Does renin angiotensin system blockade deserve preferred status over other anti-hypertensive medications for the treatment of people with diabetes?

Joshua I. Barzilay[1], Paul K. Whelton[2], Barry R. Davis[3]

[1]Kaiser Permanente of Georgia and the Division of Endocrinology, Emory University School of Medicine, Atlanta, GA, USA; [2]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA; [3]Department of Biostatistics, University of Texas School of Public Health, Houston, TX, USA

Correspondence to: Joshua I. Barzilay, MD. 3650 Steve Reynolds Blvd, Duluth, GA, 30096, USA. Email: Joshua.barzilay@kp.org.

Submitted May 02, 2016. Accepted for publication May 09, 2016.
doi: 10.21037/atm.2016.05.24
View this article at: http://dx.doi.org/10.21037/atm.2016.05.24

Introduction

For more than 20 years it has been "accepted medical dogma" that patients with diabetes mellitus (DM) and hypertension, renal disease, or cardiovascular disease (CVD) should be treated with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) that blocks the renin angiotensin system (RAS) (1). So widely held is this belief that RAS blockers are commonly prescribed to individuals with DM who do not have a diabetes-related illness because of their perceived "protective" effects. Recently, several studies and meta-analyses have questioned this practice and have reported that RAS blocking agents do not offer any advantages compared to other antihypertensive medications for the treatment of adults with DM. The most recent such study was published by Bangalore *et al.* in the February 11, 2016 issue of the *BMJ* (2).

Here we review the evidence that has been used to support the use of RAS blockade as a preferred treatment for adults with DM. We then review the studies that call this recommendation into question.

Renal studies

DM is associated with an increased risk of albuminuria and a decline in renal function. Treatment studies in patients with diabetic kidney disease laid the foundation for the widespread use of RAS blockade in the management of DM.

Survey reports in the mid-1980s showed that microalbuminuria was highly prevalent in persons with type 1 DM (3). It was hypothesized that microalbuminuria was a marker for future renal failure. Specifically, it was suggested that after many years of low grade albuminuria, there was commonly a transition to heavy urinary protein (proteinuria), followed by a decline in glomerular filtration rate (GFR). This model assumed that heavy proteinuria predicted loss of renal function and that lowering levels of microalbuminuria/proteinuria would lessen the risk of a progressive decline in renal function. Initially, research findings seemed to corroborate this theory. In 1992, the ACEi enalapril was reported to offer more reno-protection in diabetic nephropathy for an equal blood pressure reduction compared with metoprolol in a small study of 40 adults with insulin dependent DM and moderately impaired renal function (4). In a larger study of 409 patients with insulin dependent DM, captopril was reported to significantly lower the risk for doubling of serum creatinine compared to standard therapy (5). In a 1994 European study of 92 non-hypertensive persons with insulin dependent DM and microalbuminuria, captopril also slowed progression to overt proteinuria significantly and prevented an increase in albumin excretion compared to placebo (6).

Similar reno-protective results were noted in patients with type 2 DM. In the IRMA 2 trial, conducted in patients with hypertension and microalbuminuria, there was a 70% reduction in progression to overt nephropathy with the ARB irbesartan compared to placebo (7). In the

IDNT study of participants with overt nephropathy, there was a 20% reduction in the incidence of a composite endpoint of serum creatinine doubling, end-stage renal disease (ESRD) or death during treatment with the ARB irbesartan compared with placebo (8). The RENAAL study demonstrated that addition of the ARB losartan to standard antihypertensive therapy significantly reduced doubling of creatinine, ESRD or death by 16% compared with placebo (9). Based on these results the United States Food and Drug Administration in 1994 recommended the use of RAS blockade medications as a treatment for diabetic kidney disease.

Recently, the conclusions based on these studies have been called into question for four reasons:

(I) First, many of the previously mentioned studies were small and of short duration. Also, analysis of one of the studies (5) showed that the relative risk (RR) reduction for doubling of creatinine level in patients treated with captopril was limited to those with creatinine levels above but not below 1.5 mg/dL. Other studies have confirmed this observation (10);

