Editorial

Interventional Cardiology

# Renal artery stenosis: 'an answer looking for a question'?

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## The answer

Renal artery stenosis (RAS) is a frequently encountered problem in clinical practice, causing three major syndromes: hypertension, nephropathy and destabilizing cardiac syndromes. Much like opening a coronary artery to increase perfusion of the myocardium, opening a stenotic renal artery to improve creatinine clearance or mitigate renovascular hypertension makes intuitive sense: open the lesion, improve perfusion and fix the problem. In the early 1990s, uncontrolled trials suggested that revascularization may be beneficial for both blood pressure reduction and the stabilization of chronic kidney disease [1,2]. Following this early data, the use of percutaneous revascularization rapidly expanded, with annual volume increasing by 2.4-fold from 1996 to 2000 [3]. Unfortunately, this therapy has not lived up to its much hoped for and expected potential, and any observed benefits have only been marginal. In addition, the major trials that have largely shaped our understanding of the treatment of RAS are fraught with bias, rendering their findings uninterpretable at best. We are left with may unanswered questions, or more appropriately, in the case of renal artery stenosis, we are left with an answer looking for a question.

## Analysis of major clinical trials

Among the first large clinical trials that shaped our understanding of the treatment of RAS was the DRASTIC trial [4]. In this study, 106 patients with RAS (50%) and resistant hypertension were randomized to renal angioplasty versus medical therapy. At both 3 and 12 months, there were no significant differences in diastolic or systolic blood pressures. The authors concluded that in the treatment of patients with hypertension and RAS, angioplasty has little advantage over medical therapy. Significant limitations of this trial included a small sample size, the use of angioplasty alone without stenting, inclusion of non-hemodynamically significant lesions (50–70% stenosis), and significant cross-over. Notably, 22 of the 55 patients originally randomized to medical therapy crossed over to the angioplasty arm and were still analyzed as intention to treat. The flaws inherent in this trial's study design prevent the formation of any definitive conclusions.

A second major clinical trial is known as the STAR trial [5]. STAR was a multicenter, randomized study of 140 patients with RAS and renal impairment (glomerular filtration rate: 80 ml/min). Patients were randomized to renal artery stenting and medical therapy, or medical therapy alone. The primary outcome of the study was a 20% decrease in creatinine clearance over 2 years of follow-up. Ten out of 64 patients (16%) in the stent placement group and 16 patients (22%) in the medication group reached the primary end point (hazard ratio: 0.73; 95% CI: 0.33–1.61). There was not a significant difference in the progression of renal failure between the two groups. In addition, there was no statistically significant difference in any of the secondary end points. Due to a small number of significant procedure-related complications without any clear effect on progression of renal impair-

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ment, the authors believe that their findings favored a conservative, drug-based approach with avoidance of stenting. Once again, however, design flaws and bias hinder meaningful interpretation of the data. The STAR study population included a large proportion of patients (33%) with only mild RAS (50–70%). Again, crossover was a noteworthy problem, with only 72% of patients originally randomized to the stunting arm actually undergoing the procedure with the remainder still analyzed as intention-to-treat. Of note, 50% of the study population had only unilateral disease. Usually changes in creatinine clearance (the primary end point) are only observed in patients with bilateral RAS.

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ASTRAL was a randomized, unblinded study of 806 patients with uncontrolled or refractory hypertension or unexplained renal dysfunction with radiographic evidence of ARAS [6]. The primary outcome was change in renal function as measured by the reciprocal of the serum creatine level. Over a 5-year period, there was no clinically relevant difference between the two groups in the rate of progression of renal impairment. In addition, there were no significant improvements in blood pressure, rates of renal or cardiovascular events, or mortality. A closer look at the inclusion criteria reveals a huge potential for selection bias in this study. Patients thought to need revascularization within 6 months were excluded, while others were only enrolled if their doctor deemed the benefit of revascularization to be uncertain. In addition, a large proportion (17%) of patients randomized to the stunting group failed to undergo the procedure. Other concerns include an unusually high adverse event rate as well as a protracted recruitment period.

The CORAL trial is a multicenter, randomized trial recently published in the *New England Journal of Medicine* [7]. This eagerly awaited study was designed to compare medical therapy alone to stenting with medical therapy. It is believed that CORAL has corrected for several of the flaws that plagued the preceding trials by including more stringent inclusion criteria in regards to degree of stenosis and reduction of crossover. After completion of the study, the authors found no significant difference between the two groups in regards to the composite end point of major cardiovascular and renal adverse events.

## Conclusion & future perspective

In summary, while much of the available data are inherently flawed, a review of the major clinical trials reveals an obvious lack of evidence to support the use of endovascular revascularization for the routine treatment of hypertension and nephropathy. With the recent publication of CORAL, the case against renal artery stenting has only grown stronger. At the very least, the results of these studies make a strong case for an optimum trial of medical therapy, reserving revascularization as a second-line therapy. Furthermore, the results of these trials are averaged over a study population and are not always applicable to individuals. It is likely that within certain subgroups, revascularization may provide substantial benefits over medical therapy. It possible that with the discovery of new and effective clinical predictors, these patients could be identified and more appropriately treated. As a final note, it is important to remember that while stenting as a treatment for hypertension and nephropathy remains controversial, there is general consensus on the treatment of RAS in the setting of a cardiac destabilizing syndromes. In fact, the only class I indication for revascularization is for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or flash pulmonary edema (level of evidence: B) [8].

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## References

1 Blum U, Krumme B, Flügel P *et al.* Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. *N. Engl. J. Med.* 336, 459–465 (1997).

2 Burket MW, Cooper CJ, Kennedy DJ *et al.* Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am. Heart J.* 139, 64–71 (2000).

3 Murphy TP, Soares G, Kim M. Increase in utilization of percutaneous renal artery interventions by Medicare beneficiaries, 1996–2000. *AJR Am. J. Roentgenol.* 183, 561–568 (2004).

4 van Jaarsveld BC, Krijnen P, Pieterman H *et al.* The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N. Engl. J. Med.* 342(14), 1007–1014 (2000).

5 Bax L, Woittiez AJ, Kouwenberg HJ *et al.* Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann. Intern. Med.* 150(12), 840–841, W150 (2009).

6 Wheatley K, Ives N, Gray R *et al.*; ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. *N. Engl. J. Med.* 361(20), 1953–1962 (2009).

7 Cooper CJ, Murphy TP, Cutlip DE *et al.*; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N. Engl. J. Med.* 370(1), 13–22 (2014).

8 Hirsch AT, Haskal ZJ, Hertzer NR *et al.*; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guide-lines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans Atlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/ Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans Atlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 13(11), e463–e654 (2006).