Symptomatic Renal Artery Stenosis and Infra-renal AAA

R.A. Benson *, K.I. Paraskevas, B.O. Patterson, I.M. Loftus
St George’s Vascular Institute, St George’s Healthcare NHS Trust, London, UK

Objectives: To identify evidence to guide the vascular surgeon as to the relevance of renal artery stenting in a patient with symptomatic renal artery stenosis undergoing elective endovascular aortic aneurysm repair (EVAR).

Methods: A comprehensive literature search of MEDLINE was performed without time limits. The following terms were used in the first instance: renal artery stenting and renal artery stenosis, and any other analogous terms identified during the search. Selection criteria were set to randomised control trials.

Results: Despite several large, randomised controlled trials investigating renal artery stenting against medical treatment alone in symptomatic renal artery stenosis, there has been no significant benefit identified in terms of improvement in renal function, control of blood pressure, or need for dialysis. The stented populations were also more likely to suffer from complications caused by the procedure such as bleeding, cholesterol embolisation and flash pulmonary oedema.

Conclusion: There is no evidence for the use of renal artery stenting over optimal medical management in the treatment of patients with symptomatic atherosclerotic renal artery stenosis, irrespective of the degree of stenosis. In the setting of EVAR, prevention of deterioration of renal function should be with involvement of the renal physicians, adequate hydration, and use of minimal contrast agent. Repair should be undertaken in centres with access to 24-hour haemofiltration services.

BACKGROUND
Patients with abdominal aortic aneurysms (AAAs) and occlusive arterial disease often have concomitant atherosclerotic renal artery stenosis (RAS; Fig. 1).1 RAS can be associated with hypertension, progressive ischaemic nephropathy, renal failure, and eventually lead to renal replacement therapy.2 Following endovascular AAA repair (EVAR), a 10% decrease in creatinine clearance in the first year has been observed, independent of the type of graft or the use of suprarenal fixation.3 There are likely to be several factors influencing this decline, including progressive atherosclerotic disease, pre-existing impairment and the effects of contrast induced nephropathy (CIN).4

Baseline renal dysfunction prior to EVAR is associated with peri-operative mortality rates as high as 27%.5 Consequently, for a patient with bilateral atherosclerotic RAS, hypertension, and mild renal impairment, preventative measures should be considered to prevent worsening dysfunction and therefore improve peri-operative outcome.

Single case reports have demonstrated the usefulness of successful renal artery stenting in specific scenarios. One such report described a patient awaiting repair of a thoracoabdominal aneurysm with uncontrolled hypertension, worsening heart failure, and progressive renal insufficiency (serum creatinine: 3.8 mg/dL), caused by a high-degree (80%) atherosclerotic RAS in a solitary functioning kidney. Treatment led to normalisation of serum creatinine and blood pressure prior to successful surgical treatment of the aneurysm.

EVIDENCE FOR RENAL ARTERY STENTING IN RAS
For patients without such clear manifestations of RAS, there is little evidence that treatment with renal artery stenting
confers additional benefits over medical treatment alone. Meta-analysis of three small randomised controlled trials of renal artery stenting compared with medical therapy alone failed to demonstrate significant improvements in serum creatinine or blood pressure in a combined total of 210 patients followed up to 6 months.\(^6\) Since then, several larger multicentre randomised trials have looked into the effects of stenting in this group of patients.

The STAR trial recruited 140 patients with a creatinine clearance of less than 80 mL/min/1.73 m\(^2\) and stenosis of 50% or greater, and randomised them to renal artery stenting plus medical therapy versus medical therapy alone (Table 1).\(^{10}\) The primary endpoint was a >20% decrease in creatinine clearance in the absence of arterial restenosis. There was no significant difference between the two groups: 16% of patients (10/64) in the stent placement group reached primary endpoint compared with 22% (16/76) in the medication group. Stenting was associated with several complications, including three deaths (two following renal artery perforation, one septic haematoma). Morbidity was caused by false aneurysms of the femoral artery (two), and deteriorating renal function and dialysis following cholesterol embolisation. In conclusion, stenting did not demonstrate benefit in impaired renal function compared with medical therapy alone and led to a number of significant procedure-related complications. Of 140 patients, 33% had only mild (50–70%) atherosclerotic RAS on invasive imaging. Furthermore, 12/64 patients in the stenting arm with stenosis <50% did not receive a stent but were still analysed in the intention-to-treat analysis. Six patients also did not receive a stent (one angioplasty only, one mortality pre-placement, two declined, two technical failures) despite inclusion in analysis for the intention-to-treat cohort.

