Approach to atherosclerotic renovascular disease: 2016

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Abstract

The management of atherosclerotic renal artery stenosis in patients with hypertension or impaired renal function remains a clinical dilemma. The current general consensus, supported by the results of the Angioplasty and Stenting for Renal Atherosclerotic Lesions and Cardiovascular Outcomes for Renal Artery Lesions trials, argues strongly against endovascular intervention in favor of optimal medical management. We discuss the limitations and implications of the contemporary clinical trials and present our approach and formulate clear recommendations to help with the management of patients with atherosclerotic narrowing of the renal artery.

Key words: atherosclerosis, chronic renal insufficiency, CKD, hypertension, renal artery stenosis

Introduction

Atherosclerotic renal artery stenosis (ARAS) accounts for >90% of cases of renal artery stenosis [1]. It is most commonly seen in older patients (>65 years) and is usually associated with atheromatous disease in other vascular beds. The incidence and prevalence are hard to estimate given the asymptomatic nature of the majority of cases. A study in the US Medicare population estimated an incidence of 3.7/1000 patient-years in patients ≥65 years of age [2]. Another population-based study by Hansen et al. [3] showed a prevalence of 6.8% in elderly patients. The clinical significance of ARAS and its optimal management have been topics of great controversy. Early studies reported that renal artery stenosis is a progressive problem that can lead to resistant hypertension (HTN) and gradual loss of functional renal mass resulting in chronic kidney disease (CKD) [4–8]. Its presence has been linked to increased rates of cardiovascular events and mortality in patients with atherosclerotic cardiovascular disease [9–11]. This triggered an increasing interest in the treatment of ARAS by surgical or intravascular intervention. In 1996, the number of endovascular stent procedures done in the USA tables was estimated to be ~7600. Over the next decade this number ballooned to ≥35 000 by the year of 2005 [12]. Interventional cardiologists may have contributed to the rapid increase in renal artery revascularization via convenient renal intervention during cardiac catheterization. However, enthusiasm for renal revascularization diminished in the era of statin therapy and renin–angiotensin system (RAS) blockade, which are believed to slow the rate of atherosclerosis progression. Major contemporary clinical trials, such as the Cardiovascular Outcomes for Renal Artery Lesions (CORAL) [13] and the Angioplasty and Stenting for Renal Atherosclerotic Lesions (ASTRAL) [14] trials, have failed to show statistically significant benefit of revascularization over optimal medical management in controlling blood pressure (BP) or preserving kidney function. These two trials have influenced medical decision making away from vascular intervention. A timeline of the clinical approaches to atherosclerotic renovascular disease is shown in Figure 1 and reflects the introduction of new technical and therapeutic advances used in addressing this clinical problem.

The complex relation of ARAS to renal function

It has been long recognized that renal blood flow largely exceeds tissue metabolic needs. The kidneys receive ~20% of the cardiac
output but utilize <10% of the renal perfusion for tissue metabolism [15]. This was demonstrated again recently with the use of blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI), a new technique that allows direct evaluation of oxygenation at the renal tissue level using the paramagnetic characteristics of deoxyhemoglobin [16, 17]. Under physiological conditions and in healthy subjects, BOLD-MRI consistently demonstrates an oxygenation gradient between the cortex and the deeper medullary areas [18–20]. A 30–40% reduction in single kidney perfusion in the context of moderate ARAS was associated with preservation of tissue oxygenation and cortex to deep medulla oxygen gradient in agreement with the high renal perfusion relative to tissue needs [21]. However, more severe stenosis (>70%) did overwhelm the kidneys’ adaptive capacity and resulted in overt cortical hypoxia and inflammation [22].

The clinical response to intervention in fibromuscular hyperplasia is more predictable and appears to be true to the physiology of the Goldblatt kidney [23]. On the other hand, the clinical response to intervention in the atherosclerotic lesion is unpredictable. This speaks to the differences in the underlying pathophysiology between the two conditions and highlights the presence of factors other than the reduction in renal blood perfusion that contribute to tissue injury in ARAS. Mounting evidence supports the presence of an inflammatory state in the post-stenotic kidney that results in parenchymal tissue damage by means of endothelial injury, increased generation of reactive oxygen species and oxidative stress [24–26]. Markers of such an inflammatory state can be detected early in the course of ARAS before any hemodynamic compromise takes place [27]. This inflammation is believed to be secondary to the atherosclerotic milieu itself [28]. Moreover, reversal of hypoxia by methods of vascular stenting did not result in down-regulation of renal vein inflammatory biomarkers such as neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1 and tumor necrosis factor-α [29].

