

# Precision medicine meets vascular disease: innovations in atherosclerotic renal artery stenosis management

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Atherosclerotic renal artery stenosis (ARAS) is a significant cause of secondary hypertension and kidney injury with important cardiovascular consequences. This review briefly discusses the pathophysiology of ARAS, evaluates in-depth the diagnostic performance of duplex ultrasound, computed tomography angiography, and magnetic resonance angiography, and synthesizes results from major randomized trials and observational studies to explore current treatment options. The objective is to define the current diagnostic and therapeutic landscape of ARAS in a manner that supports evidence-based clinical decision making, and identify which treatment modality may be appropriate based on clinical presentation. The preference for optimized medical therapy as the initial standard of care is largely based on multiple randomized controlled trials

(RCTs), which found no overall benefit from invasive endovascular treatments in conjunction with medical therapy. However, the limitations in trial design indicate that these results do not rule out the benefit in carefully selected patients. Evidence from subgroup analyses and non-randomized studies supports invasive endovascular revascularization in presentations such as recurrent flash pulmonary edema, progressive decline in renal function, and hypertension resistant to pharmacologic medical therapy. Endovascular stenting is preferred when anatomy is favorable, while open surgical reconstruction, including aortorenal bypass or endarterectomy, is reserved for complex lesions, failed prior endovascular intervention, or concomitant aortic surgery. The review also discusses emerging strategies, including novel stent platforms and drug-eluting technology, which may improve outcomes if validated in targeted high-risk cohorts.

**Key Words:** atherosclerosis, renal artery obstruction, hypertension, renovascular, diagnostic imaging, angioplasty, stents

## Introduction

Renal artery stenosis is a leading cause of secondary hypertension (HTN), most often due to atherosclerotic renal artery stenosis (ARAS). The condition involves narrowing of the renal artery lumen, usually in the ostial or proximal segments which disrupts

renal blood flow and contributes to renovascular HTN and ischemic nephropathy (Figure 1).<sup>1,2</sup> ARAS is associated with accelerated cardiovascular disease, including heart failure and stroke, and can lead to irreversible kidney injury.<sup>1,2</sup> It is also linked to cardiac destabilization syndromes such as flash pulmonary edema, recurrent acute decompensated heart failure, and acute coronary syndromes. Among patients with end stage renal disease receiving dialysis, ARAS is associated with reduced survival.<sup>2,3</sup>

ARAS affects 10–15% of hypertensive adults older than 50 years and up to 50–60% of elderly hypertensive patients, with 10–20% of affected individuals

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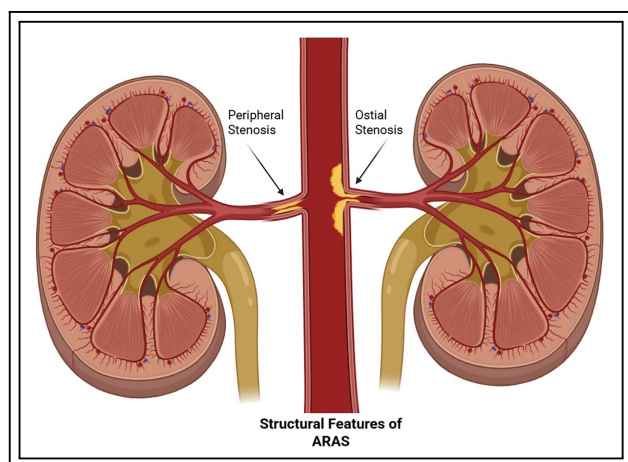


**FIGURE 1.** Diagram of the structural features of atherosclerotic renal artery stenosis (ARAS). This diagram illustrates both patterns of ARAS, clarifying the anatomical differences for clinical interpretation, with peripheral stenosis occurring further along the vessel's course and the ostial stenosis occurring at the origin of the renal artery

progressing to end-stage renal disease requiring dialysis.<sup>3,4</sup> The condition is progressive and the rate of decline in estimated glomerular filtration rate (eGFR) is approximately five times faster in vascular kidney disease such as ARAS than in other causes of chronic kidney disease (CKD).<sup>5</sup> Studies show that more than half of patients experience worsening stenosis within five years, and 16% progress to complete occlusion.<sup>3,5</sup> Approximately 6.8% of adults older than 65 years have ARAS with more than 60% occlusion.<sup>2</sup> Major risk factors include systemic atherosclerosis, CKD, and heart failure.<sup>6,7</sup>

Because early symptoms are nonspecific, ARAS is often undiagnosed, and resistant HTN or renal dysfunction may be attributed to other causes.<sup>1</sup> Progressive stenosis activates the renin-angiotensin-aldosterone-system (RAAS), which promotes vasoconstriction, sodium retention, and interstitial fibrosis.<sup>1,3</sup> In unilateral ARAS, the contralateral kidney initially compensates through pressure natriuresis, but this mechanism weakens with chronic HTN. In bilateral ARAS, compensation is absent, which leads to volume overload and worsening renal and cardiac failure.<sup>3,8</sup>

Management of ARAS remains controversial. Optimized medical therapy is the recommended first line approach, but the role of endovascular revascularization has been questioned by mixed results from major randomized controlled trials. Landmark clinical studies such as STAR, ASTRAL, and CORAL

did not show a clear benefit of routine angioplasty or stenting.<sup>1,3</sup> However, findings from trials such as HERCULES and multiple observational studies suggest that selected high-risk patients may benefit from revascularization.<sup>1</sup> Given the prevalence of ARAS in older adults with vascular disease, its contribution to HTN and renal decline, and the potential for improvement in specific clinical scenarios, accurate diagnosis and appropriate treatment selection are essential.

The purpose of this review is to evaluate current diagnostic and treatment strategies for ARAS management, with an emphasis on patient selection and clinical settings in which each approach may offer meaningful benefit.

