Part Two: The Vast Majority of Patients with Atherosclerotic Renal Artery Stenoses do not Require Intervention

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Evaluation

ARAS is suspected in patients with the onset of hypertension after 50 years of age. Confirmation of the diagnosis is made by imaging. Doppler measurement of renal artery velocity provides an assessment of the severity of the stenosis. Alternative methods include MRA, computed tomographic angiography (CTA) and digital subtraction angiography with the use of small catheters and limited amounts of contrast media. All these tests are useful in confirming the diagnosis of ARAS, but Drieghe et al. 9 have shown that even if renal angiography and color duplex ultrasound correlate well, both approaches tend to overestimate the ARAS severity when compared with the measured trans-stenotic pressure gradient using 0.014 pressure wires. Again none of these techniques can establish the functional significance of ARAS. Even the documentation of a trans-stenotic pressure gradient in ARAS does not necessarily mean that the given stenosis is the cause of hypertension.

Risk Factors and Medical Treatment

A major confounder related to the treatment of ARAS is competing risk from other manifestations of atherosclerosis including stroke, acute coronary syndrome, and congestive heart failure. The risk of these events is greater than the risk of complications related specifically to ARAS. They reflect widespread atherosclerotic disease elsewhere.10 In this context, medical therapy remains the cornerstone of treatment for ARAS. Multi-drug regimens are needed for blood pressure control including renin-angiotensin-aldosterone inhibitor, alpha or beta-blocker, diuretic and calcium channel antagonist. The demonstrated benefits of antiplatelet therapy and statins in patients with atherosclerotic disease also provide support for their use in patients with ARAS.

Prospective Randomized Controlled Trials

Benefit of renal stenting over angioplasty alone

Primary stenting of ARAS was compared to angioplasty alone in one small RCT.11 The results of this trial were comparable with those of a meta-analysis that compared these two techniques.12 There was a 65% reduction in risk of restenosis with stents at 6-months angiography but there was no difference in blood pressure or renal outcome. Primary stenting thus showed a more favorable outcome with fewer reinterventions than angioplasty for ARAS.13

Benefit of renal artery stenting vs. surgery

Only one RCT compared renal artery stenting vs. open surgical revascularization in patients with ARAS.14 Inclusion criteria were severe hypertension and ARAS >70%. There was no significant difference in treatment outcome i.e., blood pressure, renal outcome, mid-term patency and complications. But as surgery was associated with a longer duration of hospitalization (18 days vs. 10 days), the authors suggest that renal artery stenting should be preferred to surgery in patients who do not need concomitant aortic revascularization.
In addition to this RCT, a large meta-analysis comparing the outcome of open surgical revascularization vs. endovascular treatment showed that endovascular patency declined by 0.26% per month and that open revascularization showed greater improvement for hypertension by 21% (95% CI: 9–33%, \( p = 0.001 \)) and for renal function by 34% (95%CI: 18–54%, \( p = 0.001 \)) but with a higher surgical mortality, 3.1% (95%CI: 1.8–4.4%, \( p = 0.01 \)) that became insignificant when concomitant aortic surgery was excluded. Despite the advantages of open revascularization, the attendant morbidity and mortality of surgery ensures a significant role for renal artery stenting in most patients. However there will continue to be a role for open renal artery revascularization in young patients with severe renal artery stenosis who are more likely to benefit from the durability of renal bypasses.

**Comparison of renal artery stenting with medical treatment alone**

Comparison of renal artery stenting plus medical treatment with medical treatment alone was available in three RCTs. (Table 1). Two RCTs of limited power compared stent placement with medical treatment in ARAS patients with severe hypertension or recent impairment of renal function. These two studies did not show any significant improvement in renal function, blood pressure outcome or survival in patients with renal stenting as compared with medical treatment alone.

A larger trial, Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) further question the benefit of ARAS stenting vs. medical therapy alone. This RCT involved 806 patients with ARAS. Patients were enrolled if clinical findings (recent onset of hypertension or unexplained decreasing renal function) suggested a diagnosis of ARAS confirmed by duplex echography, CTA or MRA in at least one renal artery and if the physician was uncertain that the patient would benefit from revascularization. ARAS severity was between 50 and 70% diameter-reducing lesion in 40% of the patients enrolled in the trial and exceeded 70% in 60% of them. After 5-years, change in renal function, mean systolic arterial pressure, and number of cardiovascular events or death did not differ significantly between the two groups. This result was confirmed in a subgroup of patients with high-grade or bilateral ARAS. Among patients with renal artery stenting, 4.2% suffered procedure-related major complications including renal artery rupture, dissection, thrombosis, embolization and worsening of renal insufficiency (Table 1). The ASTRAL study concluded that there was no advantage of revascularization as compared with medical treatment in patients with ARAS.