In summary, renal tissue injury distal to the atherosclerotic renovascular lesion is likely a multifactorial process that includes activation of multiple injurious pathways by the atherosclerotic environment. ARAS may superimpose hypoxic injury upon the preexisting atherosclerotic tissue injury in case of advanced and severe stenosis.

With these observations and evidence in mind, the question of when to intervene in ARAS remains open for debate.

**Current clinical approach**

The current attitudes toward the management and treatment of ARAS have shifted sharply toward optimal medical management. This shift was largely driven by the publication of several randomized clinical trials [13, 14, 30–33] that failed to show superiority of revascularization over optimal medical therapy in terms of BP control, preservation of renal function or major cardiovascular or renal events. Based on the conclusions of such a body of evidence, one might think that the question of how to manage ARAS has been answered. However, each of these trials had its own limitations and shortcomings that stem from their recruitment and inclusion criteria and limit their universal applicability. As summarized in Table 1, it can be seen that the studied cohorts across the different trials are very similar. All of the trials excluded patients with advanced kidney disease, malignant or accelerated HTN, history of unstable heart failure (HF) or recent acute coronary syndrome. The resulting study cohorts consisted predominantly of patients with normal to moderate renal dysfunction and hypertension that is best described as not optimally controlled. This excluded a subset of patients who were considered to be ‘high risk’ but who exhibited the clinical features traditionally believed to be associated with renovascular disease [19, 34–37]. An example of such a high-risk patient is illustrated in Case 1, who presents with malignant hypertension and acute kidney injury (AKI) following three decades of stable BP control with minimal antihypertensive medication requirements.

The significance of ARAS has traditionally been based on estimation of anatomical stenosis obtained by means of renal

![Fig. 1. Timeline of the clinical approaches to atherosclerotic renovascular disease.](https://academic.oup.com/ckj/article-abstract/9/5/713/2196845/714-R-Daloul-and-A.R.-Morrison)
<table>
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<tr>
<th>Study, number of patients</th>
<th>Inclusion criteria</th>
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<th>Baseline renal function, angioplasty versus control</th>
<th>Method of ARAS diagnosis</th>
<th>HTN requirement</th>
<th>Primary outcome</th>
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<tr>
<td>EMMA [30], 49</td>
<td>DBP ≥95 mmHg on three occasions and/or on antihypertensive medications</td>
<td>&gt;75 years old, CrCl &lt;50 mL/min, Malignant HTN, History of stroke, pulmonary edema or MI within 6 months, Stenosis affecting the main renal artery that had not been previously dilated, Functional contralateral kidney without stenosis</td>
<td>CrCl: 73 versus 73 mL/min</td>
<td>Angiography, no hemodynamic studies</td>
<td>DBP ≥95 mmHg on at least three occasions and/or receiving antihypertensive medications</td>
<td>Ambulatory BP at termination of the study</td>
</tr>
<tr>
<td>DRASTIC [31], 106</td>
<td>DBP ≥95 mmHg on three occasions despite being on two antihypertensive medications</td>
<td>Age &lt;18 or &gt;75 years, HTN caused by other condition, Single functioning kidney, sCr &gt;1.7 mg/dL, Affected kidney &lt;8 cm, Total renal artery occlusion, AAA requiring surgery, Unstable CAD or HF, Cancer, Pregnancy</td>
<td>CrCl: 67 ± 23 versus 60 ± 24 mL/min</td>
<td>Angioplasty, no hemodynamics studies</td>
<td>DBP ≥95 mmHg on three occasions despite being on two antihypertensive medications</td>
<td>SBP and DBP at 3 and 12 months after randomization</td>
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<tr>
<td>STAR [33], 140</td>
<td>CrCl &lt;1.33 mL/s on two measurements 1 month apart, Unilateral or bilateral stenosis ≥50%, Controlled BP &lt;140/90 mmHg for 1 month prior to randomization</td>
<td>Renal size &lt;8 cm, Renal artery diameter &lt;4 mm, CrCl &lt;0.25 mL/s, Diabetes mellitus with proteinuria &gt;3 g/day, Malignant HTN</td>
<td>CrCl: 45 versus 46 mL/min</td>
<td>CTA, MRA, angiography; no hemodynamic testing</td>
<td>Stable BP control with BP &lt;140/90 mmHg for 1 month prior to randomization</td>
<td>Worsening renal function defined as ≥20% decrease in CrCl compared to baseline</td>
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Table continues
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<tr>
<td>ASTRAL [14], 806</td>
<td>Substantial anatomical atherosclerotic stenosis in at least one renal artery. Patients' doctor is uncertain that patient would definitely benefit from revascularization.</td>
<td>Requirement of surgical revascularization. Have high likelihood of requiring revascularization within 6 months. Nonatheromatous cardiovascular disease. Previous revascularization of RAS.</td>
<td>eGFR: 40.3 versus 39.8 mL/min/1.73m²</td>
<td>CTA, MRA, angiography, renal US; no hemodynamic studies reported</td>
<td>No clear definition of uncontrolled or refractory HTN.</td>
<td>Change in renal function measured by the mean slope of the reciprocal of the sCr level over time.</td>
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| CORAL [13], 947          | Severe stenosis defined as:  
- >80% stenosis or 60–80% with peak systolic gradient of ≥20 mmHg by angiography  
- Systolic velocity >300 cm/s by duplex sonography  
- MRA, CTA: SBP ≥155 mmHg on two or more antihypertensive medications or CKD with eGFR <60 mL/min/1.73 m² | Fibromuscular dysplasia  
CKD from to other causes  
- sCr >354 μmol/L  
- Kidney length <7 cm  
- Lesion not treatable with a single stent  
- Hospitalization for HF in the last month | eGFR: 58 ± 23.4 versus 57.4 ± 21.7 mL/min/1.73m² | CTA, MRA, angiography, renal US; duplex study not done in all patients | SBP ≥155 mmHg on two or more antihypertension medications | Major cardiovascular or renal events |