(II) Second, our understanding of the pathophysiology of diabetic renal disease is far better now than in the 1980s. Prospective studies of type 1 DM have demonstrated that microalbuminuria is more likely to remit than to progress (11-13) and only ~15–25% develop proteinuria (14-16). Moreover, several studies have demonstrated that renal functional impairment is already present prior to the onset of albuminuria (17). Also, approximately 10% of diabetic adults without albuminuria show evidence of a reduced GFR. Taken together, these findings show that the association of albuminuria and GFR decline in the setting of DM is complex and quite different than previously suggested. Recent studies have failed to confirm the earlier reports that drug therapy leading to a reduction in albuminuria improves renal function. A meta-analysis of nine studies in patients with type 1 DM failed to demonstrate a beneficial effect on the percent decrease in GFR despite suppression of microalbuminuria with RAS blockade (10). Likewise, in the ONTARGET trial (~26,000 participants, with ~35% having type 2 DM) treatment with a combination of the ACEi ramipril and the ARB telmisartan resulted in an increased risk of primary renal disease end points (dialysis, doubling of creatinine, or death) and also reduction in eGFR compared to treatment with ramipril alone, despite more effective lowering of albuminuria with the combination therapy (18);

(III) The third line of evidence that refutes recommendations for preferential use of RAS agents in patients with diabetic nephropathy comes from a more recent multi-center, controlled trial of 285 normotensive patients with type 1 DM and normoalbuminuria (19). These participants were randomly assigned to receive losartan, enalapril, or placebo and were followed over a period of 5 years. The primary end point was based on renal biopsy findings of change in the fraction of glomerular volume occupied by mesangium. The study found no difference for the primary outcome in the three study groups during 5 years of treatment, nor were there any significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6%, 17% and 4% in the placebo, losartan and enalapril group, respectively. The authors concluded that RAS blockade in patients with type 1 DM did not slow nephropathy progression.

Finally, despite more than 20 years of therapy with agents that block the RAS, the prevalence and incidence of diabetic and non-diabetic kidney disease continue to increase (20). Surely, if RAS blockade was an effective means of treatment and prevention of diabetic nephropathy, such trends would not be seen!

Cardiovascular disease (CVD)

The preferential use of RAS blockade for treatment and prevention of CVD in patients with DM, beyond its known beneficial effects on CVD, was based on two hypotheses. First, if RAS blockade had a favorable effect on the kidney, then it should also have a favorable effect on the cardiovascular system because renal disease is a major risk factor for CVD. Second, early studies suggested that RAS blockade with an ACEi could lower glucose levels and there was a belief that this might prevent heart disease.

In the HOPE trial (21) the ACEi ramipril, as compared to placebo, decreased the risk of a primary composite end point of myocardial infarction, stroke, or death from CVD and of microalbuminuria among adults with and without DM. After adjustment for changes in systolic and diastolic blood pressure, those who had been assigned to treatment

with ramipril remained at lower risk for the combined primary end point. These findings provided the basis for the notion that RAS blockade is effective for cardio-renal protection independent of blood pressure lowering. The HOPE findings have not been confirmed in other studies. In the NAVIGATOR trial, the ARB valsartan did not reduce the rate of cardiovascular events compared to placebo (22). Other placebo-controlled trials of RAS blockade in high risk diabetic and non-diabetic study groups, including PROGRESS, CAMELOT, and PEACE have also failed to demonstrate the superiority of RAS blockade for prevention of CVD (23-25).

With regard to the glucose lowering effects of RAS blocking agents, meta-analyses of hypertension studies show that these agents are more effective than drugs from other classes of antihypertensive medication for preventing incident DM (IDM) (26). It is less clear that RAS blockade, compared to placebo, reduces the risk of IDM when added to usual care therapy in adults at high risk for CVD or DM. In the MICRO-HOPE substudy (27), the ACE inhibitor ramipril decreased the risk of self-reported IDM among participants at high risk for CVD (3.6% *vs.* 5.4%, RR, 0.66, 95% CI: 0.51–0.85, P<0.001). In the NAVIGATOR trial (22), the ARB valsartan significantly decreased the risk of IDM (33.1% *vs.* 36.8%, RR: 0.86, 95% CI: 0.80–0.92, P<0.001). In contrast, in the DREAM study (28), which was designed to specifically study the effects of RAS blockade on DM prevention, ramipril did not significantly reduce IDM incidence in adults with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (17.1% *vs.* 18.5%, RR, 0.91, 95% CI: 0.80–1.03, P=0.15). Likewise, in the TRANSCEND study (29) of individuals at high risk for CVD randomized to the ARB telmisartan 80 mg (n=1,726) or placebo (n=1,762) in addition to usual care, 22.3% of the participants treated with telmisartan and 23.3% of those treated with placebo developed IDM (RR, 0.94, 95% CI: 0.82–1.08, P=0.37) during 56 months of follow-up. Participants with impaired glucose (IFG and/or IGT) were equally likely to regress to normoglycemia (NG) (26.9% *vs.* 24.5%) or to progress to DM (20.1% *vs.* 21.1%; P=0.59) on telmisartan or placebo on follow-up. These conflicting results may be explained by the fact that the studies reporting a glucose lowering effect with RAS blockade were post hoc analyses in which IDM was not a pre-specified outcome, and did not measure glucose levels systemically or obtain 2 hours post challenge levels, relying instead on physician report or self-report of DM.

