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New Treatment Strategies for Patients with Hypertension and Insulin Resistance

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ABSTRACT

The metabolic syndrome is characterized by the clustering of insulin resistance, dyslipidemia, and hypertension and is associated with increased risk of cardiovascular disease and type 2 diabetes mellitus. However, older antihypertensive agents such as thiazide diuretics and β-blockers have potentially adverse effects on glucose and lipid metabolism and may even the exacerbate the metabolic syndrome and increase risk of type 2 diabetes. Recent clinical trials have suggested that antihypertensive agents that inhibit the renin-angiotensin system may reduce risk for new-onset type 2 diabetes, but only a few of these studies were placebo controlled, and in most cases, the absolute antidiabetic effects were relatively modest. Evidence is accumulating that telmisartan, in addition to blocking the angiotensin II type 1 receptor, activates the peroxisome proliferator-activated receptor (PPAR)–γ a well-known target for treatment of the metabolic syndrome and diabetes. By contrast, other angiotensin-receptor blockers are largely devoid of activity on PPAR-γ. Telmisartan is a partial agonist of PPAR-γ and has a superior tolerability profile without causing the fluid retention and edema associated with full agonists of PPAR-γ such as pioglitazone and rosiglitazone. Recent studies have indicated that in addition to antidiabetic properties, PPAR-γ activators may also provide protection against atherosclerosis and coronary events. Thus, the ability of telmisartan both to activate PPAR-γ and to block the angiotensin receptor may provide added value not only in the treatment of the metabolic syndrome and prevention of type 2 diabetes but also in prevention and treatment of atherosclerotic cardiovascular disease.

KEYWORDS: Angiotensin II type 1 receptor blockers; Antihypertensive agents; The metabolic syndrome; Peroxisome proliferator-activated receptor–γ; Telmisartan; Type 2 diabetes mellitus

The term *metabolic syndrome* describes a cluster of cardiovascular risk factors, characterized by insulin resistance, dyslipidemia, and hypertension,[1,2] that is estimated to affect 15% to 25% of individuals in industrialized countries.[3,4] The metabolic syndrome is an important disease risk factor, being associated with a 2- to 4-fold increase in cardiovascular morbidity and mortality,[5,6] and a 5- to 9-fold increase in risk of developing type 2 diabetes mellitus.[3,7]

Recently, some controversy has emerged regarding how best to define the metabolic syndrome and whether the term should be used as a diagnostic label in clinical practice.[8] However, there is no controversy about the fact that risk factors for both diabetes and cardiovascular disease often cluster together and that all such risk factors should be aggressively treated.[8] In many patients, the metabolic risk factors that accompany hypertension such as fasting hyperglycemia and hypertriglyceridemia are often not considered abnormal enough to warrant pharmacologic therapy. Although weight loss and exercise should be considered as first-line therapy in such patients, lifestyle modification may be difficult to achieve. As a result, treatment of such patients generally focuses on controlling blood pressure. But the attendant metabolic risk factors may go untreated in the absence of diabetes or marked hypertriglyceridemia. Although older antihypertensive drugs, such as diuretics and β-blockers, are helpful in controlling blood pressure, they have the potential for adverse metabolic effects that may

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Table 1 Potential mechanisms by which angiotensin II may affect glucose metabolism

- Impairment of insulin-signaling pathways
- Induction of oxidative stress
- Reduction of tissue blood flow
- Stimulation of sympathetic nervous activity
- Inhibition of adipocyte differentiation
- Impairment of pancreatic function

exacerbate the metabolic syndrome and increase the risk of type 2 diabetes. For example, studies with thiazide diuretics and β-blockers have shown that these agents tend to increase low-density lipoprotein (LDL) cholesterol and triglycerides and decrease insulin sensitivity.[9-11] Moreover, thiazide diuretics and β-blockers appear to be associated with greater risk of new-onset diabetes than are other antihypertensive drugs.[12-15] As a result, increased attention is being focused on antihypertensive drugs that inhibit the renin-angiotensin system (RAS), since there is evidence suggesting that such drugs may have beneficial metabolic effects and protect against the development of diabetes.

