Optimal Treatment Strategies for Patients With Hypertension and Diabetes
Are Effects on Metabolism Important?

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Ruggenenti et al1 conducted a multicenter randomized, controlled 3-arm trial in 380 hypertensive patients with type 2 diabetes mellitus without albuminuria to examine whether treatment with an angiotensin-converting enzyme (ACE) inhibitor alone, an ACE inhibitor with a third generation calcium channel blocker, or placebo, would ameliorate target organ complications over a period of 3 years. At baseline, measured glomerular filtration rate (GFR) was well preserved at \( \approx 100 \) \( \text{mL/min per 1.73 m}^2 \) in each group. Urinary albumin excretion was minimal (\( \approx 5 \) to 6 \( \mu \)g/min), and >10% of the patients had no evidence of microalbuminuria. The primary plan of this study was to evaluate whether different forms of antihypertensive treatment would impact changes in measured GFR over time in patients with minimal or no evidence of diabetic kidney disease. Given the diminished likelihood that the different antihypertensive treatments could measurably affect kidney function at such an early stage of diabetes mellitus, the investigators also considered other biomarkers of diabetic complications, such as cardiovascular events, retinopathy, and nephropathy progression. Even so, it was a bold plan to evaluate the possibility of treatment effects at such an early stage of disease.

The observations of this clinical trial are fascinating and raise some important questions about treatment. The first interesting observation was the amazingly fast loss of GFR in this population of nonproteinuric diabetic patients with mild-to-moderate hypertension, \( \approx 4 \) \( \text{mL/min per 1.73 m}^2 \) per year. This rate of loss of renal function is on par with the trials of renin-angiotensin-aldosterone system (RAAS) blockade in patients with established diabetic nephropathy.1–3 In addition, there did not appear to be any specific benefit of the different antihypertensive treatment strategies on renal disease progression, even comparing the ACE inhibitor groups, compared with placebo. Was this a methodologic issue, a power issue, or is early disease progression in nonproteinuric diabetics with mild-to-moderate hypertension mediated by mechanisms that are unaffected by specific antihypertensive interventions? Given that these well-trained investigators used measured GFR, it is unlikely that a methodologic problem could explain the lack of difference. Moreover, a type 2 error attributed to insufficient power is unlikely, given the nearly identical GFR declines in the 3 different treatment arms. What we are left with considering is whether early disease progression is affected by modification of the RAAS or calcium channel blockade. Thus, one must consider other factors, such as the metabolic influences of diabetes mellitus, oxidative stress, and/or inflammation. As the investigators appropriately note in their article, the study emphasizes the importance of future research in identifying the mechanisms of progressive renal injury in patients with diabetes mellitus so that appropriate treatment strategies can be used.

The observations in this trial of patients with type 2 diabetes mellitus and well-preserved kidney function are remarkably similar to the observation of Mauer et al,4 who studied normotensive normoalbuminuric patients with type 1 diabetes mellitus in the Renin Angiotensin System Study. In the Renin Angiotensin System Study, \( \approx 500 \) patients were randomly assigned to receive an ACE inhibitor, an angiotensin receptor blocker, or placebo for 5 years to examine the influence of treatment on albuminuria and glomerular structural changes. As in the study by Ruggenenti et al,1 there was no evidence that early treatment with RAAS blockade modified renal disease progression.

The second interesting observation in the study by Ruggenenti et al1 was the evidence that combined use of the ACE inhibitor and calcium channel blocker significantly reduced the incidence of cardiovascular disease, retinopathy, and peripheral neuropathy compared with the ACE inhibitor, alone, or placebo. These improvements in clinical outcomes correlated with improved insulin sensitivity observed in those patients receiving the ACE inhibitor and the calcium channel blocker. Might this indicate that improvement in insulin sensitivity serves as a biomarker of therapeutic success in hypertensive patients with type 2 diabetes mellitus with minimal evidence of kidney disease? This is an important question, because it may provide a plausible explanation linking improvements in metabolism with clinical outcomes, which may be independent of changes of blood pressure. Some might argue that the differences in hemoglobin A1C levels in the 3 different treatment arms were a play of chance. However, the antidiabetic therapy was similar among the treatment groups, and the randomized, controlled trial design eliminates treatment bias. Thus, the favorable change of hemoglobin A1C in the patients receiving the ACE inhibitor/
calcium channel blocker combination can likely only be explained by improvements in insulin sensitivity. One has to consider whether the observations in the trial by Ruggenenti et al with improved outcomes with the ACE inhibitor/calcium channel blocker combination, with the associated improvements in insulin sensitivity, might explain the observations in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial. This study included patients with hypertension and type 2 diabetes mellitus (>60%) who were at high risk for cardiovascular events. In this large trial of >11 000 patients, those treated with an ACE inhibitor/calcium channel blocker combination had a 20% reduction in the cardiovascular end point composite compared with patients treated with an ACE inhibitor/hydrochlorothiazide combination. This cardiovascular risk reduction benefit was also observed in the subset of patients with diabetes mellitus when analyzed separately. Medications like RAAS blockers are known to improve insulin sensitivity. Vasodilators like calcium channel blockers may improve insulin sensitivity by enhancing the delivery of insulin to its site of action in skeletal muscle.

Thiazide diuretics and β-blockers may worsen insulin sensitivity, especially in people who are obese. Interestingly, in the study by Ruggenenti et al, there was a reduced need for concomitant treatment with diuretics and β-blockers in those patients receiving the ACE inhibitor/calcium channel blocker combination.

The third interesting observation from the trial by Ruggenenti et al was the effect of different antihypertensive therapy on clinical end points, such as neuropathy, retinopathy, and cardiovascular events. These observations in patients with type 2 diabetes mellitus and well-preserved kidney function are remarkably similar to the observations of Mauer et al in the Renin Angiotensin System Study (in patients with type 1 diabetes mellitus) where they described evidence that RAAS blockade modified the progression of retinopathy, despite no apparent effect on the progression of early diabetic nephropathy.

Overall, this study is of great interest to the scientific community because it demonstrates that renal disease progression may be substantial in the early stages of type 2 diabetes mellitus with hypertension, even in the absence of microalbuminuria. Although this study demonstrates that RAAS inhibition and calcium channel blockade may improve insulin sensitivity and nonrenal clinical outcomes in comparison with other treatment strategies, there is still an urgent need to identify the mechanisms of early renal injury in type 2 diabetes mellitus and hypertension so that appropriate treatment strategies can be developed. The results of this trial provide more evidence that improving insulin sensitivity may serve as a biomarker of therapeutic benefit and that treatment strategies that improve insulin sensitivity may offer advantages in patients with type 2 diabetes mellitus compared with treatment strategies that do not. One has to also consider whether lower achieved levels of blood pressure during the study would have altered the rate of progression of renal disease. Another interesting question is whether lower achieved levels of blood pressure also quench differences between the antihypertensive treatments on the secondary outcomes. In summary, this study is an important addition to the literature and indicates the need for more early intervention trials in higher risk hypertensive patients.

Disclosures

None.

References


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