Commentary

Value of Angiotensin Receptor Blocker Therapy in Diabetes

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There are more clinical trials investigating angiotensin receptor blockers (ARBs) in diabetes than any other drug class, ranging from early "prevention" trials to the treatment of individuals with advanced organ damage. In its earliest manifestations, visceral adiposity predisposes to hypertension and hyperglycemia (metabolic syndrome). In these individuals, ARB therapy delays the progression to chronic hypertension and may also delay the progression to overt diabetes. Based on the increased cardiovascular disease risk of the metabolic syndrome, which is similar to stage 1 hypertension, both lifestyle modification and ARB therapy are justifiable. ARB therapy has also been found to delay the onset of microalbuminuria and retinopathy. In established diabetic nephropathy, ARB therapy is recommended as a standard alternative to angiotensin-converting enzyme inhibition to reduce macroalbuminuria and delay the progression to end-stage disease. Finally, large trials in ischemic heart disease, heart failure, and stroke have demonstrated clear benefits of ARB therapy. Because ARBs have side effect rates equal to placebo and far lower than any other antihypertensive drug class, the benefit/risk ratio is highly favorable across the entire spectrum of diabetic disease. Thus, ARB therapy is a highly attractive alternative for individuals at any stage of diabetes and with any pattern of complications. J Clin Hypertens (Greenwich). *2011;13:290–295.* ©*2011 Wiley Periodicals, Inc.*

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The most common causes of premature death in individuals with diabetes are consequences of accelerated vascular disease. Intrinsic to the following discussion are the principles that: (1) the ultimate goal of therapy is to retard or reverse the rate of disease progression, and (2) the value of any drug class must be judged on the balance it achieves between reducing adverse outcomes (or improving disease surrogates such as hypertension) and causing adverse effects. Adequate blood pressure (BP) control is paramount in achieving long-term cardiovascular disease (CVD) risk reduction.[1,2] Advanced BP targets (<130/80 mm Hg) are recommended in patients with diabetes,[3] but how far to lower BP is a hotly debated topic.[2] What is also not fully clear is whether there are additional therapeutic benefits of specific antihypertensive drugs. This review focuses on whether the benefits of angiotensin receptor blockers (ARBs), which are considered here as a class effect, justify their use as "preventive," as well as therapeutic agents in diabetes and its complications. The main focus is on clinical trials in large diabetic populations that have investigated diabetes incidence, microalbuminuria, retinopathy, and nephropathy. Because ischemic heart disease (IHD), heart failure (HF), and stroke are so prevalent in patients with diabetes, commentary on clinical trials in these areas is also included.

HYPERTENSION

The Trial of Preventing Hypertension (TROPHY) study tested whether inhibition of the renin-angiotensin system (RAS) with an ARB could prevent or delay the onset of hypertension.[4] Overweight middle-aged patients (body mass index, 30 kg/m^2) with prehypertension (entry BP values 130–139 mm Hg/85–89 mm Hg) who overwhelmingly met criteria for the metabolic syndrome were randomized to treatment with candesartan 16 mg/d or placebo. At 2 years, the cumulative incidence of hypertension (BP $\geq$140/90 mm Hg) occurred in 40% of patients taking placebo and 14% of patients taking candesartan (66% reduction, $P<.001$). For the next 2 years, both groups received placebo. The primary dependent variable, the cumulative incidence of hypertension at 4 years, occurred in 53% of patients taking placebo and in 63% taking candesartan (16% reduction, $P<0.01$).

Another important aspect of TROPHY is the insight it afforded into the pathophysiology of prehypertension and the implications for early ARB treatment. In patients taking candesartan, there was an immediate decrease in BP (10/4 mm Hg by the first repeat visit) and, after ARBs were discontinued at 2 years, BP equally quickly returned to near-baseline values. These observations demonstrate that: (1) RAS overactivity is a major contributor to BP elevation in metabolic syndrome–type individuals, and (2) effective renin-angiotensin blockade prevents or treats but cannot "cure" prehypertension. TROPHY also provides a partial rationale for drug treatment of patients with the metabolic syndrome. Because their CVD risk scores are roughly double those of individuals with normal BPs (<120/80 mm Hg), patients with the metabolic syndrome are at a risk equivalent to stage 1 hypertension and as such should be treated similarly with antihypertensive drugs.[5]

A significant disconnect is that advanced BP targets (<130/80 mm Hg) are recommended for individuals with established diabetes[3] but not for prediabetic individuals, regardless of CVD risk levels. There is much debate about appropriate BP targets. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the investigators concluded that treating diabetics to a lower systolic BP (<120 mm Hg vs 140 mm Hg) confers no benefit because fatal or nonfatal CVD rates were not different (1.87% vs 2.09%, respectively; *P*=not significant [NS]). However, stroke rates were much lower in the low BP group (0.32% vs 0.53%, respectively [a 41% reduction]; *P*=.01).[6] The ACCORD trial was simply too short a study to allow long-term conclusions to be drawn, but the results have been used as evidence that lower targets are unwise. Some organizations have even suggested that advanced BP targets are not necessary.[7]

