Use of Renin-Angiotensin System Blockade in Patients with Renal Artery Stenosis

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In his work as a pathologist in the early 20th century, Harry Goldblatt recognized that patients with hypertension were exceptionally prone to renovascular sclerosis on autopsy. The renal lesions were more frequent and severe than the atherosclerotic changes appreciated in any other organ in these patients (1). He applied this notion to the development of his animal models, which ultimately revealed a link between renovascular disease, hypertension, and humoral dysregulation (2). Goldblatt demonstrated that clamping the renal artery (i.e., inducing renal ischemia) resulted in hypertension. However, simultaneously clamping the renal artery and renal vein yielded a normotensive response. He concluded that renal ischemia precipitated the release of a pressor substance into the circulation. This pressor (vasoconstrictive) substance was later found to be angiotensin II (AT), which is generated by the release of renin by the ischemic kidney and activated by angiotensin-converting enzyme (ACE). Subsequent animal and human studies further elaborated on these findings. Individuals with unilateral renal artery stenosis develop renin-dependent hypertension and increased peripheral vascular resistance (2,3). By contrast, individuals with bilateral renal artery stenosis or solitary kidney with renal artery stenosis develop volume-dependent hypertension, which is notable for a normal to decreased renin activity over time (referred to as Goldblatt hypertension) (4–6).

The role of renin-angiotensin system (RAS) blockade in renal artery stenosis has been of considerable interest and debate since the first ACE inhibitor, captopril, became commercially available in the late 1970s. In 1983, Hricik et al. (7) and Curtis et al. (8) observed the phenomenon of acute renal insufficiency from high-dose captopril in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary (e.g., transplanted) kidney. Both articles hypothesized that RAS blockade augmented the glomerular hyperperfusion already present in renovascular disease. Moreover, the adverse renal effects of captopril often occurred independently of systemic lowering of BP. Although azotemia reversed upon discontinuation of captopril, these early reports essentially stigmatized the use of RAS blockade in renovascular disease over the next 3 decades. Multiple randomized controlled trials corroborated that RAS blockade decreases the rate of progression of various underlying causes of renal disease (9–11).

Although observational studies of RAS blockade in patients with renal artery stenosis demonstrate significant benefit on BP control, progression of renal disease, adverse cardiovascular outcomes, and all-cause mortality (12,13), there are no randomized controlled trials to support these findings. Thus, the use of RAS blockade in renal artery stenosis remains controversial to this day.

Based on the information gained from the Goldblatt kidney experiments, vascular intervention of renal artery stenosis has been widely explored since the 1970s. In 1974, Juncos et al. reported the results of 75 patients who underwent nephrectomy or surgical resection of renal artery lesions (14). The patients in the study were diagnosed with renovascular disease preoperatively, using a combination of renography or urography and elevated plasma renin levels sampled from the renal veins. More than 90% of patients in the study demonstrated significant improvement in BP postoperatively. In addition, patients who underwent surgical intervention had improved renal and cardiac outcomes, as well as decreased mortality risk, compared with patients treated with medical therapy (15). However, these surgical interventions were highly invasive, and were associated with considerable morbidity.

Along with advances in vascular interventions and diagnostic techniques, multiple observational studies subsequently exhibited significant improvements in BP and renal function after renal artery angioplasty or stenting in patients with both unilateral and bilateral atherosclerotic renovascular disease (16–19). However, randomized controlled trials by van Jaarsveld et al. (20), Plouin et al. (21), and Webster et al. (22) demonstrated little benefit from renal artery angioplasty over medical therapy (which often included the use of RAS blockade). Randomized controlled trials evaluating renal artery stenting by Bax et al. (23) and the Angioplasty and Stenting for Renal Artery Lesions trial investigators (24) similarly demonstrated no significant improvement in BP or renal outcomes. Although they are less invasive than surgical interventions, both angioplasty and stenting were associated with significant complication rates in each of these studies.

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study, a randomized controlled trial published in 2014, evaluated renal artery stenting in patients with atherosclerotic renovascular disease (25).
In this international multicenter trial, 931 patients were randomized to stenting plus medical therapy versus medical therapy alone. Optimal medical therapy included an angiotensin receptor blocker (ARB), candesartan, as the first-line therapy, substituted by ACE inhibitors in patients who were ARB intolerant (26). In contrast to the previous randomized controlled trials, the CORAL study was specifically designed to investigate clinical cardiovascular and renal outcomes. The primary outcome was a composite end point including cardiovascular or renal death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine, and need for RRT. The secondary outcomes included changes in renal function and BP control (26). Similar to the previous trials, the CORAL study demonstrated no significant benefit from angioplasty and stenting over optimal medical therapy (25).

In this edition of CJASN, Evans et al. (27) point out, the cross-sectional nature of the data makes it difficult to draw any robust conclusions about the cause of this heterogeneity in prescribing patterns. Regardless, these findings highlight the ongoing controversy and uncertainty with regard to the safety and appropriateness of RAS blockade in renal artery stenosis.

What benefits, beyond BP reduction, might accrue to patients with renovascular disease who are treated with RAS inhibition? Because renovascular disease is frequently accompanied by vascular disease in other beds, we turn to our cardiological, vascular, and neurologic colleagues for insight here. Among the various classes of antihypertensive agents, RAS inhibitors seem to be more effective at left ventricular hypertrophy regression compared with other therapies providing a similar degree of BP reduction (28,29). ACE inhibition has improved survival after myocardial infarction (30,31). ACE inhibitors were among the first agents shown to improve survival in heart failure (32,33). In addition, ACE inhibitors significantly decrease the risk of adverse cardiovascular events in CKD (34,35). ACE inhibitors, in particular, appear to outperform other classes of antihypertensive agents when it comes to destifing the aorta in hypertension (36). Some ACE inhibitors appear to be lipophilic enough to traverse the blood-brain barrier, and preliminary studies suggest a possible benefit on the course of cognitive function loss in dementia (37), although randomized trials using RAS inhibition for this have not been very encouraging (38,39). Much is made in the basic science literature on the potential value of ARBs in the limitation of stroke consequences (40) because of AT1 receptor stimulation from greater availability of ligand (angiotensin II) when selective AT1 blockade is in use (41). However, despite early encouraging signals in this regard (42), the utility of ARBs in that area remains an unfulfilled promise based upon completed large randomized ARB trials (43,44). Finally, ACE inhibitors and ARBs have the cleanest metabolic profile when it comes to the development of new-onset diabetes in randomized clinical trials of antihypertensive drug treatment (45).

Overall, it seems that the established clinical profiles of ACE inhibitors and ARBs (after 33 and 19 years of clinical usage, respectively), their antihypertensive effectiveness in renovascular disease, and their potential for outcome benefit in other target organs, such as the heart and aorta, do much to reassure us that the risks of RAS therapy (azotemia, increased potassium, and angioedema) are more than balanced by their benefits when patients are suitably coached and monitored.

Disclosures
None.

References


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See related article, “Use of Renin-Angiotensin Inhibitors in People with Renal Artery Stenosis,” on pages 1199–1206.