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

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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: 0.80–0.92, P<0.001). 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 and a small benefit for ESRD (RR 0.87, 95% CI: 0.75–0.99).

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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.

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**Footnote**

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