and peripheral glucose utilization.7,21,23,28,29,49 However, weight gain, decreased skeletal muscle blood flow, and unopposed stimulation of β2-receptor-mediated glycogenolysis also may explain the adverse metabolic effects of β-blocker therapy.7,21,23,28,29,49 In contrast, third-generation β-blockers possess vasodilator actions, perhaps attributable to nitric oxide release, antioxidant effects, and Ca2+ blockade and, as a result, may improve insulin sensitivity.28,36,53 Consequently, these newer-generation agents may become the preferred β-blockers for patients with both insulin resistance and hypertension.

**Antihypertensive Agents Associated With Reduced Risk of New-Onset Diabetes**

The RAAS is ubiquitously expressed throughout human tissues, including the vasculature, skeletal muscle, adipocytes, and pancreatic islet cells.52-56 Trials suggesting that ACE-Is and ARBs reduce the risk of new-onset diabetes have generated interest in the effects of RAAS inhibition on insulin sensitivity and the development of diabetes. The following sections discuss these clinical studies, relevant animal study data, and the potential mechanisms of action that affect insulin sensitivity.

### Table 3. Clinical Criteria for Metabolic Syndrome (From Third Report of the National Cholesterol Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults)58

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL*</td>
</tr>
</tbody>
</table>

*The American Diabetes Association has recently revised the definition of impaired glucose tolerance to ≥100 mg/dL.

**Insulin Sensitivity**

Clinically, the clustering of specific metabolic factors that predict CVD identifies the metabolic syndrome, also commonly known as the insulin resistance syndrome, syndrome X, or a variety of other names. The “cardiometabolic syndrome” recently has gained favor in that it recognizes the crucial link between metabolic abnormalities and CVD.59 Further, there is good evidence that insulin resistance appears to be a common component of this syndrome, which is defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) as 3 or more of the abnormalities shown in Table 358 (Note: The World Health Organization [WHO] provides an alternate definition of this syndrome that includes insulin resistance as a required component; however, for the purpose of this discussion we will use the NCEP ATP III criteria). Obesity, usually associated with physical inactivity, appears to be a driving force behind the metabolic syndrome.58 Excess adipose tissue is associated with changes (eg, increased inflammatory mediators, decreased adiponectin) that predispose an individual to insulin resistance at the levels of the liver and skeletal muscle, as well as increasing CV risk directly (eg, via effects on endothelial function).59 Prognostically, the metabolic syndrome significantly increases cardiovascular risk. In the Kuopio Ischemic Heart Disease Risk Factor Study, the risk of coronary heart disease (CHD) mortality was increased 3- to 4-fold in middle-aged men with the metabolic syndrome, compared with those without this condition.58 Although it remains uncertain whether insulin resistance represents the unifying mechanism underlying the syndrome, addressing insulin resistance is now considered an important part of a comprehensive approach to reducing CV risk.60 Weight reduction and physical activity are considered to be core strategies. However, antihypertensive therapies that also improve insulin sensitivity may have beneficial effects on the metabolic syndrome and associated CV risk.

Although clinical studies of RAAS inhibitors specifically examining outcomes related to insulin resistance have produced mixed results, the data have been less heterogeneous for ARBs than for ACE-Is.61 In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, patients with hypertension and left ventricular hypertrophy randomized to losartan potassium had 25% fewer cases of new-onset diabetes than did those randomized to atenolol.62 Results from a recently published LIFE substudy using measurements of peripheral vascular hypertrophy suggest that peripheral vascular changes in hypertension actually induce insulin resistance.62
Agents that inhibit the RAAS, such as losartan potassium, may reduce the incidence of new-onset diabetes in treated hypertensive patients by preserving insulin sensitivity. Support for this concept is provided from a small experimental study in 5 hypertensive men, wherein it was found that losartan potassium 50 mg/day increased insulin sensitivity by 27%. Various mechanisms have been proposed to explain how RAAS inhibitors may improve insulin sensitivity. Essential hypertension is known to be associated with skeletal muscle changes, such as a reduction in total skeletal muscle mass, proportional shifts to less insulin-sensitive muscle fiber types, and intramyocellular lipid accumulation, that may be responsible for coexisting insulin resistance. Animal studies have shown that RAAS inhibitors improve blood flow to skeletal muscle microcirculation and normalize fiber-type proportions. These mechanisms may underlie the observed beneficial effects of ACE-Is and ARBs on insulin sensitivity. More recently, certain ARBs have been noted to have thiazolidinedione-like actions in interacting with the nuclear hormone receptor peroxisome proliferator-activated receptor-γ, which may represent another important mechanism by which ARBs can improve insulin sensitivity.