ANTIDIABETIC EFFECTS OF DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

The results of several large outcome trials suggest that angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) may reduce the incidence of new cases of type 2 diabetes in high-risk patients, compared with other classes of antihypertensive therapies.[12-17] It should be noted that the development of diabetes was not a primary end point in these trials, and that most[12,13,15,16] were not placebo controlled. Nevertheless, the overall trend showing lower rates of diabetes in patients treated with ACE inhibitors or ARBs seems fairly clear. This has motivated the launch of trials specifically designed to investigate the impact of ACE inhibitors and ARBs on the development of type 2 diabetes, such as the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study with ramipril[18] and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial with valsartan.[19]

Laboratory and clinical studies have suggested that angiotensin II may adversely affect glucose metabolism via a number of mechanisms, including impairment of insulin-signaling pathways, increased oxidative stress, and decreased tissue blood flow (**Table 1**).[20] Inhibition of the RAS might thus be expected to reduce insulin resistance and improve glucose metabolism.

Because ACE inhibitors and ARBs both block the RAS, it might be anticipated that the antidiabetic properties of different agents in these classes should be similar. However, recent studies suggest that the antidiabetic effects of ACE inhibitors may not only be mediated via inhibition of the RAS, but also through activation of bradykinin and nitric oxide pathways and glucose transporter 4 (GLUT 4).[20] ARBs may also exert effects on bradykinin and nitric oxide pathways, but evidence supporting a role for these effects in the antidiabetic properties of ARBs is less compelling than that for ACE inhibitors. In contrast, mounting evidence is emerging to indicate that some ARBs may have other actions that extend beyond angiotensin-receptor blockade, giving a subset of ARBs special potential to treat the metabolic syndrome and prevent both type 2 diabetes and atherosclerosis.[20] These ARBs appear to be bifunctional molecules capable of activating the nuclear peroxisome proliferator-activated receptor (PPAR)–γ in addition to blocking the angiotensin II type 1 receptor.

ACTIVATION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR–γ BY TELMISARTAN

PPAR-γ as a Therapeutic Target

PPAR-γ is a nuclear transcription factor that exists in the form of a heterodimer complex with the retinoid X receptor–α.[21] Activation of PPAR-γ causes the receptor complex to affect the expression of key target genes that mediate beneficial effects on glucose and lipid metabolism.

Evidence for the importance of PPAR-γ in regulating key features of the metabolic syndrome and diabetes comes from genetic studies of individuals with mutated forms of the receptor.[22] Such individuals exhibit multiple features of the metabolic syndrome, including severe insulin resistance, hypertriglyceridemia, elevated concentrations of nonesterified fatty acids (FAs), low concentrations of high-density lipoprotein cholesterol, and hypertension.

Moreover, PPAR-γ is an established therapeutic target in the treatment of insulin resistance, diabetes, and the metabolic syndrome.[21,22] Two thiazolidinedione PPAR-γ activators, pioglitazone and rosiglitazone, are currently available, and these agents have been shown to increase insulin sensitivity and decrease FA and triglyceride concentrations in patients with type 2 diabetes.[23]

Studies of PPAR-γ Activation with ARBs

A recent study[24] has compared the ability of different ARBs to activate PPAR-γ. In a cell-based transient transfection assay, telmisartan was the only ARB to show significant activation of PPAR-γ at concentrations ≤5 μmol/L, which is comparable to the highest plasma concentrations ob-

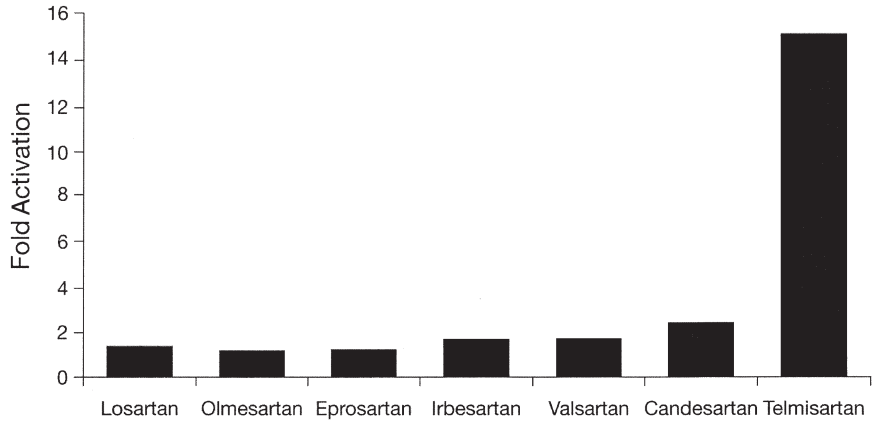

Figure 1 Activation of peroxisome proliferator-activated receptor (PPAR)–γ by angiotensin II receptor blockers (ARBs) in a cell-based transient transfection assay. ARBs were tested at a concentration of 5 μmol/L, which is near the highest plasma concentration attained after usual oral dosing. (Adapted from *Hypertension*.[24])