This trial was criticized because of its enrollment strategy excluding patients who would likely benefit more from renal stenting. In addition 40% of patients with renal artery stenting had moderate renal artery stenosis between

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| Ziakka et al., 2008 | 36 with Stents| Hypertension       | 74% (mean)            | Scr: 2.3 mg/dL | 48                | Renal function improved or stabilized in 64% of patients with stents vs. 70% with medication alone. (NS) Hypertension cured or improved in 78% of patients with stents vs. 71.4% in the medical group. (NS) No difference in renal event-free survival. (Hazard ratio: 0.73, 95%CI, 0.33–1.61). Procedure-related major complications
|                     | 46 with MT    |                    |                       |                |                   | – 2 procedure-related deaths (3%)                                       |
|                     |               |                    |                       |                |                   | – 1 late death due to infected hematoma                                 |
|                     |               |                    |                       |                |                   | – 1 patient requested dialysis secondary to cholesterol embolism        |
| STAR, 2009          | 64 with stents| Impaired renal function | ≥50%                 | Creatinine clearance < 80 mL/min/1.73 m² | 24                | No difference in renal event-free survival. (Hazard ratio: 0.73, 95%CI, 0.33–1.61). Procedure-related major complications
|                     | 76 with MT    |                    |                       |                |                   | – 2 procedure-related deaths (3%)                                       |
|                     |               |                    |                       |                |                   | – 1 late death due to infected hematoma                                 |
|                     |               |                    |                       |                |                   | – 1 patient requested dialysis secondary to cholesterol embolism        |
| ASTRAL, 2009        | 403 with stents| Uncontrolled hypertension or unexplained impaired renal function | ≥50%                 | GFR: 40 mL/34 min/1.73 m² |                   | No difference in renal event-free survival, GFR decline rate, blood pressure, cardiovascular events and survival. Procedure-related major complications (n = 17, 4.2%):
|                     | 403 with MT   |                    |                       |                |                   | – 5 kidney embolism                                                     |
|                     |               |                    |                       |                |                   | – 4 renal artery occlusions                                             |
|                     |               |                    |                       |                |                   | – 4 renal artery perforations                                          |
|                     |               |                    |                       |                |                   | – 1 renal artery aneurysm                                               |
|                     |               |                    |                       |                |                   | – 3 peripheral embolisms (amputations)                                  |

MT: Medical treatment alone, Scr: Serum creatinine, GFR: Glomerular filtration rate, NS: not significant.
50% and 70% diameter-reducing lesions for which only limited benefit from revascularization could be expected. Pressure gradient across the stenosis was not measured in this study and there was no core laboratory to validate the on-site visual estimates of ARAS. There were also significant crossovers in this study with only 359 of 403 patients randomized to renal artery stenting who underwent the procedure while 24 of 403 patients assigned to medical treatment underwent intervention. But when examined on a per-protocol analysis, there was still no apparent benefit for renal artery stenting.

**Randomized Controlled Trials: What Have We Learned?**

The results of these three RCTs need to be considered carefully in light of their design. The enrollment strategy of the ASTRAL trial regarding the doubt of the effectiveness of revascularization meant that clinicians were uncertain as to whether they should intervene; consequently they considered the randomization to be appropriate. Despite some criticisms almost all patients enrolled in these RCTs would have been considered for renal artery stenting in normal clinical practice. In the ASTRAL trial, the skills of the physicians performing renal stenting were not formally assessed but their expertise was reflected in a technical success rate of 95% and the rate of serious complications was similar to that of other methodologically solid studies with rigorous recording keeping. In summary, these trials provide evidence that in typical patients considered for renal revascularization in today current clinical practice, intervention offers no clinical benefit and has some risk as compared to best medical treatment alone. It is possible however that renal artery stenting might benefit a minority of patients with specific clinical presentations that were not specifically addressed in these RCTs.