CAD, coronary artery disease; CrCl, creatinine clearance; MI, myocardial infarction; sCr, serum creatinine; US, ultrasound.
Case 1: A 74-year-old female with stage 3 chronic kidney disease, baseline creatinine (Cr) 1.7 mg/dL, estimated glomerular filtration rate (eGFR) 39 mL/min, well-controlled hypertension for three decades on a stable dose of triamterene-hydrochlorothiazide 75–50 mg daily, hypolipidemia and gout. Patient presented to the emergency room with acute onset orthopnea and resting dyspnea. She was found to be severely hypertensive with BP of 240/144 mmHg. Other vital signs showed O₂ saturation of 96% on room air, heart rate of 98 bpm and temperature of 36.1°C. Initial lab values showed an elevated Cr of 3.10 mg/dL, blood urea nitrogen (BUN) 46 mg/dL, Na 145 mmol/L K 3.9 mmol/L, and HCO₃⁻ 20 mmol/L. CBC showed a WBC of 5 × 10⁹/L, hemoglobin of 79 g/L and platelets of 132 × 10⁹/L. Urinalysis showed trace protein. Fluorine was 11.6%. She was treated with nitroglycerine drip and oral labetalol, Lasix and hydralazine with gradual improvement in BP. Cr increased to 9.49 mg/dL in the next 48 h with ongoing oliguria and respiratory distress resulting in hemodialysis initiation. Renal ultrasound showed the right kidney measuring 12.5 cm and the left kidney measuring 10.5 cm. Renal Doppler showed peaked systolic velocity (PSV) of 304 cm/s in the right renal artery, 133 cm/s in left renal artery and 142 cm/s in the aorta. Patient underwent diagnostic and therapeutic angiography that showed complete occlusion of the right renal artery that was successfully stented. Following the procedure, patient’s urine output increased to 3700 mL over the next 24 h with a decrease in serum Cr and improvement in BP control. She did not require any further hemodialysis. Cr improved to a nadir of 2.5 mg/dL and she required only amlodipine 10 mg for BP control. Almost 5 years later, the patient remains dialysis independent with patent right renal artery stent on follow-up renal Doppler studies. However, her underlying kidney disease continued to progress and she has reached stage 5 kidney disease with Cr of 4.32 mg/dL and eGFR of 12 mL/min/1.73m².