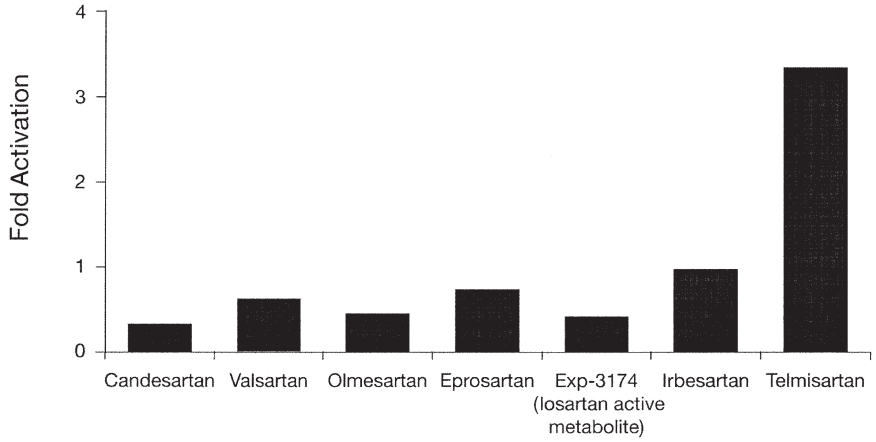

Figure 2 Effects of angiotensin II receptor blockers (ARBs) on the expression of the phosphoenolpyruvate carboxykinase (*PEPCK*) gene in mature human adipocytes. ARBs were tested at a concentration of 2.5 μmol/L. (Adapted from *Hypertension*.[24])

served after oral dosing (**Figure 1**). Slight activation of PPAR-γ was also observed with irbesartan at a concentration of 10 μmol/L, but the potential clinical relevance of such high concentrations is unclear. In contrast to other ARBs, relatively low concentrations of telmisartan were also found to increase the expression of the phosphoenolpyruvate carboxykinase (*PEPCK*) gene in human visceral adipocytes. *PEPCK* is a key target gene that contributes to the ability of PPAR-γ activators to reduce FA levels (**Figure 2**). Further evidence that telmisartan activates PPAR-γ comes from the findings that telmisartan induces adipocyte differentiation in vitro and is more effective than other ARBs in reducing serum concentrations of glucose, insulin, and triglycerides in rats fed a high-fat, high-carbohydrate diet.[24]

Clinical Evidence for PPAR-γ Activation with Telmisartan

Several recent studies support the view that telmisartan exerts beneficial effects on lipid and glucose metabolism that involve more than just its ability to block the angiotensin II receptor. In an open-label postmarketing surveillance study, which included 3,643 patients with diabetes, serum glucose and triglycerides were measured before and after treatment with telmisartan 40 to 80 mg/day for 6 months.[25] In the patients with diabetes, telmisartan treatment was associated with a mean decrease in serum glucose of 13.0 ± 26.9 mg/dL, and a mean decrease in serum triglycerides of 22.7 ± 62.2 mg/dL, compared with baseline values.

