

Inhibiting the renin-angiotensin system in patients with type 1 diabetes: is it worth it?

Irena Duka, George Bakris

Department of Medicine, Hypertensive Diseases Unit, University of Chicago Pritzker School of Medicine, Chicago, Illinois, United States

Diabetes mellitus (DM) is responsible for more than 45% of end-stage renal disease (ESRD) and is the leading cause of blindness in adults aged between 20 and 74 years in the United States.¹ The magnitude and duration of glycemic control reduces the risk of these complications although it is difficult to sustain over many years.² Blood pressure control also reduces the risk of kidney disease progression but very few studies examine blunting the rise in blood pressure over time compared to reducing the level once persistently elevated.

Initial studies in the 1980s demonstrated that angiotensin-converting enzyme (ACE) inhibitors prevent development of early changes in glomerular morphology and albuminuria in animal models of type 1 diabetes.^{3,4} Since then, outcome studies on humans have demonstrated a clear benefit of renin-angiotensin system (RAS) blockers in slowing proteinuric nephropathy.^{5,6} These clinical outcome trials were performed in patients with advanced nephropathy (i.e., glomerular filtration rate (GFR) <45 ml/min/1.73 m²) and proteinuria greater than 300 mg/day. They included patients with either type 1 or type 2 diabetes.⁷ Based on these trials both ACE inhibitors and angiotensin receptor blockers (ARB) are recommended by various guidelines as an initial part of an antihypertensive regimen with a goal of lowering blood pressure to <130/80 mmHg so as to slow nephropathy progression in patients with proteinuria, DM, decreased GFR.^{8,9} The question remains, however, what about early diabetic nephropathy, i.e., estimated GFR <60 ml/min with little to no albuminuria – are these agents effective in this setting or is blood pressure reduction all that is needed?

In their study, Mauer et al. assessed the effect of RAS blockade with either an ACE inhibitor or an ARB on both renal and retinal morphologic features in normotensive patients with type 1 diabetes who were normoalbuminuric.¹⁰ They did not

find any benefit in nephropathy progression based on changes in glomerular morphological with RAS blockers in this cohort after 5 years. Conversely, there was a reduction in progression of diabetic retinopathy by 65% and 70% with enalapril and losartan, respectively.

How do these results fit with known evidence? There is little solid evidence showing superiority of RAS blockade vs. other antihypertensive drug classes in slowing nephropathy progression in early-stage nephropathy, i.e., estimated GFR >60 ml/min, in the presence or absence of microalbuminuria. The ABCD trial (Appropriate Blood Pressure Control and Diabetes) did not show any benefit of ACE inhibition over calcium channel blockade in patients with type 2 diabetes for reduction in albuminuria or nephropathy progression assessed by creatinine clearance.^{11,12} In this study, the achieved blood pressure was around 130/80 mmHg in most people. This lack of unique benefit on nephropathy progression by ACE inhibitors was also seen in a post-hoc analysis of large community-based trials such as the ALLHAT (Antihypertensive Lipid Lowering Hypertension Trial).¹³ In addition to this study, meta-analyses of outcome trials in early nephropathy, i.e., estimated GFR >60 ml/min, demonstrated no unique advantage of RAS blockade for slowing nephropathy over other classes of antihypertensive medications in patients without proteinuria at levels higher than 300 mg/day. This meta-analysis, however, clearly confirms the benefit of RAS blockade on nephropathy progression when proteinuria exceeds 500 mg/day.¹⁴

Although the guidelines initially encouraged the use of RAS blockers in both early and advanced nephropathy, there was no evidence to support their use in early nephropathy. Most clinical trials that intervened in early nephropathy only followed the urinary albumin excretion, without looking at the decline in kidney function or morphologic changes in the kidney.

Correspondence to:

Prof. George Bakris MD,
Hypertensive Diseases Unit,
University of Chicago Medical Center,
5841 S. Maryland Ave.,
MC 1027, Chicago, IL 60637,
phone: +1-773-702-79-36,
fax: +1-773-834-04-86,
e-mail: gbakris@gmail.com

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Microalbuminuria alone is not an indicator of nephropathy because of its high variability and nonspecificity.^{15,16} Although microalbuminuria is associated with vascular inflammation¹⁷ and increased cardiovascular risk, by itself it does not equate to presence of nephropathy, unless it continues to increase over time in spite of blood pressure levels well below 140/90 mmHg.

RAS is involved in increased vascular permeability during early stage of diabetic retinopathy; this effect is mediated by vascular endothelial growth factor (VEGF).¹⁸⁻²⁰ Theoretically, these agents could be affecting a central mechanism of retinopathy related to ocular VEGF, as they inhibit its action.^{21,22} RAS blockade has demonstrated beneficial effects in animal studies of retinopathy and may have a therapeutic role in its treatment.^{19,20,23,24} Clinical evidence to support this finding came from the recent study by Mauer et al. They clearly demonstrated benefits for prevention of retinal disease progression.

This recent observation demonstrating that RAS blockade slows retinopathy progression extends earlier data from the EUCLID trial that supported a benefit of ACE inhibition to be associated with less retinopathy in type 1 diabetes.²⁴ Additionally, The DIRECT trial (Diabetic Retinopathy Candesartan Trial) showed that ARBs reduced the rate of retinopathy development in normotensive patients with type 1 diabetes and normoalbuminuria, who did not have diabetic retinopathy, but not in patients with mild-to-moderate diabetic retinopathy.²⁵

How do we translate the findings of the current study by Mauer et al. to everyday practice and care of diabetic patient? First, RAS inhibition in normotensive patients with diabetes does not show unique protective benefits for preserving kidney function in the absence of albuminuria. If proteinuria exceeding 300 mg/day is present, then there is a clear indication for the use of these agents to slow nephropathy progression. Second, data that RAS blockade slows development of retinopathy are growing and should be considered especially in patients with poor glycemic control.

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