Doppler ultrasonography (RDU) or two-dimensional imaging, including angiography, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA). A luminal cross-section reduction of 50–60% has been considered significant and is required for inclusion in clinical trials [38]. However, hemodynamic studies using latex rubber showed that a luminal stenosis of at least 70–80% is necessary to induce a reduction in blood flow and renal perfusion [39]. Activation of the RAS and renin release are believed to be markers of hemodynamic significance and major players in renovascular hypertension [40]. Gradual luminal occlusion by balloon inflation in human subjects did not result in renin release until the pressure distal to the stenosis dropped by ~10%, correlating with a distal/aortic pressure ratio (Pd:Pa) of <0.9 and a luminal occlusion of 70–80% [41]. When comparing angiographic parameters to the Pd:Pa ratio, a luminal stenosis cutoff of >50% was associated with false positive results in 38% of the cases [42]. Furthermore, the current imaging methods are likely to overestimate the actual severity of luminal stenosis. Angiography, which continues to be considered the gold standard for estimating luminal stenosis and a key inclusion criteria in most clinical trials, is far from optimal. Atherosclerotic disease is more often diffuse, with multiple areas of stenosis or post-stenotic dilation, which may affect the accuracy of luminal reduction estimation due to the lack of a good reference segment. Angiography is also vulnerable to interobserver variability and performer bias. In the STAR trial, 12 of the 64 patients assigned to the percutaneous transluminal angioplasty (PTA) arm did not receive the allocated treatment at the time of the procedure, as the stenosis was found to be <50% [33], and in the CORAL roll-in period, stenosis was decreased by core laboratory from an average of 72.5% to 67.3% [43]. On the other hand, the ASTRAL trial did not have a core laboratory confirmation of angiographic imaging. All of this highlights the tendency of the criteria used by modern clinical trials to overestimate the significance and severity of ARAS in the studied cohort.

It is important to recognize that the mere presence of an anatomical lesion does not necessarily translate into hemodynamic significance, nor does a certain degree of stenosis exert the same effect on different patients. When comparing patients with severe renal artery stenosis as evident by increased hypoxia signal on BOLD-MRI to patients with moderate renal artery stenosis and no evidence of increased hypoxia signal, the degree of renal artery stenosis assessed by CTA scan was not statistically significant between the two groups [22]. This speaks to the inability of two-dimensional imaging used by most clinical trials to accurately evaluate the hemodynamic significance of a renal artery stenotic lesion, as it does not provide any insight regarding renal flow, translesional pressure gradient or tissue oxygenation. Parameters obtained noninvasively by renal duplex sonography have been proposed to better predict the hemodynamic effect of a lesion. Peak systolic velocity (PSV) has been reported to have the highest sensitivity (85%) and specificity (92%) among other parameters in evaluating renal artery stenosis [44]. Multiple cutoffs ranging from 180 to 300 cm/s have been proposed by different studies for the diagnosis of a stenosis of ≥70% [45–49]. A PSV > 300 cm/s was used in the CORAL trials. However, these suggested values still may be overestimating the severity of stenosis. Evidence of cortical and medullary hypoxia by BOLD-MRI was seen with a PSV >384 cm/s [22] and a PSV >320 cm/s correlated best with a Pd:Pa ratio of <0.9 [42].

In summary, the currently available clinical trials have some limitations in their abilities to screen and adequately identify severe and hemodynamically significant stenosis. Additionally, these trials have excluded patients with the highest likelihood of having clinically significant disease. This greatly restricts their applicability to low-risk cohorts with stable or slowly progressive renal failure and amenable to control of hypertension.

**When is it reasonable to intervene in ARAS?**

The key for the management of ARAS lies in establishing the functional significance of the stenosis, that is, when the ARAS is actually responsible for activation of the RAS or induces renal tissue ischemia that is still amenable for reversal by reperfusion techniques. The ongoing uncertainty regarding the benefit of revascularization reinforces that this is not an easy task. We believe that two essential criteria must be met for consideration of intervention with endovascular stenting. The first is a clinical criterion, that is, a clinical presentation that can result from ARAS such that it produces an acute to subacute change in BP control or rate of chronic kidney disease progression. The second is demonstration of a functional lesion. Renal Doppler ultrasonography is probably the best noninvasive method for such evaluation. Below we outline some of the clinical scenarios that we believe
warrant consideration of intravascular intervention and discuss the evidence with and against such an approach. Table 2 summarizes our clinical approach to patients with ARAS.