## Modalities to Diagnose ARAS

The diagnosis of ARAS relies on various imaging modalities. According to The American College of Cardiology Foundation (ACC) and the American Heart Association (AHA) guidelines for the management of patients with peripheral artery disease, such as ARAS, it is indicated to perform diagnostic studies in patients with severe or accelerated HTN, HTN resistant to treatment, sudden flash pulmonary edema, or in patients with diminishing renal function.<sup>9</sup> The three most common non-invasive diagnostic imaging techniques employed are duplex ultrasound (DUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA).<sup>1</sup> Digital subtraction catheter angiography is recommended when there is high clinical suspicion of ARAS and when the results of the noninvasive methods are inconclusive; it is considered the gold standard.<sup>1</sup> Angiography is not generally utilized as a screening tool due to its invasiveness and cost. Instead, it is typically reserved for cases requiring endovascular intervention. Given its limited role in initial diagnosis, this paper will focus on the utility, strengths, accuracy, and limitations of DUS, CTA, and MRA in the evaluation of ARAS. Figure 2 illustrates the various imaging modalities to diagnose ARAS. Emerging artificial intelligence (AI) based imaging tools are also increasingly used to aid in diagnosis.

### *DUS to diagnose ARAS*

DUS is an effective, affordable, non-invasive method that visualizes the renal arteries and provides hemodynamic data. It is recommended as a screening tool for ARAS.<sup>10</sup> Diagnostic accuracy depends on operator skill because of arterial size, tortuosity, and retroperitoneal depth. Bilateral renal arteries are localized by



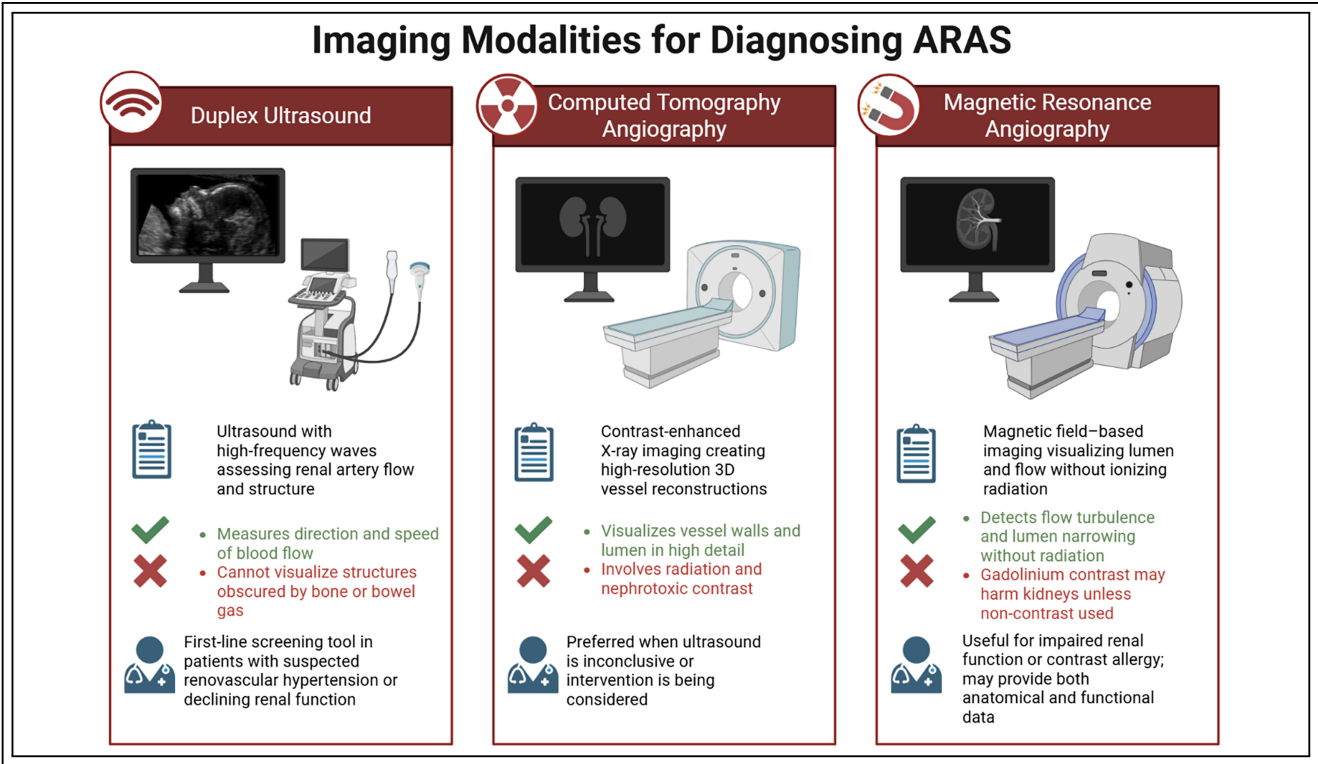


**FIGURE 2.** Imaging modalities for diagnosing atherosclerotic renal artery stenosis (ARAS) This figure summarizes duplex ultrasound (DUS), computer tomography angiography (CTA), and magnetic resonance angiography (MRA), highlighting their respective mechanisms, clinical indications, advantages, and limitations

identifying the left renal vein on gray-scale ultrasound, followed by color and spectral Doppler to assess renal size, cortical echogenicity, and parenchymal perfusion.<sup>11</sup> Renal size and echogenicity help assess chronicity. A normal-appearing kidney with abnormal perfusion suggests an earlier disease stage that may benefit from revascularization, whereas a small, hyperechoic kidney indicates chronic ischemic damage in which revascularization may not be beneficial.

There are two main groups of criteria for diagnosing ARAS with DUS: the proximal and distal criteria. Proximal criteria directly assess the renal vasculature at the level of the stenosis, while the distal criteria assess distally to the site of the stenosis. Using spectral or color DUS, the peak systolic velocity (PSV) of the main branches of the renal artery is measured to determine the maximum velocity of blood flow during systole.<sup>10,12,13</sup> PSV is inversely proportional to the luminal area, and values >180 cm/s suggest >60% stenosis.<sup>10</sup> The PSV in the renal artery is compared to the PSV in the pre-renal aorta to ascertain if there are any systemic influencing factors; this is known as the renal-artery ratio (RAR).<sup>13</sup> Normal

RAR is <3.5, and RAR >3.5 traditionally indicates >60% stenosis.<sup>14</sup> Older studies reported sensitivity 84–98% and specificity 95–98% for RAR >3.5.<sup>15–17</sup> More recent studies reported sensitivity 62–73% and specificity 81–91%.<sup>18,19</sup> Zachrisson et al. report that RAR ≥2.6 results in a sensitivity 89% and specificity 69%. Despite its accessibility, no consensus exists on optimal proximal criteria. Many criteria combine PSV >180 cm/s and RAR >3.5.<sup>13,19,20</sup>