Vascular Effects

Inhibition of the RAAS has several effects on the vasculature that have been shown to improve glucose uptake and metabolism in insulin-sensitive tissues. Established effects of ACE-Is and ARBs include inhibition of kininase II, which leads to increased levels of bradykinin and enhanced nitric oxide production, improved vascular sensitivity to insulin, and improvements in endothelial dysfunction.

The concept of resistance to insulin and endothelial dysfunction progressing in parallel is well supported. Clinical evidence demonstrates that insulin resistance is linked to endothelial dysfunction through the accumulation of free fatty acids, proinflammatory adipokines, and tumor necrosis factor-α. The apparent relationship between endothelial dysfunction and insulin resistance also is reflected in the effects of angiotensin II on insulin signaling pathways, which is explored in greater detail in the next section.

In addition to direct effects on vasculature, both ACE-Is and ARBs increase skeletal muscle blood flow by diminishing the vasoconstricting effects of angiotensin II, particularly at the level of the small arteriole. However, animal studies also reveal direct effects of angiotensin II on skeletal muscle tissue, independent of vascular changes. Therefore, inhibition of the RAAS may improve insulin-mediated glucose disposal in hypertension and insulin resistance by increasing blood flow to insulin-sensitive tissues and by enhancing the muscle glucose transport system—a system that is likely to involve insulin signaling pathways.

**Signaling Pathways**

The effects of insulin in skeletal muscle are mediated via intracellular signaling pathways. Current evidence suggests that angiotensin II may interfere with insulin signaling pathways via the generation of reactive oxygen species, impairment in intracellular signaling molecules, alterations in the production and signaling of nitric oxide, as well as other mechanisms. For example, blockade of the angiotensin II type 1 receptor with valsartan reportedly reduces the produc-
tion of reactive oxygen species in rodent muscle, appears to be associated with increased insulin-mediat-
ed glucose uptake, and facilitates the insulin signaling cascade. Additional experimental studies in animals and humans have demonstrated that chronic angiotensin-converting enzyme inhibition or angiotensin receptor blockade increases whole body insulin sensitivity. The apparent crosstalk between signaling pathways involving angiotensin II and insulin has been suggested to be pivotal to understanding the relationships between CV and neuroendocrine physiology and, hence, the role of RAAS inhibition in improving insulin resistance and preventing the onset of DM2.

**Islet Cell Protection**

DM2 is associated with both insulin resistance and pancreatic β-cell dysfunction. Conversely, preserving pancreatic β-cells and insulin-secreting capacity may reduce the risk of DM2. The pancreas appears to have a local RAAS, which may be upregulated in DM2. It has been proposed that the primary mechanism by which the RAAS affects pancreatic function is via alterations in islet cell perfusion, and animal study data have demonstrated that angiotensin II produces vasoconstriction in the endocrine pancreas. ACE-Is and ARBs may offer islet cell protection by attenuating the deleterious effect of angiotensin II on fibrosis, inflammation, apoptosis, and β-cell death in the pancreas and by preferentially increasing islet blood flow.

**Treatment Strategy for Patients With Prediabetes or Metabolic Syndrome**

Both prediabetes (fasting glucose 100-125 mg/dL) and the metabolic syndrome (defined earlier) have the potential to develop into diabetes and increase the incidence of CVD. Consequently, early clinical intervention following diagnosis is essential. If a patient is diagnosed with prediabetes and/or metabolic syndrome, lifestyle modification typically is the initial recommendation (Figure). The patient should be encouraged to increase physical activity, achieve or maintain a healthy body weight, and follow a healthy diet plan. Such changes have beneficial effects on body mass index, low-density lipoprotein (LDL) cholesterol, blood pressure, triglyceride (TG) levels, and insulin resistance. In addition, the benefits of diet and physical activity in reducing or delaying the incidence of diabetes have been documented in clinical trials and the American Diabetes Association (ADA) recommends weight loss of 5% to 10% of body weight in overweight individuals and 30 minutes/day of modest physical exercise. If additional lipid modification is required, a statin or bile acid sequestrant can be added to further LDL cholesterol to goal (<100 mg/dL) and a fibrate added to reduce TG (<150 mg/dL) and increase high-density lipoprotein cholesterol (>40 mg/dL men; >50 mg/dL women).