**Clinical scenarios to raise suspicion of ARAS**

**Malignant hypertension on the background of previously well controlled BP**

Unexplained malignant or accelerated hypertension with or without acute renal failure in patients with a previous history of stable BP control should raise suspicion of acute severe renal ischemia, such as in the case of renal artery dissection or plaque rupture. In such patients, an urgent evaluation of renal blood flow is crucial. This can be initiated with noninvasive techniques such as renal Doppler study. If ARAS is present, endovascular revascularization should be attempted in patients who are considered reasonable candidates. In Case 1 we present a patient with a similar presentation where intravascular intervention resulted in prompt and sustained benefit in both BP control and renal recovery. No clinical trial has directly evaluated the efficacy of revascularization versus conservative medical therapy in such a condition, but clinical experience and case reports suggest such an approach [50, 51]. A recent retrospective study comparing medical management to revascularization in patients who presented with both accelerated or malignant hypertension and rapid loss of kidney function reported a significant reduction in risk for death [hazard ratio (HR) 0.12 [95% confidence interval (CI) 0.02–0.77], P = 0.03] and cardiovascular events [HR 0.28 (95% CI 0.10–0.60), P < 0.001] [52] with revascularization [52].

**Recent increase in antihypertensive requirement in patients with previously stable BP control**

In the absence of a clear explanation for acute worsening of BP control, such as medication or dietary noncompliance, worsening renal failure, or medication interaction, it is reasonable to evaluate for ARAS by noninvasive methods such as RDU. However, in situations where adequate BP control is still amenable with medication adjustment, conservative medical management with close monitoring of renal function and BP control is preferred. If hypertension becomes resistant, intravascular intervention should be considered after carefully weighing the benefits and risks, taking into account the patient’s comorbidities and the likelihood of improving his/her lifestyle. Clinical evidence to support intervention in case of ARAS and resistant hypertension are controversial. The CORAL and ASTRAL trials did not support the benefit of revascularization in improving BP control. However, these studies did not focus on patients with resistant hypertension, defined as BP >140/90 mmHg despite being on the maximal tolerated dose of three antihypertensive medications, including a diuretic. In the HERCULES trial [53], 99 and 71% of the patients had uncontrolled BP despite being on two or more and three or more antihypertensive agents, respectively. Angioplasty with stenting in this study resulted in a significant reduction in BP despite a stable number of antihypertensive medications. The largest mean systolic BP (SBP) reduction of 46 mmHg was seen in patients with a preoperative SBP >180 mmHg. There was no change in renal function at the end of the 36-month follow-up period. This contrasts with the result of a single-center retrospective study [52] that compared percutaneous transluminal renal angioplasty (PTRA) to medical therapy in 158 patients with refractory hypertension in which 47 (30%) underwent revascularization. No difference in terms of BP reduction, death, cardiovascular disease or progression to end-stage renal disease was noted between the two groups. However, neither study included hemodynamics assessments. A documentation of high PSV with RDU or a Pd:Pa <0.9 may better indicate clinical significance and support the need for vascular intervention.

**Rapid deterioration of renal function (>30% reduction in eGFR over ≤3 months) in patients with previously stable or slowly progressive renal disease**

While trials evaluating the efficacy of revascularization in preserving or improving renal function failed to show positive results, studies looking particularly at the subset of patients with recent rapid reduction in renal function have demonstrated some efficacy after revascularization [54–56]. Also, multiple small trials and case series have demonstrated recovery of renal function after a revascularization procedure even in patients with dialysis-dependent end-stage renal disease [57, 58].
Despite the small size and multiple limitations of these studies, their results highlight the presence of a selective subset of patients in whom ARAS has progressed to cause hypoperfusion beyond the limit of renal adaptive capacity in kidneys that are already more sensitive to changes in renal perfusion [59]. Hence we believe that a rapid decline of renal function (>30% decrease in eGFR over ≤3 months) in the absence of evidence of any other glomerulopathy warrants consideration of hemodynamic etiology. Evaluation should be initiated with noninvasive studies such as RDU. In patients with evidence suggestive of functionally significant stenosis per PSV and/or renal/aortic ratio, endovascular stenting should be considered following careful assessment of the patient’s overall condition and comorbidities. Case 2 clearly illustrates such an approach.