Direct evaluation of the main renal artery presents a set of challenges, including time and accuracy. Thus, distal criteria have been developed to supplement direct evaluation findings and are described as an indirect evaluation of renal vasculature distal to the site of the stenosis, the renal hilum, and/or interlobar arteries. These measurements include post-stenotic waveform analysis to determine the renal resistance index (RRI) and acceleration time.<sup>10</sup> RRI measures the resistance of blood flow within intrarenal vasculature at the level of the arcuate and interlobar arteries and provides insight into changes in intrarenal parenchymal perfusion and systemic hemodynamics caused by ARAS.<sup>21</sup> It may also be used as a predictor for endovascular outcomes.<sup>14</sup> RRI values of 0.50–0.60 are

considered to be normal, with 0.70 considered to be part of the upper limit of the normal threshold. Increased RRI values are indicators of parenchymal damage from atherosclerotic burden distal to the site of stenosis.<sup>22</sup> RRI >0.80 may indicate poor response to revascularization.<sup>14,21</sup> Acceleration time is another distal criterion, defined as the interval from systolic rise at the end of diastole to PSV in the hilar or interlobar arteries. Acceleration times, longer than 70 ms, represents a significant renal artery stenosis. Diminished flow downstream of the site of stenosis produces a characteristic “tardus-parvus” waveform, in which there is a prolonged rise in systole and low peak height.<sup>10–13</sup> Although distal criteria are less time-intensive, their diagnostic accuracy is variable and insufficient as standalone measures.<sup>21</sup> The findings on the direct and indirect criteria through DUS are the most common and easily accessible modality to diagnose ARAS. However, CTA and MRA have been seen to be more accurate.<sup>23</sup>

### *Computer tomographic angiography in diagnosing ARAS*

CTA is defined as a non-invasive contrast-enhanced CT imaging modality that allows for the visualization of arterial structures in a short timeframe. It provides high-resolution two-dimensional multiplanar cross-sections that can be manipulated into constructing three-dimensional images of the renal vasculature. Although CTA offers high-resolution images to visualize the renal vasculature, there is the risk of the patient being exposed to contrast-induced nephrotoxicity. Ongoing renal dysfunction, radiation exposure, and difficulty in visualizing heavily calcified arteries must also be considered.<sup>5,12,24</sup> CTA directly estimates the stenosis by measuring the size of the lumen from the imaging datasets. Several studies report sensitivity ranging from 64–94% and specificity ranging from 67–99% for ARAS lesions greater than 50% stenosis.<sup>25,26</sup>

CTA has also been used to evaluate renal artery stenosis in children, contributing to additional diagnostic data for this modality. When compared with the gold standard digital subtraction angiography (DSA), CTA demonstrated a sensitivity of 90.0% and a specificity of 89.7%.<sup>27</sup> However, it should be noted that renal artery stenosis in children is typically non-atherosclerotic. Imaging modalities are not selective for atherosclerotic stenosis, but rather stenosis of any underlying etiology affecting the renal artery. Thus, in adults, other symptoms must be evaluated to determine the nature of the lesion. Another study reported a sensitivity of 85.7% and a specificity of 91.5% in detecting renal artery stenosis in children in

comparison to the gold standard DSA.<sup>28</sup> In addition to measuring the degree of stenosis, newer methods such as contrast-enhanced multidetector computed tomography (CE-MDCT) have been studied. These techniques aim to directly measure luminal diameter at the site of stenosis and correlate it with renal blood flow assessed via DUS, potentially improving diagnostic accuracy compared to relative measures like percent lumen diameter reduction.<sup>26</sup>

### *MRA in diagnosing ARAS*

Due to the nephrotoxic risks associated with iodinated contrast material used in CTA, gadolinium-enhanced MRA serves as an alternative. It assesses the lumen diameter and the flow-related signal intensity of the renal artery segments to determine stenosis. Non-contrast MRA is also capable of obtaining hemodynamic data, including increased turbulence from stenosis.<sup>25</sup> However, in patients with impaired kidneys with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>, gadolinium poses a risk of nephrogenic systemic fibrosis. Therefore, gadolinium-enhanced MRA is not recommended in patients with renal stents.<sup>8</sup> A study compared the diagnostic accuracy of contrast-enhanced MRA with that of DUS. Among individuals <60 years of age, the sensitivity and specificity were 92.31% and 36.36%, respectively, whereas in those ≥60 years, they were 100% and 73.3%, respectively.<sup>29</sup> Another study found that the overall sensitivity and specificity were 90% and 94.1%, respectively, in detecting stenosis greater than or equal to 50% with gadolinium-enhanced MRA.<sup>25</sup>

Non-contrast MRA has been studied as an alternative to Gadolinium-enhanced MRA for patients with impaired renal function.<sup>30</sup> A retrospective study compared the use of non-contrast MRA between 1.5-T and 3.0-T magnetic resonance imaging, a modality that is being used increasingly more often in clinical settings. The sensitivity and specificity for significant stenosis >50% reduction in lumen diameter were 97.4% and 89.8% for 1.5 T and 95.7% and 91.1% for 3.0 T, respectively.<sup>30</sup> A comparative analysis studied non-contrast MRA versus contrast-enhanced MRA in detecting renal artery stenosis and found that overall, the sensitivity of non-contrast MRA was 97.93% and the specificity was 98.01%.<sup>31</sup> The purpose of utilizing MRA to diagnose renal artery stenosis is to identify patients with hemodynamically significant stenosis, in which the diameter of the lumen is decreased by around 50% and may benefit from revascularization procedures such as endovascular stenting.