HYPERGLYCEMIA

Several meta-analyses are available in the literature that test whether ARBs reduce or delay the onset of type 2 diabetes mellitus (T2DM). The two most recent are included here. In 10 large clinical trials that included 36,167 patients (8 studies of hypertension; 5 with an ACE inhibitor, 5 with an ARB compared with placebo [n=4] or a reference drug β-blocker/diuretic [n=5] and amlodipine [n=2]) the incidence of new T2DM was 9.6% in individuals taking non-RAS agents compared with 7.4% in those receiving ACE inhibitors or ARBs (22% reduction, $P<.00001$). The number needed to treat to avoid 1 new case of T2DM was 45 patients treated for 4 to 5 years.[8] In 11 trials in 59,862 nondiabetic patients, ARB therapy reduced the incidence of new-onset diabetes by 17% compared with placebo, by 27% compared with β-blockers, and by 24% compared with calcium channel blockers (CCBs) (all highly significant). When the analysis was limited to patients with hypertension, ARBs were associated with 26% fewer cases of T2DM and a 15% lower incidence of impaired glucose tolerance, independent of achieved BP. Similar patterns were found in Western and Japanese patients.[9] The underlying mechanisms and clinical significance of improved glycemic control during RAS blockade are unclear. Using a rigid cutoff for diabetes probably accentuates the effect, in that a difference as small as 1 mg/dL in fasting glucose could change the diagnostic category.

MICROALBUMINURIA

Microalbuminuria is an indicator of diabetic nephropathy and is also a robust CVD risk factor.[10] The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study assigned 4447 patients with T2DM to olmesartan 40 mg daily or placebo (in addition to other antihypertensive agents to keep BP <130/80 mm Hg but not ACE inhibitors or spironolactone) for a median of 3.2 years.[11] Kaplan-Meier analysis demonstrated that the risk of developing microalbuminuria (>25 mg/g creatinine in men and >35 mg/g creatinine in women on at least 2 of 3 consecutive samples) was 8.2% in those taking olmesartan and 9.8% in those taking placebo (risk reduction, 23%; *P*=.01). Estimated glomerular filtration rate (eGFR)

was marginally lower in olmesartan-treated patients (80.1 mL/min/1.73 m^2 vs 83.7 mL/min/1.73 m^2; $P<.001$) but there was no end-stage renal disease (ESRD). In both groups, BP values and CVD morbidity were very low (<130/80 mm Hg and about 4%, respectively). CVD mortalities were also very few but were higher with olmesartan (15 vs 3; $P=.01$), apparently due to low BP values in individuals with pre-existing CVD.

HIGH CVD RISK

Overall, clinical trial information strongly suggests that ARBs have similar benefits as ACE inhibitors and CCBs in hypertension and that these benefits are proportional to the degree of BP elevation present. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Telmisartan Randomized Assessment Study (ONTARGET) in 25,925 individuals with high CVD risk including end-organ damage[12] included 37% diabetics. At 4.5 years, the primary outcome (CVD death, myocardial infarction, stroke, hospitalization for HF) occurred in 16.5% of patients taking ramipril 10 mg to 20 mg daily, 16.7% taking telmisartan 80 mg daily, and 16.3% taking the combination (P=NS). Compared with patients taking ramipril, those taking telmisartan had lower rates of cough (1.1% vs 4.2%; $P=.001$) and angioedema (0.1% vs 0.3%; $P=.01$), and the combination therapy caused more hypotensive symptoms (4.8% vs 1.7%; $P<.001$), syncope (0.3% vs 0.2%; $P=.03$), and renal dysfunction (13.5% vs 10.2%; $P<.001$). Noninferiority of telmisartan was formally established and tolerability was superior to ramipril or the combination. A second part of the overall program was the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trial, which compared telmisartan with placebo (plus other antihypertensive drugs as needed) in ACE inhibitor–intolerant individuals. Overall, telmisartan was not superior to placebo (ie, "usual care") in reducing the composite CVD end point, but BP values were low in both groups' at least in part because BP, cholesterol, and blood sugar were well controlled in both groups.

