LEADING ARTICLE

Do Kidneys Need Blood?

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At first sight the question appears naïve and certainly there is consensus that a kidney with no blood supply is not going to function. But what if the blood flow is just reduced, that is, by a renal artery stenosis (RAS), what does that mean for a patient and should it be corrected by arterial stenting? The much awaited CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial published recently in the *New England Journal of Medicine*[1] concluded that in patients with a >60% atherosclerotic RAS and either hypertension and/or impaired renal function gained no additional benefit from renal artery stenting over medical therapy alone. This is not an unfamiliar story and adds one more trial to the list of five that have been unable to demonstrate any benefit from renal stenting for atherosclerotic RAS.[2–6] CORAL is the largest trial to date ($n = 947$), and used a composite end point of mortality and major non-fatal cardiovascular and renal events as its primary outcome measure. ASTRAL (Angioplasty and Stent for Renal Artery Lesions; $n = 806$) and STAR (Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function; $n = 140$) used renal function as the primary outcome, but, irrespective of the outcome measure, all these trials have come to the same conclusion of no benefit. Although the procedural clinical adverse event rate in CORAL was very low, both ASTRAL and STAR reported several serious clinical adverse events in stented patients, including occasional deaths.[2,3] However, the procedural complication rate (vessel dissection, occlusion, distal embolization, etc.) was 5.2% in CORAL, a figure similar to that seen in ASTRAL.

No one likes a negative study, and even more so when the results sound counterintuitive, surely it must be good medicine to correct an impaired blood supply to an organ?[7]

What are the possible flaws with these six trials? Initial criticism of the earliest trials (EMMA [Essai Multicentrique Medicaments vs Angioplastie], Scottish and Newcastle study) was leveled at the unlikelihood that plain old balloon angioplasty would lead to a sustained correction of the anatomical lesion and we had to await the advent of stents before that could be resolved. Stents certainly correct the anatomical problem so why have subsequent post-stent era trials (DRASTIC [Dutch Renal Artery Stenosis Intervention Cooperative], STAR, ASTRAL, and CORAL) failed to demonstrate benefit? Perhaps the wrong patients were put into these trials—patients who had relatively minor degrees of RAS who might not be expected to benefit? The ASTRAL trial did not specify a lower limit for the degree of stenosis, but nearly 60% of the patients had a stenosis of >70%, and the lower limit in CORAL was 60%. ASTRAL found no difference in outcome with respect to baseline pre-specified subgroup stenosis severity and also in a post hoc subgroup analysis of 163 patients with more "severe" anatomic lesions—bilateral >70% stenosis or unilateral >70% RAS in a single kidney. CORAL looked at a pre-specified group of "global renal ischemia" defined as >60% stenosis either affecting both kidneys or a single functioning kidney, and again failed to demonstrate any benefit in this subgroup. So criticisms of the wrong patients entering these trials seem hard to support—at least in terms of severity of anatomical RAS. Do we know if patients who were stented outside of these trials benefited? A group in Dundee, UK, looked at the 127 patients who were stented outside of ASTRAL (to which they randomized 35 patients) in the period paralleling the trial and found no significant benefit in this cohort.[8] Put another way, when doctors tried to identify patients whom they thought would definitely benefit from stenting they failed miserably.

There is a big focus on stenosis severity in other vascular territories, for example carotid and coronary, but perhaps the kidney is different. When looking at stenosis severity and renal function Cheung et al.[9] failed to show any clear relationship until the artery had occluded. So the relationship between main vessel narrowing and dysfunction in the kidney is almost certainly different to that in other organs, and the term "atherosclerotic renovascular disease" (ARVD) is, in our opinion, preferable to "atherosclerotic renal artery stenosis", allowing other pathological entities, such as cholesterol embolization and hypertensive small vessel disease, to be encompassed. Stenting is only going to correct the stenosis and will not improve small vessel disease within the kidney, and it may, in fact, aggravate cholesterol embolization and hypertensive damage.

Another explanation for the lack of benefit in CORAL and ASTRAL is the effectiveness of vasculoprotective medical treatment, which appears to have improved outcomes over time. Back in 2001–02 the annual mortality of patients with ARVD in the US Medicare population was 16%,[10] whereas annual mortality was 8% in ASTRAL and now only 4% in CORAL, although the latter trial included patients with much better preserved renal function than those in ASTRAL

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(estimated glomerular filtration rate 58 mL/minute vs. 40 mL/minute in ASTRAL).

Do any patients benefit from renal artery stenting? The answer to this is a definite "yes", but as there is major heterogeneity in the clinical make-up of patients with ARVD it is likely that clinical phenotype is far more influential in determining response to renal stenting than is the rather simplistic degree of anatomical RAS. This is exemplified in a recent retrospective study of 467 patients with "higher risk" clinical presentations of ARVD, which showed that acute pulmonary edema and the combination of rapidly declining renal function with refractory hypertension (as opposed to each alone) may be two groups worthy of further study.[11]

It remains to be seen whether there is any enthusiasm for another randomized trial of renal stenting, and certainly for the vast majority of patients tablets and lifestyle modification should be the mainstay of care. Nevertheless, further efforts are required to identify the phenotype of that minority subgroup of patients who do benefit from renal revascularization.

REFERENCES

1 Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**:13—22.

2 The ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953—62.

3 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* 2009;**150**:840—8.

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* 2000;**342**:1007—14.

5 Plouin PF, Chatellier G, Darne B, et al. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension* 1998;**31**:823—9.

6 Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *J Hum Hypertens* 1998;**12**:329—35.

7 White CJ. Kiss my astral: one seriously flawed study of renal stenting after another. *Catheter Cardiovasc Interv* 2010;**75**:305—7.

8 Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single centre observational study. *Nephrol Dial Transplant* 2012;**27**:734—8.

9 Cheung CM, Wright JR, Shurrab AE, Mamtora H, Foley RN, O'Donoghue DJ, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol* 2002;**13**:149—57.

10 Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen SC, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. *Kidney Int* 2005;**68**:293—301.

11 Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis*; 2013. pii:S0272-6386(13)0112-8.