In a randomized, parallel-group study, 40 patients with hypertension (mean 24-hour ambulatory systolic blood pressure ≥130 mm Hg, diastolic blood pressure [DBP] ≥85 mm Hg) and insulin resistance, impaired glucose tolerance, or type 2 diabetes were treated with telmisartan 80 mg/day or losartan 50 mg/day for 3 months.[26] Telmisartan produced an 8% reduction in fasting plasma glucose, a 26% reduction in the homeostasis model assessment of insulin resistance (HOMA-IR), and a 9% reduction in glycosylated hemoglobin, compared with baseline (all $P < 0.05$); there was also a 10% decrease in fasting plasma insulin that was of borderline statistical significance ($P < 0.06$). By contrast, losartan

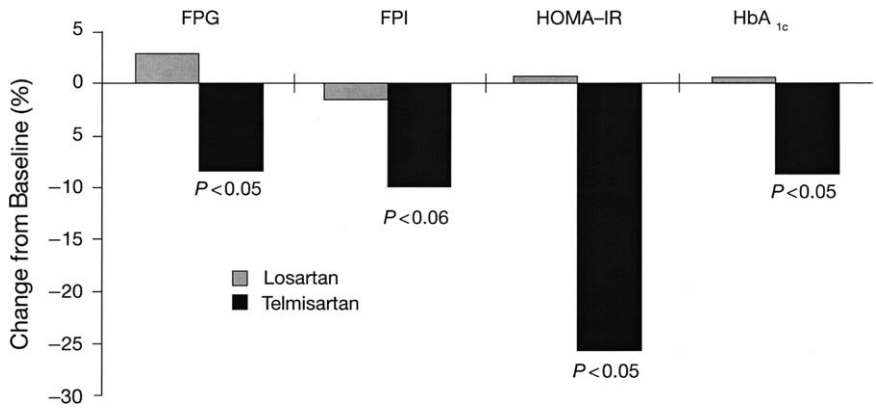

Figure 3 Changes in fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment of insulin resistance (HOMA-IR), and glycosylated hemoglobin (HbA_{1c}) in patients with hypertension and insulin resistance, impaired glucose tolerance, or type 2 diabetes, who were treated with telmisartan 80 mg/day (n = 20) or losartan 50 mg/day (n = 20) for 3 months. (Reprinted with permission from *Cardiovasc Diabetol*.[26])

had no significant effect on any of these measures (**Figure 3**).

In a further study,[27] 119 patients with mild hypertension (DBP 90 to 99 mm Hg) and type 2 diabetes were randomized to receive telmisartan 40 mg/day, eprosartan 600 mg/day, or placebo for 12 months. Telmisartan produced significant reductions in plasma total cholesterol ($P < 0.01$), LDL cholesterol ($P < 0.01$), and triglycerides ($P < 0.05$), compared with placebo, whereas eprosartan had no significant effect on these measures.

A recent study has investigated the metabolic effects of replacing valsartan or candesartan with telmisartan in patients with hypertension and type 2 diabetes.[28] Patients who had previously been stable on valsartan 80 mg/day or candesartan 8 mg/day for >6 months were switched to telmisartan 40 mg/day for 12 weeks. The switch to telmisartan was associated with significant reductions in plasma insulin and serum triglycerides, compared with values at the end of valsartan or candesartan treatment (**Figure 4A**). There also were significant increases in serum concentrations of adiponectin and reductions in serum levels of high-sensitivity C-reactive protein (hs-CRP) following the switch to telmisartan treatment (Figure 4B); increases in adiponectin levels and decreases in CRP levels have been previously observed with other PPAR-γ activators and are known to be associated with protection from diabetes and atherosclerosis.[29,30]

These studies, together with other trials comparing telmisartan with different antihypertensive agents,[31-36] have consistently shown that telmisartan has beneficial effects on lipid and glucose metabolism. There is thus an accumulating body of clinical and laboratory evidence to indicate that telmisartan is not only an ARB but also an effective activator of PPAR-γ.

Structural Basis of PPAR-γ Activation by Telmisartan

The ability of telmisartan to activate PPAR-γ is likely related to its distinctive chemical properties. For example, telmisartan is very lipid soluble and has an extraordinarily high volume of distribution of approximately 500 L, which is far greater than the volumes of distribution of the other ARBs.[20] This very high volume of distribution and the lipophilic nature of telmisartan suggests that it may have a greater capacity to enter intracellular compartments and gain better access to PPAR-γ than other ARBs may have. In addition, molecular modeling studies have shown that the unique chemical structure of telmisartan enables it to interact with key amino acid residues in the ligand-binding domain of PPAR-γ that are not affected by other ARBs.[24] Thus, telmisartan is unique among the ARBs in that it appears to have a special ability to structurally interact with PPAR-γ.