The larger and more robust Angioplasty and STenting for Renal Artery Lesions (ASTRAL) trial was a multicentre randomised unblinded clinical trial, recruiting 806 patients with atherosclerotic renovascular disease.\(^{11}\) Patients were randomised to undergo angioplasty and stenting plus medical therapy or medical therapy alone (as per the local centre protocols — management of hypertension, statin, and anti-platelet). Primary outcome was creatinine clearance out to 5 years. Secondary outcomes included blood pressure, time to first renal or major cardiovascular event, and mortality. As with studies before it, there were no significant differences in primary outcome between any cohort (\(p = .06\)), although there appeared to be a trend towards favourable results in the stenting group. This lack of benefit persisted even after subgroup analysis for varying degrees of renal artery stenosis (\(p = .23\)). Over the course of the study, 31 serious complications of revascularisation occurred in 23 (9%) patients (Table 2). There was no apparent overall clinical benefit from revascularisation compared with medical therapy alone in those with any degree of atherosclerotic renovascular disease. Of note, patients were only enrolled if their referring physician felt there was equipoise between stenting and medical treatment. In addition, individuals requiring revascularisation within 6 months were excluded. Only 83% of the patients randomised to stenting underwent the procedure. This may be because one-quarter of the patients had normal renal function at baseline, and 41% had less than 70% atherosclerotic renal artery stenosis on invasive imaging.

The most recent, multicentre open-label randomised controlled trial was the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study. It also compared medical therapy alone versus medical therapy plus stenting in 947 patients with RAS and chronic kidney disease, hypertension, or both.\(^{12}\) Patients were categorised by degree of arterial stenosis (60–80%, 80–99%). Hypertension was classed as a systolic pressure of >155 mmHg despite two anti-hypertensive agents, and chronic kidney disease an eGFR <60 mL/min/1.73 m\(^2\). The protocol for medical therapy required use of the angiotensin II type-1 receptor blocker candesartan (with or without hydrochlorothiazide) and the combination agent amlodipine—atorvastatin. The dose was adjusted to achieve targets of <140/90 mmHg in patients without comorbidities, and less than 130/80 mm Hg in patients with diabetes or chronic kidney disease. Endpoints were progressive renal insufficiency and need for renal replacement therapy out to 2 years. They found no significant difference between the two groups in terms of decline in renal function (stenting: 68/459 [14.8%], medical therapy alone: 77/472 patients [16.3%], \(p = .58\)), or decrease in systolic blood pressure (\(p = .03\)). The CORAL investigators concluded that renal artery stenting did not

\begin{table}[ht]
\centering
\begin{tabular}{|c|}
\hline
\textbf{Table 1. Approach to Medical optimization of the patient with atherosclerotic RAS and impaired renal function.}\(^{10}\) \\
\hline
1. Management of hypertension: \\
\hline
\begin{itemize}
\item Target blood pressure <140/90 mmHg
\item 2. 10 mg of atorvastatin, titrated to 20 mg as tolerated (irrelevant of lipid levels)
\item 3. Aspirin 75–100 mg o.d.
\item 4. Smoking cessation counselling
\end{itemize}
\hline
\end{tabular}
\end{table}
confer significant benefit when combined with comprehensive medical treatment, over that seen with medical treatment alone.12

**MEDICAL MANAGEMENT AND PERI-OPERATIVE RENAL PROTECTION**

Best medical therapy should include optimal glycaemic control, aspirin, and statin therapy, smoking cessation advice, and blood pressure control using an appropriate agent.12 Studies suggest that target systolic pressure should be 140/90 or less, especially where there is co-existing comorbidity.13

EVAR can lead to renal injury even in those with normal function pre-operatively, evidenced by rises in several biomarkers of renal damage such as serum creatinine, urinary retinol-binding protein, and albumin/creatinine ratio.14 CIN (defined as ≥25% increase in estimated glomerular filtration rate at 48 hours) affects up to 20–30% of patients with pre-existing renal impairment, and is associated with increasing length of stay and higher mortality at 1 year.15 Recommendations for preventative strategies from the European Society of Vascular Surgery include adequate pre- and post-procedural fluid administration, involvement of a renal physician for guidance on optimisation of medications and restricting repair to those centres with 24-hour access to haemofiltration.16