### Emerging AI imaging tools in diagnosing ARAS

As imaging technologies evolve, AI has become an emerging tool for automated stenosis detection and measurement standardization across modalities. In a study evaluating this approach, a deep learning system was developed that analyzes information, including ultrasound images, Doppler waveforms, and basic clinical data, to assist in identifying ARAS. Using a large cohort of patients undergoing renal artery ultrasonography, the researchers demonstrated that AI can synthesize these multimodal inputs with reasonable accuracy, performing above 80% across several model types. Although the system remained less accurate than experienced physicians, models that incorporated multiple data sources performed better than those relying on a single input, suggesting that AI may help standardize interpretation and reduce variability in settings where operator experience differs. This work supports the potential role of AI as an adjunctive tool in the diagnostic evaluation of renal artery stenosis.<sup>32</sup>

Additional work has explored whether AI can extract diagnostic information directly from spectral Doppler waveforms, which remain central to duplex ultrasound interpretation. In a pilot study, a model was trained on reconstructed velocity signals from renal duplex examinations in patients with angiographically confirmed unilateral disease. The system achieved an accuracy of 0.95 with a precision of 0.94 and an area under the receiver operating characteristic curve of 0.97. Although limited by its retrospective design, manual signal reconstruction, and a highly selected population undergoing stent placement, the study demonstrates that machine learning can classify waveform patterns associated with ARAS. This approach may eventually support more consistent interpretation of Doppler criteria in clinical settings where operator experience varies.<sup>33</sup>

### Treatment Modalities of ARAS

Treatment for ARAS remains a controversial and evolving challenge. There are three general treatment strategies, as depicted in Figure 3. Optimal medical therapy, which includes antihypertensive agents, statins, and aspirin to slow the progression of atherosclerosis and reduce cardiovascular risk. More invasive treatment options include endovascular revascularization, such as percutaneous transluminal renal angioplasty (PTRA) and renal artery stenting (PTRAS). Surgical treatments are less common and are rarely performed due to the invasiveness of the

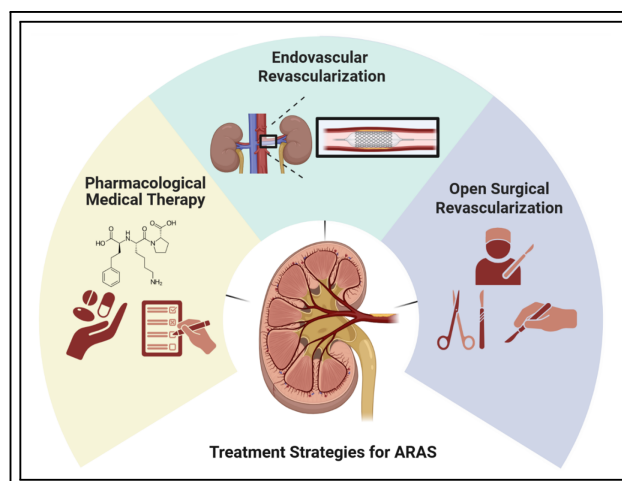


**FIGURE 3.** Treatment strategies for atherosclerotic renal artery stenosis (ARAS) This figure outlines the therapeutic continuum from optimal medical management, including antihypertensive therapy, statins, and antiplatelet agents, to selective revascularization via endovascular or surgical approaches. Indications for intervention are based on clinical presentation, severity of stenosis, and response to medical therapy

procedures and limited indications. Medical therapy is generally recommended for all patients with ARAS.<sup>5</sup>

The primary goals of treatment are to control blood pressure (BP), preserve renal function, and reduce cardiovascular risk. Stenting is commonly used for stenotic lesions in other vascular territories, such as the carotid or coronary arteries, to restore distal perfusion. Although stenting restores distal perfusion in other vascular beds (such as the carotid and coronary arteries), its efficacy in the renal arteries has been a matter of debate with respect to the goals of treatment. Renal artery stenting has not consistently demonstrated improvements in renal function or long-term outcomes, which raises questions about its therapeutic value in treating ARAS. Early observational studies indicated that stenting improved outcomes; in the 1990s, this was considered the gold standard. However, over the past two decades, there have been three major RCTs, STAR, ASTRAL, and CORAL, which compared pharmacological medical therapy and endovascular revascularization.<sup>34</sup> These studies concluded that stenting did not provide a significant benefit in ameliorating the risks imposed by ARAS, namely a decrease in BP or improvement in renal function.<sup>34</sup>

There are several major guidelines exist for the diagnosis and management of RAS: those from the



American College of Cardiology (ACC) and American Heart Association (AHA), the European Society of Cardiology (ESC), the Society of Cardiovascular Angiography and Interventions (SCAI), and the joint guidelines from the European Renal Association (ERA) and European Society of Hypertension (ESH).<sup>9,35–39</sup> Although randomized trials have not demonstrated major advantages of endovascular interventions over medical therapy, these procedures are still employed in select clinical scenarios. Identifying which patients may benefit from medical therapy, endovascular revascularization, or surgical intervention remains critical. Treatment decisions should be guided by a careful assessment of the hemodynamic significance of the lesion, as only lesions that cause substantial renal hypoperfusion may warrant invasive management.<sup>37</sup>

### *Pharmacological medical therapy for ARAS and randomized clinical trials*

Pharmacological treatment is the primary approach in approximately 90% of patients with ARAS, reflecting strong evidence that control of BP and atherosclerotic risk factors can achieve desirable outcomes. The ACC/AHA Hypertension Guidelines give medical therapy a Class I recommendation with Level A–B evidence,<sup>9,35</sup> advising optimal management of HTN with beta-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium-channel blockers for unilateral ARAS. The ESC and SCAI also recommend medical therapy as first-line treatment, noting that these agents reduce mortality and morbidity (Class I, B–C evidence) but may decrease glomerular filtration, requiring careful monitoring.<sup>36,37</sup> ERA/ESH guidelines similarly endorse ACE inhibitors and angiotensin II receptor blockers as first-line therapies, with a >30% decline in GFR prompting consideration of endovascular intervention; calcium channel blockers, beta-blockers, and diuretics are second-line options. Statins and other lipid-lowering agents are recommended to manage cholesterol based on overall cardiovascular risk.<sup>38</sup>

The pivotal study underlying these recommendations was the CORAL trial, which compared adverse cardiovascular and renal events, including stroke, myocardial infarction, hospitalization for heart failure, and progressive renal dysfunction, in patients with ARAS treated with medical therapy alone versus medical therapy plus PTRAS. The trial was designed to test whether strict control of BP and other cardiovascular risk factors could manage ARAS with or without stenting, with medical therapy aimed at mitigating RAAS activation and the broader effects of atherosclerosis.<sup>40</sup>

A total of 947 patients with HTN and hemodynamically significant renal artery stenosis were enrolled, defined as  $\geq 80\%$  and  $< 100\%$  luminal narrowing, or 60–80% narrowing with a systolic pressure gradient  $\geq 20$  mmHg, confirmed by DSA and catheter-based measurements. Patients without HTN were eligible if they had chronic kidney disease, defined as an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>. Participants received candesartan with or without hydrochlorothiazide, amlodipine combined with atorvastatin, and antiplatelet therapy such as aspirin, clopidogrel, or ticlopidine.<sup>40</sup> The CORAL study is frequently cited as a model of optimized medical therapy in ARAS.