Molecular-modeling studies[24,37] have also indicated that telmisartan interacts with PPAR-γ in a manner different from full agonists of PPAR-γ such as rosiglitazone or pioglitazone. In contrast to the thiazolidinediones, telmisartan does not cause full stimulation of PPAR-γ and interacts with the receptor in a manner characteristic of other partial agonists.[38] Such partial agonists appear to exert more limited effects on gene expression than full agonists of PPAR-γ. This may likely account for the better safety profile of telmisartan compared with the full-agonist thiazolidinediones that promote fluid retention, edema, and weight gain, side effects not seen with telmisartan.

CLINICAL IMPLICATIONS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR–γ ACTIVATION BY TELMISARTAN

The finding that telmisartan acts as both an ARB and a partial agonist of PPAR-γ has important implications for safety and therapy. As noted above, selective or limited activation of PPAR-γ target genes by telmisartan might be expected to avoid certain side effects caused by excessive receptor stimulation associated with full-agonist ligands of PPAR-γ. Furthermore, some of the fluid retention observed with thiazolidinediones is likely related to their vasodilator

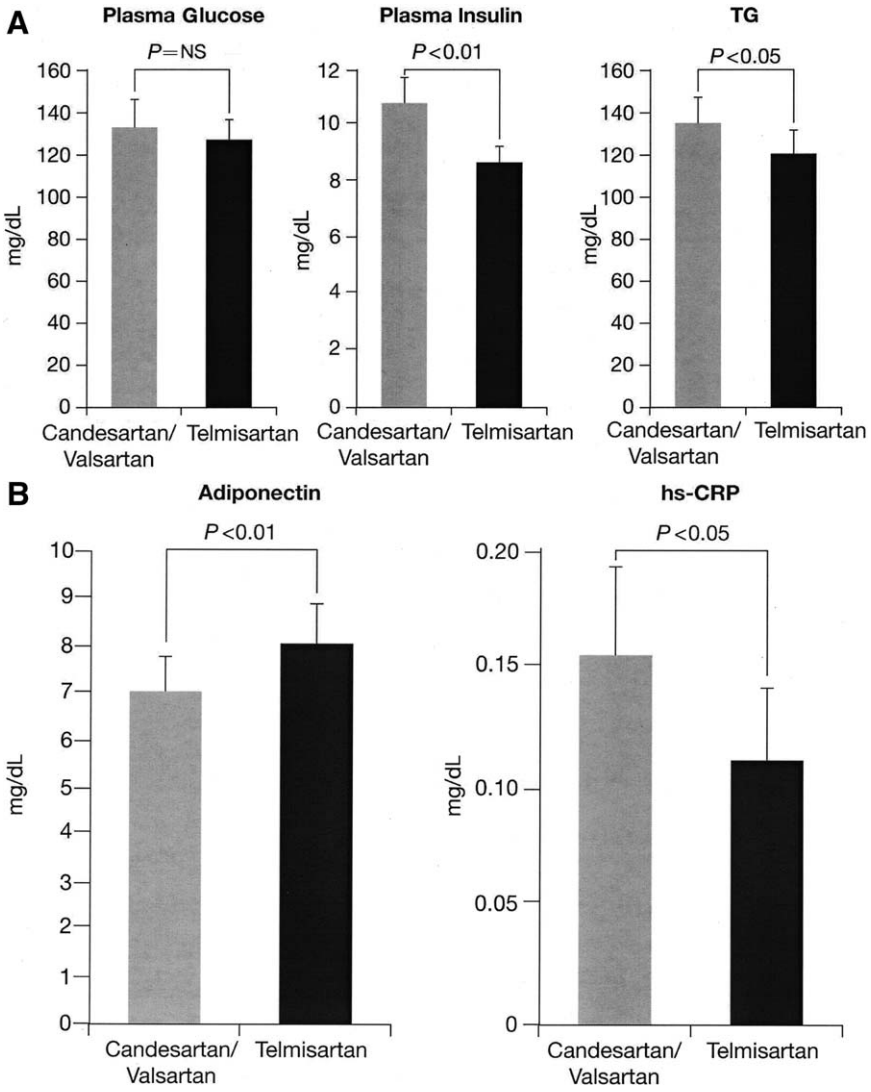

Figure 4 Changes in (*A*) plasma glucose, plasma insulin, and serum triglycerides (TG) and (*B*) serum adiponectin and high-sensitivity C-reactive protein (hs-CRP) in 18 patients with hypertension and type 2 diabetes switched to telmisartan 40 mg/day for 12 weeks after previous treatment for ≥6 months with valsartan 80 mg/day or candesartan 8 mg/day. (Adapted from *Diabetes Care*.[28])

effects and reflex activation of the renin–angiotensin–aldosterone system (RAAS).[39] Telmisartan's ability to block the angiotensin II receptor may serve to attenuate salt and water retention mediated through the RAAS.[20]