Other meta-analyses, population studies, and ALLHAT

Given the above information, the report by Bangalore *et al.* (2) is not surprising. This is not the first meta-analysis to report that RAS blockade offers no advantage over other antihypertension medications for the treatment of people with DM. Two meta-analyses and two large studies showed similar results (30-34).

In a network meta-analysis of 42 randomized trials, Psaty *et al.* studied the effect of different classes of antihypertensive drug therapy on CVD (30). None of the first-line agents—beta-blockers, ACEi's, calcium channel blockers (CCBs), alpha-blockers, or ARBs—was significantly better than low-dose diuretics for prevention of CHD, CHF stroke, CVD, and total mortality. Compared with ACEi's, low-dose diuretics were associated with reduced risks of CHF (RR, 0.88; 95% CI: 0.80–0.96), CVD events (RR, 0.94; 95% CI: 0.89–1.00), and stroke (RR, 0.86; 95% CI: 0.77–0.97). Blood pressure changes were similar between treatment groups.

Casas *et al.* (31) examined randomized trials through 2005 assessing antihypertensive drugs and progression of renal disease. Effects on primary endpoints such as doubling of creatinine, ESRD and secondary endpoints such as creatinine, albuminuria, and GFR were studied. Comparisons of ACEi's or ARBs with other antihypertensive drugs yielded a RR of 0.71 (95% CI: 0.49–1.04) for doubling of creatinine and a small benefit for ESRD (RR 0.87, 95% CI: 0.75–0.99). Analyses of the results by study size showed a smaller benefit in large studies. In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on the doubling of creatinine (RR, 1.09, 95% CI: 0.55–2.15), ESRD (RR, 0.89, 95% CI: 0.74–1·07), GFR, or creatinine levels. Placebo-controlled trials of ACEi's or ARBs showed greater benefits than comparative trials on all renal outcomes, but were accompanied by substantial reductions in blood pressure in favor of ACEi's or ARBs. The authors concluded that the benefits of ACEi's or ARBs on renal outcomes in placebo-controlled trials probably resulted from a blood-pressure-lowering effect.

In a population-based study from Canada, Suissa *et al.* (32) found that ACEi's do not appear to decrease and might actually increase the long-term risk of ESRD in diabetes. This study was based on a registry of medication prescription, including diabetic patients who were prescribed antihypertensive agents from 1982 to 1986. The 6,102 patients were followed to the end of 1997 with respect

to development of ESRD. Relative to thiazide diuretic use, the adjusted rate ratio of ESRD associated with the use of ACE inhibitors was 2.5 (95% CI: 1.3–4.7), whereas it was 0.8 (95% CI: 0.5–1.4) for beta-blockers and 0.7 (95% CI: 0.4–1.3) for calcium antagonists. The rate ratio of ESRD with the use of ACE inhibitors was 0.8 (95% CI: 0.3–2.5) during the first 3 years of follow-up, but increased to 4.2 (95% CI: 2.0–9.0) after 3 years. The authors concluded that ACEi use did not decrease the long-term risk of ESRD in DM.

Finally, the ALLHAT investigators reported no advantage for prevention of clinical outcomes during first-step treatment of hypertension with the ACEi lisinopril compared to the diuretic chlorthalidone or the calcium blocker amlodipine. ALLHAT was an active-controlled double-blind trial conducted in 31,512 adults, 55 years or older, with hypertension and at least one other indication of risk for coronary heart disease, stratified into DM (n=13,101), IFG (n=1,399), and NG (n=17,012) groups on the basis of national guidelines (33). The study failed to find any significant difference in RR for fatal coronary heart disease or nonfatal myocardial infarction in the DM or NG participants assigned to amlodipine or lisinopril *vs.* chlorthalidone or in IFG participants assigned to lisinopril *vs.* chlorthalidone. Stroke was more common in NG participants assigned to lisinopril *vs.* chlorthalidone [RR, 1.31 (range, 1.10–1.57)]. Heart failure was more common in participants with DM and NG who were assigned to amlodipine [RR, 1.39 (range, 1.22–1.59) and 1.30 (range, 1.12–1.51), respectively] or lisinopril [RR, 1.15 (range, 1.00–1.32) and 1.19 (range, 1.02–1.39), respectively] compared to chlorthalidone. The authors concluded that there was no evidence of superiority for treatment with CCBs or ACEi's compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG. Likewise, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of ESRD or a 50% or greater decrement in GFR (34).