The usefulness of anti-oxidant compounds such as N-acetylcysteine (NAC), sodium bicarbonate, and ascorbic acid is debatable. These compounds act by scavenging a variety of oxygen free radicals, protecting renal tissue and DNA from direct damage. Their effects on CIN must be extrapolated from work performed in the setting of coronary and peripheral angiography, which as a rule use less contrast material than EVAR. A detailed meta-analysis of trials looking at sodium bicarbonate versus normal saline for prevention of CIN in those undergoing cardiac or peripheral angiography found an apparent benefit for bicarbonate administration (odds ratio 0.41 in patients with pre-existing renal failure) in a combined cohort of 1539 patients across seven trials.17 This did not extend to any differences in mortality rates, heart failure, or development of end stage renal failure between groups, irrelevant of pre-existing renal function. A randomised trial investigating various hydration strategies to attenuate CIN in 326 patients receiving intravenous contrast found the combination of intravenous sodium bicarbonate and NAC most effective.18 There is little evidence for anti-oxidant strategies in patients undergoing EVAR. In a small randomised study of 20 men undergoing EVAR, NAC administration had no attenuating effect on degree of acute renal injury in the peri-operative period.14 It is clinically relevant to note that serum creatinine, and therefore estimated glomerular filtration rate are relatively slow markers of renal injury. Future research lies in identification of novel biomarkers to allow earlier identification of CIN.19

**CONCLUSION**

Current evidence does not support renal artery angioplasty/stenting over medical treatment alone for the management of either symptomatic or asymptomatic atherosclerotic RAS, regardless of the degree of stenosis. No randomised controlled or observational studies have so far evaluated whether or not revascularisation of a symptomatic RAS protects from the adverse effects that EVAR might inflict on kidney function. Pre-operative review by a renal physician, early admission for intravenous hydration pre-EVAR, and minimising contrast use during the procedure are likely to

---

**Table 2. Complications following renal artery stenting in ASTRAL trial.11**

<table>
<thead>
<tr>
<th>Peri-procedural complications (within 24 hours)</th>
<th>Revascularisation (N = 335)</th>
<th>Medical therapy (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal or stent embolisation</td>
<td>5 (1.5%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Renal arterial thrombosis or occlusion</td>
<td>4 (1%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Renal arterial perforation or dissection</td>
<td>3 (1%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Non-renal embolisation leading to peripheral gangrene and amputation of toes or limbs</td>
<td>3 (1%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Stent misplacement requiring additional stent</td>
<td>10 (3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Distal stent retrieval or deployment</td>
<td>1 (0.3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Balloon rupture</td>
<td>1 (0.3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Need for surgical rescue</td>
<td>0 (—)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Access vessel damage</td>
<td>7 (2%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>1 (0.3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Femoral artery aneurysm at puncture site</td>
<td>1 (0.3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.3%)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Number of events/number of patients</td>
<td>37/30</td>
<td>1/1</td>
</tr>
<tr>
<td>Post-operative complications (between 24 hours and 1 month post procedure)</td>
<td>(N = 280)</td>
<td></td>
</tr>
<tr>
<td>Groin haemorrhage/haematoma</td>
<td>32 (11%)</td>
<td></td>
</tr>
<tr>
<td>Deterioration in renal function</td>
<td>30 (11%)</td>
<td></td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Renal artery occlusion</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Local infection at puncture site</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>2 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Number of events/number of patients</td>
<td>69/55</td>
<td></td>
</tr>
</tbody>
</table>
be the best renoprotective strategies (Table 3). There is some evidence recommending use of anti-oxidant agents for pre-operative hydration over normal saline alone. Close monitoring of markers of acute kidney injury in the post-operative period should continue for at least 48 hours to allow for any potential rise in serum creatinine to be observed and acted upon.

There is no evidence supporting the use of angioplasty or stenting of the bilateral RAS of the male patient described in this clinical vignette prior to EVAR. Conservative management and pre-operative optimisation of renal function together with close post-operative monitoring of renal function are adequate measures for the management of the bilateral RAS in this patient with symptomatic RAS and concomitant AAA.

**CONFLICT OF INTEREST**

None.

**FUNDING**

None.

**REFERENCES**