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial in 15,245 patients, 50 years or older, with treated or untreated hypertension and at high risk for CVD complications, demonstrated similar efficacy of valsartan-based therapy and amlodipine-based therapy over a mean of 4.2 years with respect to a composite end point of cardiac mortality and morbidity.[13]

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial included 9306 patients with impaired glucose tolerance and established CVD or high CVD risk who received valsartan (≤160 mg daily) or placebo for 5 years.[14] Valsartan reduced diabetes incidence by 14% but did not reduce the extended cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for HF or unstable angina, revascularization; 14.5% vs 14.8%, respectively) or the core cardiovascular outcome (composite outcome excluding unstable angina and revascularization, 8.1% vs 8.1%, respectively) compared with placebo. Underdosing of valsartan (80–160 mg daily) is a major weakness of the study, as is the fact that other cardiovascular drugs were allowed and risk factors were well controlled.

EARLY DIABETIC NEPHROPATHY AND RETINOPATHY

In the Renin-Angiotensin System Study (RASS) of 285 patients with type 1 diabetes included individuals with optimal BP (mean, approximately 112/74 mm Hg) and no microalbuminuria. Patients received losartan (100 mg daily), enalapril (20 mg daily), or placebo for 5 years. The primary end point (change in mesangial volume on kidney biopsy) did not differ significantly among treatments, but the 5-year cumulative incidence of microalbuminuria was 6% with placebo, 4% with enalapril ($P=.96$), and 17% with losartan ($P=.01$). In contrast, the secondary end point of retinopathy progression was reduced by 65% with enalapril and by 70% with losartan (both highly significant), independent of changes in BP. Thus, when BP remains normal in type 1 diabetes, blockade of the RAS does not prevent early nephropathy but may delay or prevent early retinopathy.[15]

In the Diabetic Retinopathy Candesartan Trial (DIRECT) program, 1905 normotensives patients, aged 37 to 75 years with type 1 or 2 diabetes and mild to moderate retinopathy but no microalbuminuria, were randomized for a mean of 4.7 years to candesartan (16 mg/d titrated to 32 mg/d) or placebo. The primary end point (progression of retinopathy by ≥3 steps on the Early Treatment Diabetic Retinopathy Study scale) occurred in 161 (17%) patients taking candesartan and 182 (19%) taking placebo ($P=.20$), but retinopathy regression while taking ARBs was 17% less ($P<.01$), independent of baseline risk factors or changes in BP. Candesartan did not affect the onset of microalbuminuria (urinary albumin excretion rate >20 μg/min on at least 3 of

4 collections) but did ameliorate the increase in albuminuria by 5.5% (P=.024). Adverse events did not differ between treatment groups. This study was not powered to detect changes in renal function or CVD outcomes, and the limited number of visits (annual assessments) blunted its sensitivity.[16]

A secondary objective of TRANSCEND was to ascertain the long-term renal effects of telmisartan 80 mg/d vs placebo (plus other antihypertensive treatments but not ACE inhibitors). In participants with diabetes or CVD plus end-organ damage but no macroalbuminuria or HF, the composite renal outcome was similar in both groups (telmisartan 2.0%, placebo 1.6%; P=.20): 7 and 10 patients started dialysis (P=NS), while 56 and 36 patients, respectively, experienced doubling of serum creatinine (P=.031). Albuminuria increases were attenuated by telmisartan (41% vs 63%, $P<.001$) but the decline in eGFR was less with placebo (0.26 ± 18.0 mL/min/1.73 m^2 vs -3.2 ± 18.3 mL/min/1.73 m^2; $P<.001$). The authors concluded that adults with vascular disease but no proteinuria show no renal benefits of ARB therapy.[17] As previously observed, however, all risk factors were well controlled.

ESTABLISHED DIABETIC NEPHROPATHY

Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study was a double-blind, randomized, placebo-controlled study in 1513 patients with T2DM and advanced renal disease. Losartan (50–100 mg daily) was compared with placebo when either was added to conventional antihypertensive treatments (but not ACE inhibitors) for a mean of 3.4 years.[18] Losartan lowered the incidence of the composite end point (doubling of the serum creatinine, occurrence of ESRD, or death) by 16% (P=.02), doubling serum creatinine by 25% (P=.006), ESRD by 28% (P=.002), proteinuria by 35% ($P<.001$), and HF hospitalization rate by 32% (P=.005) but did not reduce all-cause or CVD mortality or morbidity, apparently independent of BP lowering. In a secondary analysis of the interaction of BP and ARB effect, every 10-mm Hg rise in baseline systolic BP increased the risk for ESRD or death by 6.7% (P=.007), while an equivalent increase in diastolic BP *decreased* ESRD risk by 10.9% (P=.01) after adjustment for urinary albumin-creatinine ratio, serum creatinine, serum albumin, hemoglobin, and hemoglobin A_{1c}, demonstrating the importance of pulse pressure as a risk factor. Patients taking losartan who have baseline pulse pressures >90 mm Hg had a 53.5% risk reduction in ESRD (P=.003) and a 36% risk reduction in ESRD or death (P=.02). Thus, high systolic and pulse pressures confer the highest risk for nephropathy progression but also define the population with the greatest potential benefit when systolic BP is lowered to <140 mm Hg.[19]