Recurrent flash pulmonary edema (Pickering syndrome) in the setting of bilateral ARAS

Pickering syndrome was first described by in 1988 [60] in a series of 11 hypertensive patients with recurrent episodes of flash pulmonary edema (FPE) and evidence of bilateral ARAS. The pathophysiology of this condition has been well described and delineated [61] in which the bilateral nature of ARAS prevents pressure natriuresis and leads to volume expansion. Multiple studies [62–65] have reported excellent response ranging from 77 to 100% in terms of FPE recurrence and BP control with either surgical or percutaneous revascularization. None of these studies was a randomized controlled trial. However, a matched cohort-controlled study done by Kane et al. [66] compared 50 patients with HF and ARAS who underwent percutaneous transluminal renal angioplasty (PTRA) with 1:1 age-matched patients with HF and ARAS who were treated medically. PTRA resulted in better control of HF symptoms as evidenced by lower average New York Heart Association functional class, fewer HF-related hospitalizations, higher utilization of angiotensin-converting enzyme inhibitors and better control of BP. However, there was no difference in terms of all-cause mortality.

Case 2: A 84-year-old female with past medical history of left nephrectomy at age 53 years, stage 4 chronic kidney disease with creatinine (Cr) of 1.4–1.6 mg/dL (eGFR 27 mL/min/1.73 m²), and hypertension well controlled with a single agent. One month prior to her presentation to our facility, the patient developed progressive weakness, lack of appetite and lower extremity swelling. She initially presented to an outside hospital 2 weeks after the onset of symptoms and was found to have a BP of 210/90 mmHg and acute renal failure. Labs showed Cr of 6.5 mg/dL, blood urea nitrogen (BUN) 127 mg/dL, Na 132 mmol/L, and K 7.0 mmol/L. Hemodialysis was initiated with improvement in BP and symptoms. No further evaluation of her acute-on-chronic renal failure was performed and she was set up for outpatient hemodialysis. The patient presented to our institution 1 week later for a second opinion after having already received four outpatient hemodialysis treatments. Her vital signs were BP 143/76 mmHg, heart rate 80 bpm, SaO₂ 96% on 2 L oxygen via nasal cannula and temperature 36.7°C. Laboratory studies revealed WBC 16 × 10⁹/L, hemoglobin 119 g/L, platelets 273 × 10⁹/L, Na 127 mmol/L, K 4.7 mmol/L, Cl −29 mmol/L, HCO₃ −24 mmol/L, BUN 36 mg/dL, and Cr 3.6 mg/dL. Renal ultrasound showed absent left kidney, right kidney measuring 8.3 cm with normal echogenicity and no hydronephrosis. Doppler study demonstrated a peak systolic velocity of 481 cm/s at the origin of the right renal artery and 163 cm/s at the aorta, consistent with severe ostial stenosis of the renal artery. Patient underwent renal angiography with limited contrast exposure that revealed 95% stenosis at the ostium of the right renal artery. Angioplasty and placement of a drug-eluting stent was performed. Within the next 24 h the patient made >3 L of urine. Cr decreased to 2.3 mg/dL on the day of discharge. Eleven months following discharge, the patient continues to be dialysis independent with Cr of 2–2.3 mg/dL (eGFR 18 mL/min/1.73 m²) with good control of BP with two antihypertensive agents.

Conclusion

The results of the ASTRAL and CORAL trials have answered part of the question of when to intervene in the case of ARAS. These trials have shown that in patients with stable kidney function and adequate BP control, the mere presence of renal artery stenosis does not require intervention. On the other hand, clinical evidence for the benefit or lack of benefit in patients with the high-risk clinical presentations described above is lacking. A large, well-designed, randomized clinical trial targeted towards such a population is still needed. In the meanwhile, we believe that the conclusion of these contemporary clinical trials should not be generalized to all patients with ARAS. The benefit of invasive intervention should be weighed against the risks in each patient individually.

Conflict of interest statement

The primary author and all involved coauthors of this article have no financial or nonfinancial conflicts of interest to declare. The manuscript is original and is currently not under consideration by any other journal and has not been published before.

References