Summary

Many medical societies, including the American Diabetes Association (35), American Association of Clinical Endocrinologists (36), and British National Institute for Health and Excellence (37), continue to advocate for use of RAS blockade as the primary treatment of DM and its complications. In contrast, the panel members appointed to the Eighth Joint National Commission on the Treatment of Hypertension (38) suggested that combinations of antihypertensive medications that lower blood pressure effectively is the preferred approach to treatment and did not advocate for preferential use of any class of antihypertensive medication. We note that it is now customary to treat people with DM and hypertension with multiple blood pressure lowering agents, so the question of the "primacy" of RAS blockade is probably moot.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Xiaoyan Wang, MD (Master of cardiology in reading, Dalian Medical University, General Hospital of Shenyang Military Region, Shenyang, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ruilope LM, Solini A. RAS blockade for every diabetic patient: pro and con. Diabetes Care 2011;34 Suppl 2:S320-4.
2. Bangalore S, Fakheri R, Toklu B, et al. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438.
3. Mogensen CE. How to protect the kidney in diabetic patients: with special reference to IDDM. Diabetes 1997;46 Suppl 2:S104-11.
4. Björck S, Mulec H, Johnsen SA, et al. Renal protective effect of enalapril in diabetic nephropathy. BMJ 1992;304:339-43.
5. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-62.
6. Viberti G, Mogensen CE, Groop LC, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA 1994;271:275-9.
7. Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.

8. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
9. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
10. Jerums G, Panagiotopoulos S, Premaratne E, et al. Lowering of proteinuria in response to antihypertensive therapy predicts improved renal function in late but not in early diabetic nephropathy: a pooled analysis. Am J Nephrol 2008;28:614-27.
11. Araki S, Haneda M, Sugimoto T, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes 2005;54:2983-7.
12. Amin R, Turner C, van Aken S, et al. The relationship between microalbuminuria and glomerular filtration rate in young type 1 diabetic subjects: The Oxford Regional Prospective Study. Kidney Int 2005;68:1740-9.
13. Amin R, Widmer B, Prevost AT, et al. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. BMJ 2008;336:697-701.
14. Roy MS, Affouf M, Roy A. Six-year incidence of proteinuria in type 1 diabetic African Americans. Diabetes Care 2007;30:1807-12.
15. de Boer IH, Sibley SD, Kestenbaum B, et al. Central obesity, incident microalbuminuria, and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. J Am Soc Nephrol 2007;18:235-43.
16. Costacou T, Ellis D, Fried L, et al. Sequence of progression of albuminuria and decreased GFR in persons with type 1 diabetes: a cohort study. Am J Kidney Dis 2007;50:721-32.
17. Perkins BA, Ficociello LH, Ostrander BE, et al. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 2007;18:1353-61.
18. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.
19. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40-51.
20. United States renal data system. Accessed 18 March, 2016. Available online: http://www.usrds.org
21. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53.
22. NAVIGATOR Study Group, McMurray JJ, Holman RR, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477-90.
23. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.
24. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004;292:2217-25.
25. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058-68.
26. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007;369:201-7.
27. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9.
28. DREAM Trial Investigators, Bosch J, Yusuf S, et al. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355:1551-62.
29. Barzilay JI, Gao P, Rydén L, et al. Effects of telmisartan on glucose levels in people at high risk for cardiovascular disease but free from diabetes: the TRANSCEND study. Diabetes Care 2011;34:1902-7.
30. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534-44.
31. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet 2005;366:2026-33.
32. Suissa S, Hutchinson T, Brophy JM, et al. ACE-inhibitor use and the long-term risk of renal failure in diabetes. Kidney Int 2006;69:913-9.
33. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2

diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401-9.
34. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:936-46.
35. American Diabetes Association. Cardiovascular Disease and Risk Management. Diabetes Care 2015;38:S49-S57.
36. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association Of Clinical Endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm - 2016 executive summary. Endocr Pract 2016;22:84-113.
37. NICE guidelines [CG127]. Hypertension in adults: diagnosis and management. Available online: https://www.nice.org.uk/guidance/cg127
38. James PA, Oparil S, Carter B, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.

Cite this article as: Barzilay JI, Whelton PK, Davis BR. Does renin angiotensin system blockade deserve preferred status over other anti-hypertensive medications for the treatment of people with diabetes? Ann Transl Med 2016;4(10):202. doi: 10.21037/atm.2016.05.24