The ability of telmisartan to activate PPAR-γ may not only provide potential benefits in treatment of the metabolic syndrome and prevention of diabetes, it may also contribute to protection against atherosclerosis and cardiovascular disease. For example, the PPAR-γ activator pioglitazone was recently reported to reduce the risk for death, myocardial infarction, and stroke when added to existing therapy in patients with type 2 diabetes.[40] Many of the pathogenetic processes involved in the development of atherosclerosis are modulated by PPAR-γ, angiotensin II, or both (**Figure 5**). Thus, bifunctional compounds that both activate PPAR-γ and inhibit the effects of angiotensin II might therefore be expected to be particularly effective in the prevention of atherosclerosis and cardiovascular disease.[20] Furthermore, PPAR-γ activation has been shown to inhibit the expression of the angiotensin II type 1 receptor and modify the effects of angiotensin II on intracellular signaling pathways.[41,42] These actions might further enhance the effects of angiotensin-receptor blockade with telmisartan.[20]

Demonstration that PPAR-γ activation and angiotensin-receptor blockade reduce the risk of atherosclerotic disease in high-risk patients would require large outcome trials. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study is currently comparing the effects of telmisartan, ramipril, and the combination of the 2 agents in 25,260 patients at high risk for cardiovascular events; a companion study, Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) is comparing telmisartan and placebo in 5,926 high-risk patients who are unable to tolerate ACE inhibitors.[43] Both of these studies will investigate the effects of telmisartan on a

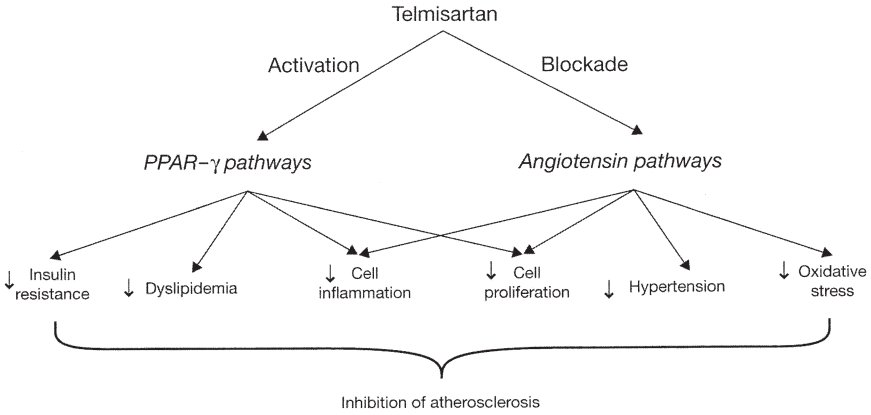

Figure 5 Potential influence of telmisartan on atherogenic processes mediated by peroxisome proliferation-activated receptor (PPAR)–γ, angiotensin II, or both. (Reprinted with permission from *J Hypertens*.[20])

variety of cardiovascular and metabolic end points, including the development of new-onset type 2 diabetes.

SUMMARY

Although all ARBs are effective in blocking the angiotensin II type 1 receptor and thereby reduce blood pressure and attenuate other deleterious effects of angiotensin II, evidence for the existence of 2 classes of ARBs has recently emerged. Telmisartan belongs to the newly recognized class of bifunctional ARBs that not only block the angiotensin II type 1 receptor, but also activate PPAR-γ, a well-known target of antidiabetic drugs. Evidence is accumulating that telmisartan has beneficial metabolic effects that distinguish it from other ARBs. These observations should motivate future studies to investigate potential therapeutic differences between ordinary ARBs and the bifunctional molecules like telmisartan that can activate PPAR-γ in addition to blocking the angiotensin II receptor.

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