A blood pressure target of <130/80 mm Hg is recommended for patients with prediabetes or metabolic syndrome. Regarding the appropriate selection of an antihypertensive agent, the seventh Joint National Committee (JNC-7) guidelines make no specific recommendations for patients having both hypertension and insulin resistance, 2 of the clinical criteria defined by NCEP ATP III for metabolic syndrome. Because patients with impaired fasting glucose or impaired glucose tolerance are at a significant risk of developing diabetes, antihypertensive therapy with either an ACE-I or ARB may be the best initial treatment option, particularly if proteinuria or kidney disease also are present. Treating hypertension with an ACE-I or ARB has the benefit of reducing blood pressure and CVD, and increasing insulin sensitivity and reducing the risk of new-onset diabetes. As combination therapy is likely to achieve goal blood pressure if systolic blood pressure is ≥150 mm Hg, a second agent such as a low-dose thiazide diuretic should be added. Inhibitors of the RAAS have been shown to be effective in reducing stroke in high-risk patients, mortality due to heart failure, and post-myocardial infarction (MI) morbidity and mortality; however, outcomes trials have also shown that a diuretic may be significantly better than ACE-I in preventing congestive heart failure and stroke. Diuretics also have the benefit of being the least expensive class of antihypertensive agents. However, in patients with prediabetes, reducing the incidence of new-onset diabetes may outweigh short-term economic gains. It currently is not known whether combining an ACE-I or an ARB with a diuretic may actually counteract some of the negative impact of the diuretic on insulin sensitivity, although this would clearly be a desirable effect. Additional studies will be needed to address this issue. The final decision to use a particular class of antihypertensive agents will be based upon both the patient’s risk factors and the ultimate therapeutic goals. Whenever possible, the objective should be to treat the hypertension in such a way as to lower the blood pressure to goal without worsening other risk components.

**Conclusion**

CVD is associated with numerous risk factors, including hypertension and DM. The metabolic syndrome comprises a group of abnormalities that are important to recognize clinically as this syndrome warrants definitive intervention to reduce adverse CV outcomes. The risk factors that cluster in this syndrome probably share a common pathway, with environmental (eg, physical inactivity) and genetic factors likely to be involved in its origins.
although the NCEP and WHO have defined risk criteria and treatment recommendations for the metabolic (insulin resistance) syndrome, the ADA takes the position that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker.79 The ADA recommends that additional information be gathered before it can be classified as a "syndrome." However, the ADA does recommend that clinicians evaluate and treat the individual CVD risk components associated with what the NCEP and WHO more formally define as the insulin resistance or metabolic syndrome.

Clinical trials reveal that different classes of antihypertensive agents are associated with either noticeably negative or positive effects on the development of new-onset DM.2,7,15,18-21,23-28,33-40 Thiazide diuretics and β-blockers have long been associated with an increased risk of new-onset diabetes, which might be caused by electrolyte disturbances, impaired pancreatic insulin secretion and peripheral glucose utilization, weight gain, and unopposed stimulation of B2-receptor-mediated glycogenolysis.7,21,23,28,29,49 Conversely, antihypertensive agents that block the RAAS, such as ACE-I and ARBs, may increase insulin sensitivity and also significantly reduce the risk of new-onset DM.2 A wide variety of mechanisms have been proposed to explain this benefit, including the effects of these agents on skeletal muscle, adipocyte differentiation, insulin signaling pathways,6,41 and protection of pancreatic islet cells.8,42,43 Recently, certain ARBs have also been noted to have peroxisome proliferator-activated receptor-γ agonist activity, a pleiotropic effect that may further explain the results of clinical trials.8,49

It also should be mentioned that although in clinical trials diuretics and β-blockers resulted in a higher incidence of diabetes than RAAS-inhibiting agents, it is not yet entirely certain how this finding translates into clinical practice. For example, in a recent subanalysis of data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, the authors concluded that there was no evidence of superiority in protecting against CHD death and nonfatal MI during first-step treatment with ACE-I or CCBs versus thiazide-type diuretics in patients with DM, impaired fasting glucose (IFG), or normoglycemia,84 although it may be that the study duration (6 years) was too short to determine the overt manifestations associated with diabetic CV complications. Nevertheless, even if all these agents result in similar rates of CV outcomes in patients with prediabetes (ie, IFG), the added benefit of reducing new-onset diabetes may justify the use of an ACE-I or an ARB as a first-line therapy in patients with prediabetes or metabolic syndrome. Furthermore, the use of an agent that inhibits the RAAS may have the most application when a patient has IFG or impaired glucose tolerance and the physician would like to avoid placing them on a medication to treat the glucose abnormality.

The high prevalence of the metabolic syndrome and its substantial consequences warrant consideration when selecting an antihypertensive treatment. Results from ongoing clinical trials should further our understanding of the therapeutic role of RAAS blockade in increasing insulin sensitivity and reducing new-onset DM.

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