For patients with HTN but no comorbid conditions, the target BP was  $< 140/90$  mmHg. In those with comorbidities such as diabetes or CKD, the goal was more stringent at  $< 130/80$  mmHg. For hyperlipidemia, the aim was to reduce LDL-C to below 70 mg/dL. Each of these protocols was based on different guidelines in managing the respective conditions, such as the JNC-7 HTN guideline and the AHA guidelines for managing atherosclerosis. CORAL was the first study to use angiotensin inhibitors as the first line of therapy in managing HTN.<sup>40–42</sup>

The trial assessed the incidence of mortality secondary to major cardiovascular events due to a decline in renal function, such as myocardial infarction, stroke, and congestive heart failure. Ultimately, the CORAL study demonstrated that protocol-driven medical therapy led to improved clinical outcomes, while there was no meaningful difference in outcomes when medical therapy was paired with PTRAS.<sup>43</sup> The study further emphasized the therapeutic value of angiotensin receptor blockers and ACE inhibitors in attenuating the pathophysiologic consequences of RAAS activation. The study concluded that there was no significant benefit from PTRAS, when added with medical therapy, on all-cause mortality.

Medical therapy was seen as insufficient in certain areas, particularly among patients with ARAS presenting with high-risk clinical symptoms. This included ischemic nephropathy, characterized by a rapid decline in kidney function associated with ARAS, or from acute kidney injury from the use of ACE inhibitors. Patients with resistant renovascular HTN and recurrent flash pulmonary edema secondary to ARAS often failed to respond to medical therapy. Criticisms of the CORAL study and earlier RCTs expressed that these high-risk subgroups were not adequately represented, supporting the consideration of endovascular treatments. Greco and Freda recommended that special attention be placed

on patients with high-risk symptoms who do not respond to medical therapy.<sup>41</sup>

Despite the CORAL study serving as the basis for the AHA medical therapy recommendations for ARAS, a recent article from the AHA discussed the limitations of the study, which contributed to the ongoing discussion about the potential benefits of revascularization. It was determined that the data in the CORAL study, as well as previous STAR and ASTRAL studies, did not clearly establish the criteria to define hemodynamically significant severe stenosis of the renal artery.<sup>39</sup> Additional criticisms included the fact that many participants were already receiving two antihypertensive agents at baseline, over 25% had BP at goal, and the average degree of stenosis was less than 70%.<sup>39</sup> The exclusion of patients hospitalized for heart failure or myocardial infarctions suggested that the study underrepresented high-risk patients who would have benefited from endovascular treatment.<sup>44,45</sup> The 2021 KDIGO further emphasizes that many patients with ARAS also have CKD and therefore fall into a population at disproportionately high cardiovascular risk. The 2021 KDIGO guideline recommends the use of SGLT2 inhibitors in patients with diabetes and CKD with an eGFR greater than 30 mL/min per 1.73 m<sup>2</sup>, noting that these agents reduce CKD progression, heart failure hospitalizations, and cardiovascular events independent of BP control.<sup>46</sup>

### *Endovascular treatment for ARAS*

Before the pivotal STAR, ASTRAL, and CORAL trials reshaped practice, endovascular revascularization was the primary treatment for ARAS. These minimally invasive procedures restore renal artery blood flow to improve perfusion, reduce BP, and limit renal and cardiovascular dysfunction. PTRAS alone is associated with high restenosis rates in atherosclerotic lesions, leading to preference for PTRAS, which maintains vessel patency using a metallic stent.<sup>2,5</sup> However, complications such as cholesterol embolization, contrast induced nephropathy, renal artery or aortic dissection, and in stent restenosis are particularly relevant in older patients with diffuse atherosclerosis.<sup>42,43</sup> These risks must be weighed against the morbidity and mortality of untreated disease.

### *Guideline-based indications for endovascular treatment and patient selection*

While broad RCTs did not demonstrate population-wide benefit, limitations in trial design leave space for selective revascularization. Both the ESC and ACC/AHA recommend revascularization when medical therapy fails, such as in cases

with resistant HTN, worsening renal function, and recurrent heart failure symptoms.<sup>9,35,38</sup> The 2022 AHA Scientific Statement similarly supports selective revascularization in high-risk clinical presentations that do not respond adequately to optimal medical therapy.<sup>39</sup> SCAI provide detailed criteria in 2014, advising revascularization for patients with hemodynamically significant stenosis accompanied by resistant HTN unresponsive to antihypertensive therapy, recurrent congestive heart failure, flash pulmonary edema, or progressive renal dysfunction. Hemodynamically significant is defined as 50–70% luminal narrowing with either a resting mean translesional pressure gradient  $\geq 10$  mmHg, a resting peak systolic gradient  $\geq 20$  mmHg, or a renal fractional flow reserve (FFR)  $\leq 0.8$ . Ischemic nephropathy in the setting of CKD, particularly when the eGFR is  $\leq 45$  mL/min/1.73 m<sup>2</sup>, is also considered an appropriate indication for PTRAS. Patients with hemodynamically mild to moderate stenoses, defined as  $<50\%$  stenosis with a peak-to-peak translesional gradient  $<20$  mmHg, a mean translesional gradient  $<10$  mmHg, or renal FFR  $>0.8$ , do not merit revascularization.<sup>37</sup> These recommendations are supported by prospective data, most notably the HERCULES trial, which evaluated the efficacy of stenting in patients with ARAS and uncontrolled HTN meeting hemodynamic and clinical criteria for revascularization.<sup>37</sup>