The Irbesartan Diabetic Nephropathy Trial (IDNT) examined 1715 hypertensive patients with diabetic nephropathy and was similar to RENAAL.[20] In fact, pooled data from both studies permitted losartan and irbesartan to receive labeling for routine use in diabetic nephropathy and initiated consideration by the US Food and Drug Administration that ARB benefits represent a class effect. In IDNT, patients were treated with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo for 2.6 years, with other drugs as needed to reach target BP <135/85 mm Hg. The composite end point (doubling of the serum creatinine, development of ESRD, or death) was reduced with irbesartan by 20% compared with placebo (P=.02) and 23% compared with amlodipine (P=.006), but there were no differences in all-cause or CVD mortality. Irbesartan reduced the rate of doubling of serum creatinine by 33% compared with placebo (P=.003) and 37% compared with amlodipine ($P<.001$), while reducing ESRD by 23% against either comparator (P=.07 for both). The authors concluded that irbesartan was effective in protecting against the progression of nephropathy independent of its effects on BP.

CARDIOVASCULAR DISEASES

CVD remains the leading cause of death in patients with diabetes and many large-scale trials have been performed with different ARBs in patients with IHD, HF, and stroke. Full discussion of all CVD trials conducted with ARBs is beyond the scope of this paper but a brief summary of large trials and current guidelines regarding the role of ARB therapy seems appropriate. In most studies, a large fraction of the enrollees had diabetes, and in many, this subgroup was subjected to secondary analyses.

In 1195 patients with diabetes, hypertension, and signs of left ventricular hypertrophy from the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, the primary composite end point (cardiovascular death, stroke, or myocardial infarction) occurred in 103 of 586 patients taking losartan-based therapy compared with 139 of 609 assigned to atenolol (24% risk reduction; P=.031).[21] In contrast, in the main trial (diabetics and nondiabetics included), ARBs were only 13% more beneficial against the composite end point than β-blockade (P=.021).[13] Of note, the benefits of ARB were largely driven by a 25% reduction in

the incidence of first stroke. Also, in a small retrospective analysis, 44 patients with diabetes and sudden cardiac death from the LIFE study, 14 deaths occurred in the losartan group and 30 in the atenolol group (P=.027).[22]

In HF, the Valsartan Heart Failure Trial (Val-HeFT) in 5010 patients (mean age 62.7 years) demonstrated that valsartan 160 mg twice a day reduced the composite end point (mortality, cardiac arrest with resuscitation, hospitalization for HF, or use of intravenous inotropic or vasodilator therapy) by 13.2% compared with placebo (P=.009), largely due to lower HF hospitalizations (14% with valsartan, 18% with placebo; P<.001). Overall mortality was similar but valsartan improved New York Heart Association (NYHA) functional class, ejection fraction, signs and symptoms of HF, and quality of life compared with placebo (P<.01). Somewhat more favorable outcomes occurred with valsartan in the subgroup with diabetes.[23] The Candesartan In Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program tested candesartan in systolic and diastolic HF.[24,25] Unadjusted mortality rates were 23% with candesartan and 25% with placebo (P=.055) but hospital admissions for HF were less in patients randomized to candesartan (20% vs 24%; P<.0001).

STROKE

Randomized, double-blind trials with a primary stroke end point have not been performed for ARB therapy in a diabetic population. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) included 20,332 hypertensive patients with a recent ischemic stroke randomized to telmisartan (80 mg daily) or placebo for a mean of 2.5 years. The primary end point, recurrent stroke, occurred in 8.7% of patients taking telmisartan and 9.2% taking placebo (a 5% risk reduction; P=.23). Major cardiovascular events did not differ between treatments (about 14% overall).[26] In the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention: Principal Results of a Prospective Randomized Controlled Study (MOSES), an eprosartan-based regimen (600 mg/d) was similar to nitrendipine (10 mg/d) in reducing stroke recurrence (24.5% vs 22.3%; P=NS) in 1405 hypertensive patients with a history of cerebrovascular events.[27]

CURRENT GUIDELINES FOR ARB THERAPY

ARBs are indicated alone or in combination for hypertension and also for many of its complications and associated high-risk conditions (“compelling indications”), including diabetic nephropathy and chronic kidney disease.[3] For the treatment of hypertension in patients with IHD, either ARBs or ACE inhibitors are recommended.[28] Similarly, in dilated cardiomyopathies, including HF post–myocardial infarction, both ARBs and ACE inhibitors confer benefit and are considered to be essentially interchangeable.[3,29] ARB therapy has not been specifically recommended for stroke care but benefits have been demonstrated.

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