**Ongoing Trials**

Following the ASTRAL study, three ongoing RCT’s were designed to better assess renal and cardiac outcomes after renal artery stenting. The Renal Atherosclerotic Revascularization (RAVE) compares renal stenting with best medical treatment alone with a composite end-point that includes death, dialysis, and doubling of serum creatinine. The RADAR study compares best medical treatment with best medical treatment plus renal artery stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis. The primary end-point being the change in estimated glomerular filtration rate between the two groups during 12-months follow-up. Secondary end-points included technical success; change in average blood pressure and in left ventricular mass index. Finally the CORAL trial compares best medical treatment alone with renal stenting on a composite heart, vascular and renal end-point. In this trial, angiography and transluminal pressure gradients were used to determine entry in the study with a core laboratory using quantitative analysis. Patients with a gradient ≥20 mm Hg and a renal artery ≥35 mm in diameter were considered for randomization.

**Technical Issues Related to ARAS Stenting**

Renal artery stenting has improved over recent years with small-platform including less traumatic pre-mounted low profile stent on 0.014 or 0.018 inch wire, less traumatic 2.5 to 4-Fr shaft balloons, steerable catheters, smaller puncture site and rapid exchange systems avoiding need for long wires. Despite these significant improvements, ARAS stenting is not an easy procedure and atheroembolic disease remains a major concern with manipulation of the renal artery, which is a predictor of embolic events. Distal embolic protection devices have been logically used to avoid this complication. But in an RCT, Cooper et al. showed a decline in estimated glomerular filtration rate in both groups of patients with and without protection device. In this series, the only group with no loss of glomerular filtration was receiving both the embolic protection device and a platelet glycoprotein inhibitor (abciximab) suggesting a risk of intra-arterial thrombosis triggered by the use of the embolic protection device.

**Refining the Approach to Renal Artery Revascularization**

As renal artery stenting falls short in these RCTs, many nephrologists have moved toward a more conservative approach concerning ARAS (Table 2) probably also to counterbalance the attitude of aggressive cardiologists and radiologists. Despite the difficulty in demonstrating benefits of renal artery stenting in large groups that included heterogeneous populations with a mixture of high

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<td>1. Failure to define causal role of atherosclerotic renal artery stenosis (ARAS) in disease syndromes such as hypertension or worsened renal function.</td>
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<td>2. Imprecise definition of ARAS with inclusion of subcritical ARAS in trials and lack of methods to assess renal hemodynamics.</td>
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<td>4. Advances in medical management: Blockade of the renin-angiotensin system, effective anti-hypertensive drugs, antiplatelet agents and statins.</td>
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<td>5. Complications of ARAS stenting: Kidney embolism, occlusion, perforation or dissection of the renal artery, contrast nephropathy.</td>
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and low risk patients, pathophysiological rationale and the positive results of some small series have provided valid arguments for renal stenting in a few ARAS patients with deteriorating renal function after receiving ACE inhibitors or angiotensin-receptors blockers and in patients with flash edema or uncontrolled heart failure. In addition, many physicians recognize that some patients with severe stenosis particularly affecting both renal arteries or a solitary kidney should be considered as potential candidates for renal artery stenting even if the ASTRAL study showed no difference in outcome between renal artery lesions of varying severity.

Conclusions

Recent evidence shows that optimal medical treatment including statins and risk reduction factors should be the preferred option for most patients with ARAS. It is almost certain that the vast majority of typical patients now being subjected to renal artery stenting show no added benefits regarding blood pressure and kidney function as compared to best medical treatment alone. But it is equally important to recognize that a minority of patients with rapidly progressive hypertension or renal insufficiency and flash pulmonary edema or with specific lesions such as bilateral severe renal artery stenosis or solitary kidney do have a benefit from restoring kidney perfusion.

References

EDITORS’ COMMENT

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It was expected that information resulting from recently completed randomized controlled trials would clarify the role of renal artery interventions in patients with atherosclerotic renal artery stenoses. Unfortunately, in this respect, we were left disappointed. Concerns regarding such issues as inclusion criteria limited the validity of these studies’ conclusions leaving a persistent knowledge gap into which our debators step.

Although the authors were given separate charges, their conclusions are more similar, than different. They both recognize the need for further study and information to elucidate the role of renal artery interventions. They recognize that we currently cannot accurately predict the natural history of any individual renal artery lesion, nor recognize entirely which lesions are responsible for a patient’s hypertension or renal insufficiency. So instead of recommending whether the majority, or the minority of patients should be intervened upon, they appropriately meet somewhere in the middle.

With the present uncertainty the authors propose a multidisciplinary, collaborative approach to these often complicated clinical situations to arrive at decisions regarding individual patients. They propose a more aggressive approach in patients with specific criteria, including progressive hypertension, renal insufficiency with flash pulmonary edema, bilateral severe renal artery stenoses, and stenoses with a solitary kidney. Until further information is hopefully obtained from ongoing trials, this selective approach seems reasonable and most prudent.