### *Outcomes after endovascular treatment in select high-risk cohorts*

The HERCULES trial was a single-arm, non-randomized, prospective trial evaluating stenting in patients with ARAS and uncontrolled HTN. Between 2007 and 2009, 202 patients were enrolled through a two-step eligibility process. The first step screened for patients with uncontrolled resistant HTN, defined as systolic BP  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg despite at least two antihypertensive medications, mild to moderate renal dysfunction, and ARAS with  $\geq 60\%$  stenosis. These patients underwent PTRAS without stenting and were immediately assessed for unsuccessful results, defined as residual stenosis  $\geq 50\%$ , a persistent pressure gradient  $\geq 10$  mmHg (mean) or  $\geq 20$  mmHg (peak systolic), flow-limiting dissection, or thrombolysis in myocardial infarction flow  $<3$ . The average patient was 72 years old, 62% were female, and 99% required three or more antihypertensive medications. Comorbidities included diabetes mellitus (45%), coronary artery disease (67%), and hypercholesterolemia in most patients. Baseline BP averaged  $162 \pm 19$  mmHg systolic and  $78 \pm 12$  mmHg

diastolic. Baseline percent diameter stenosis was 81.3% by site assessment and 66% by an independent angiographic core laboratory.<sup>47</sup>

The primary endpoint was the incidence of restenosis at 9 months, determined via DUS and angiography. Secondary outcomes included changes in BP, antihypertensive medication use, and renal function. At 9 months, restenosis occurred in 10.5% of patients, and systolic BP decreased to  $145 \pm 21$  mmHg after stenting with no change in medications. The average number of antihypertensive medications remained unchanged at 3.4. Renal function was measured by serum creatinine and eGFR. The baseline averages were  $1.2 \pm 0.4$  mg/dL and  $58 \pm 21$  mL/min/1.73 m<sup>2</sup>, respectively. After 9 months, eGFR was  $57.0 \pm 23$  mL/min/1.73 m<sup>2</sup>. Renal deterioration was avoided. At 36 months, freedom from death was 90.1%.<sup>47,48</sup>

A defining characteristic of the HERCULES trial, in contrast to other investigations, was the specificity of its inclusion criteria. It used a two-step selection process to identify hemodynamically and functionally significant lesions by assessing BP and percent stenosis. Although the CORAL trial also assessed translesional pressure gradients in patients, it was not part of a strict inclusion criterion. The benefits of the procedure were sustained over 36 months. However, renal function remained stable. The results support the argument that initial patient selection is critical in determining the appropriateness of PTRAS and that it should be considered for patients with resistant HTN, hemodynamically significant ARAS, and flash pulmonary edema. It was also argued that PTRAS is reasonable for those with moderate CKD.<sup>49</sup> The favorable outcomes may be partly attributable to the contemporary stent design used in this study, as previous studies reported declines in HTN control and renal function beyond 6 months.<sup>50</sup>

While the HERCULES trial emphasized strict criteria for patient selection, it excluded several high-risk populations, including those with rapidly progressive ischemic nephropathy, advanced CKD requiring dialysis, and severe cardio-renal decompensation. Observational studies focusing on these underrepresented groups have reported improvements in renal function and BP after revascularization. Predictors of benefit include younger age, absence of diabetes, lower RRI, and lower levels of albuminuria. Patients with global renal ischemia, whether from bilaterally hemodynamically significant ARAS, severe stenosis to a single functioning kidney, or rapidly declining renal function, have also demonstrated improvement after intervention.<sup>51,52</sup> These patient subsets were

not included in earlier trials, including HERCULES and CORAL.

Data from smaller, well-characterized high-risk cohorts illustrate how patient selection influences PTRAS outcomes. One such study reviewed 65 patients with  $\geq 1$  atherosclerotic renal artery lesion  $>70\%$  stenosis plus kidney failure (eGFR  $<60$  mL/min/1.73 m<sup>2</sup>) or uncontrolled HTN (systolic BP  $>140$  mmHg or diastolic BP  $>90$  mmHg despite  $\geq 3$  antihypertensives, including a diuretic) who underwent PTRAS between 2004–2014, with long-term follow-up in 2020. At baseline, 79.9% had CKD class 3–5, 87.7% had uncontrolled HTN, 46.1% had diabetes or prediabetes, and 78.4% had dyslipidemia; mean creatinine was 1.5 mg/dL. Within 1 year, 35.3% remained CKD class 3b–5, and 18.4% had uncontrolled BP (mean  $150.8 \pm 23.5/85.8 \pm 9.4$  mmHg). In-stent restenosis occurred in 15.3% of patients. Age, male sex, CKD class 3b–5, and uncontrolled HTN predicted increased long-term mortality; diabetes and CAD did not.<sup>52</sup> These findings reinforce practical criteria for endovascular selection. Evaluation should include BP, renal function trajectory, and imaging confirmation. Higher baseline daytime ambulatory BP predicts better outcomes. Renal function assessment should include eGFR and albuminuria/proteinuria, as long-term decline and elevated albuminuria/proteinuria predict poorer outcomes.<sup>43</sup> DUS of the renal vasculature further informs prognosis: in unilateral stenosis, contralateral RRI  $>0.8$  predicts worse outcomes.<sup>51–53</sup> Retrospective studies support the role of patient selection in PTRAS outcomes. Shi et al. reported reductions in systolic and diastolic BP following stenting in 78 ARAS patients, with renal function improvement observed only in those with mild baseline impairment.<sup>54</sup> Kim et al. found that patients with high-risk clinical presentations, including pulmonary edema, refractory HTN, or rapid kidney function decline, had greater improvements in BP and renal function than low-risk patients.<sup>55</sup> Long-term single-center data showed that BP reduction was generally consistent, whereas sustained renal recovery was variable, with low rates of procedural complications.<sup>56</sup> These findings suggest that intervention is most likely to benefit patients with clinically significant, potentially reversible ischemic nephropathy.

Complementing these findings, a prospective two-center study evaluated PTRAS in 102 high-risk patients with severe ARAS  $\geq 70\%$ , resistant HTN, rapidly declining kidney function, and recurrent heart failure between 2015 and 2021. There were 5 patients who could not undergo the

procedure because of complete arterial occlusion. Hemodynamic significance was assessed using DUS and renography, and CTA/MRA confirmed stenosis  $\geq 70\%$ . Most patients had systolic BP  $\geq 150$  mmHg despite treatment with at least three antihypertensive agents, and rapidly declining renal function was defined as an eGFR loss  $>5$  mL/min/1.73 m<sup>2</sup> per year. Patients were advised to receive lipid-lowering therapy. The primary outcome was change in BP at a median follow-up of 24 months, with secondary outcomes including changes in antihypertensive medication use, kidney function, and clinical events. Over 24.4 months, 5 patients required permanent renal replacement therapy and 10 died. At 3 months, systolic BP decreased by 19.6 mmHg, eGFR increased by 7.8 mL/min/1.73 m<sup>2</sup>, and the defined daily dose of antihypertensive medications decreased, with no repeat hospitalizations among patients with prior flash pulmonary edema or heart failure.<sup>57</sup>

Additional studies examined endovascular treatment in specific clinical scenarios. Edgar et al. reviewed 74 patients who underwent PTRAS from 2008–2021, stratified by indication and by whether they met CORAL criteria. Most patients in each subgroup benefited after 1 year. The authors argued that patients excluded from CORAL still benefited and that earlier trials underestimated treatment effects by enrolling heterogeneous populations.<sup>58</sup> van der Niepen et al. similarly argued that STAR, ASTRAL, and CORAL did not adequately focus on true resistant HTN. They proposed an ideal randomized controlled trial limited to patients with resistant HTN and hemodynamically significant stenosis, defined as luminal narrowing  $>70\%$  with functional confirmation (translesional systolic gradient  $\geq 20$  mmHg or pressure ratio  $<0.9$ ). The proposed regimen included antihypertensive therapy, statins, and antiplatelets, with primary endpoints based on 24-h ambulatory BP and long-term eGFR. CT would assess procedural success and restenosis.<sup>59</sup> The ANDORRA trial attempted to follow this model but was terminated early due to recruitment challenges.<sup>60</sup>

Beyond trial design, numerous studies examined predictors of clinical benefit and renal outcomes after endovascular treatment. While multiple studies show that PTRAS can improve serum creatinine and eGFR, a retrospective uncontrolled study found that only one-third of patients with resistant HTN experienced a BP reduction, with no change in eGFR at 1 year.<sup>60</sup> High baseline systolic ambulatory BP and low body mass index were independent predictors of BP response. The authors also noted that an RRI  $>0.8$  on DUS, age  $>65$  years, proteinuria  $>1$  g/d,

and eGFR  $<40$  mL/min were associated with post-procedural loss of renal function.<sup>60,61</sup> These findings align with other reports showing that older age and reduced baseline eGFR predict poorer outcomes in patients with ARAS and concomitant kidney disease.<sup>36,59</sup> Albuminuria may also help identify patients likely to benefit from PTRAS. In a post-hoc CORAL analysis, patients with a baseline albumin/creatinine ratio  $<22.5$  mg/g had fewer cardiovascular, renal, and mortality events after stenting.<sup>62</sup>

Despite the lack of recent large RCTs addressing earlier limitations, selective cases remain appropriate for revascularization. The 2022 AHA scientific statement outlined clinical scenarios in which endovascular treatment may be warranted and reiterated that STAR, ASTRAL, and CORAL did not adequately define the clinical or hemodynamic profiles most likely to benefit. Candidates include patients with unilateral stenosis and high-risk features such as rapidly worsening HTN, declining eGFR, or flash pulmonary edema, as well as those with bilateral disease and loss of functional renal mass, stenosis of a solitary functioning kidney, or progressive eGFR decline with ARAS and ischemic nephropathy. Clinical characteristics associated with benefit include recent onset or worsening HTN within 1 year, minimal proteinuria, younger age, and elevated contralateral renin activity in unilateral disease. Complications of PTRAS, including atheroembolism, dissection, arterial rupture, and thrombosis, occur in only 3–5% of patients.<sup>39</sup>

Recent narrative reviews reinforce that the lack of benefit seen in major RCTs reflects inappropriate patient selection, as most enrolled patients had mild-to-moderate stenosis, preserved renal function, and controlled BP, thereby excluding those most likely to benefit. Optimal candidates include those with hemodynamically significant stenosis and high-risk clinical presentations such as true resistant HTN confirmed by out of office BP monitoring, recurrent heart failure or flash pulmonary edema, rapidly progressive renal dysfunction, bilateral disease, or a solitary functioning kidney. Pretreatment assessment should incorporate ambulatory BP, renal function trajectory, albuminuria, and functional imaging, as absence of albuminuria identifies salvageable kidneys, whereas high albuminuria, atrophic kidneys, or elevated resistive index predict poor response.<sup>63</sup> Revascularization remains appropriate for severe stenosis causing cardiac destabilization syndromes, hypertensive crisis with end organ damage, or recurrent pulmonary edema, and may be considered in select patients with unexplained recurrent heart failure despite optimized medical therapy.<sup>64</sup>



Multidisciplinary evaluation has emerged as a key determinant of appropriate patient selection. Cohort data demonstrate that multidisciplinary-guided decisions identify patients who derive meaningful benefit from revascularization, with improvements in BP, renal function trajectory, and heart failure admissions when revascularization is applied to anatomically significant lesions in the context of severe HTN, progressive renal dysfunction, or heart failure syndromes.<sup>65</sup> Patients selected for revascularization through structured multidisciplinary meetings had reductions in BP and antihypertensive medication use at 1 year, with no severe adverse events, suggesting that individualized assessment may identify patients most likely to benefit beyond strict guideline algorithms.<sup>66</sup>

### *Indications and outcomes of surgical management in ARAS*

When medical therapy and endovascular approaches are not viable or have been unsuccessful, surgical intervention remains a rare and selective option for anatomically complex disease. Nephrectomy, renal artery bypass, and open surgical corrections are amongst the interventions utilized in instances involving complex lesions, renal atrophy, or renal artery aneurysm repair. The AHA states that open renal reconstruction should be reserved for patients with certain indications, such as previously failed endovascular treatments, lesions affecting arterial bifurcations, or subsegmental branch vessels. Extrarenal open aortic reconstruction techniques are used to address hemodynamically significant stenosis. This includes direct reconstruction with aortorenal bypass graft. Transaortic endarterectomies are considered to be an option for patients with bilateral ostial renal stenosis. *Ex vivo* renal artery reconstructions are employed for cases involving complex lesions that affect the renal hilum or segmental arteries.<sup>39</sup>

With advances in medical and endovascular management, the use of open surgery for ARAS has declined sharply since the 1980s. There have not been any prospective randomized clinical trials that compared surgical interventions with PTRAS and medical therapy since 2000. Reviews of historical cohorts indicate that patients who underwent surgical revascularization typically reflected what are now considered appropriate indications, including severe, uncontrolled HTN, hemodynamically significant stenosis, progressive renal impairment, or ischemic nephropathy. Older studies reported reductions in BP and improvements in renal function

following surgery in certain patients. However, long-term mortality remained substantial, with survival reported at around 33.6% at 10 years. Additionally, surgical treatment was often relegated to a secondary or tertiary role, as endovascular interventions achieved comparable or greater improvements in HTN control and renal outcomes.<sup>39,67–69</sup>

Among the few randomized comparisons of surgical and endovascular revascularization for ARAS, Balzer et al. conducted a prospective trial from 1998–2004 in patients with ostial ARAS, directly comparing open surgical reconstruction with PTRAS and assessing vessel patency, BP control, and renal function. 50 patients with ARAS  $\geq 70\%$  occlusion (determined via DUS and DSA) were randomly assigned to receive either open surgical treatment or PTRAS. Although both groups were shown to have improvement in renal function, determined by serum creatinine and HTN, the interventional group had an 18% mortality rate after a four-year follow-up, whereas the surgical group had a 25% mortality rate. Primary patency was achieved in 90.1% of the surgical group and 79.9% of the interventional group. It was noted, however, that there was a higher number of patients in the surgical group who underwent bilateral renal artery reconstruction, as transaortic endarterectomy was considered to be the preferred treatment to remove atherosclerotic plaque that extended into the renal arteries from the aorta.<sup>70</sup> The in-hospital mortality rate of renal artery bypass grafts for patients with renovascular HTN and those with renovascular HTN and ischemic nephropathy has been measured to be around 10% in an analysis of patients who underwent bypass procedures from 2000–2004, providing a rationale for lower risk alternatives such as PTRAS.<sup>71</sup> These findings, although limited by sample size and era-specific techniques, illustrate the potential durability advantage of surgery and the comparable functional outcomes seen with both strategies in this population.

A retrospective analysis by Steuer et al., spanning 1993–2007, examined patients who underwent surgical repair for renal artery stenosis, which comprised several types of lesions, including ARAS. The reported indications for operative intervention included hemodynamically significant stenosis  $>70\%$ , a translesional pressure gradient exceeding 15 mmHg between the aorta and the renal artery distal to the lesion as measured by angiography, persistent elevation of BP  $\geq 140$  mmHg despite optimal medical therapy, and renal failure. Renal insufficiency was defined as a serum creatinine  $>150$   $\mu\text{mol/L}$  or GFR  $<50$  mL/min. In patients with ARAS, renal failure was attributable to renal ischemia. In contrast,

individuals with renal artery stenosis due to fibromuscular dysplasia experienced no late mortality. Notably, during the long-term follow-up period, all late deaths occurred within the ARAS subgroup.<sup>72</sup>

In cases where ARAS results in irreversible renal atrophy and loss of function, nephrectomy may be considered as a therapeutic alternative to revascularization, particularly when the affected kidney contributes to resistant HTN or overall renal compromise. In select patients with unsalvageable atrophic kidneys, surgical removal has been associated with clinical benefits, including improved BP control and stabilization of renal function. In an observational cohort study by Kane et al., nephrectomy was shown to reduce antihypertensive medication burden and improve renal parameters, suggesting compensatory function by the contralateral kidney.<sup>73</sup> A retrospective study by Thomaz et al. corroborated the results with similar findings. Patients with atrophic kidneys (average size of  $7.1 \pm 1.1$  cm), developed as a result of severe or total renal artery stenosis, demonstrated significant improvement in both systolic and diastolic BPs, as well as a 63.8% improvement in renal function 1–3 years after the nephrectomy.<sup>74</sup>

Complex anatomical and clinical presentations may require advanced surgical interventions beyond standard revascularization techniques. Somalanka et al. reported a case involving spleno-renal artery transposition in a male patient with a history of abdominal aortic aneurysm, prior stent graft placement, and a single functioning kidney. The patient presented with resistant HTN and renal dysfunction with an eGFR of 28 mL/min/1.73 m<sup>2</sup>. CTA revealed an atrophic right kidney with ostial stenosis, as well as left renal artery ostial stenosis adjacent to the AAA stent graft. Notably, the patient experienced contrast-induced kidney injury during CTA. Following splenic artery to left renal artery transposition, the patient demonstrated improved renal function and BP control.<sup>75</sup>

For complex lesions involving the distal renal artery, hilum, or segmental branches, *ex vivo* renal artery reconstruction may be employed. In a study by Ham and Weaver this technique was associated with long-term preservation of renal mass and function, alongside significant improvements in BP.<sup>76</sup> While not comprehensive studies/reviews, these cases illustrate the importance of individualized surgical approaches in patients with anatomically complex or treatment-resistant ARAS, where conventional medical therapy or endovascular treatments may be insufficient.

## Discussion

ARAS remains a complex clinical entity in which management requires a balance between the proven benefits of optimal pharmacological medical therapy for the majority of patients and the selective advantages of revascularization or surgery in carefully defined high-risk subgroups.<sup>9,34–38,44,45</sup> While major RCTs such as CORAL have consistently shown no significant advantage for endovascular revascularization over optimized pharmacologic therapy in unselected patient populations, these findings are constrained by limitations in study design, particularly the inclusion of heterogeneous patient groups, inadequate representation of unstable clinical phenotypes, and insufficient criteria for defining hemodynamically significant lesions. As such, the conclusions should not be generalized to patients with advanced or rapidly progressive disease, in whom invasive interventions such as PTRAS may provide substantial benefit. Recent analyses reinforce that prior RCTs enrolled patients with moderate anatomical stenosis, preserved renal function, and minimal hemodynamic compromise, reducing the likelihood of detecting benefit from revascularization.<sup>77</sup> The 2022 AHA Scientific Statement similarly emphasizes that high-risk phenotypes such as recurrent pulmonary edema, rapidly progressive renal dysfunction, and bilateral severe stenosis were underrepresented in earlier trials.<sup>39</sup>

Accurate diagnosis and appropriate patient selection are contingent upon the integration of a thorough clinical evaluation with high-quality vascular imaging. DUS, CTA, and MRA remain the principal modalities for diagnosing and determining the severity of the disease and anatomical complexity, each with distinct strengths that influence management. Emerging diagnostic technologies aim to detect earlier pathophysiological events, including cortical hypoxia and alterations in renal blood flow, and may have the potential to transform the routine diagnostic workup by identifying patients with reversible renal injury.<sup>78</sup> New studies argue that anatomical percent stenosis alone is an unreliable predictor of hemodynamic significance, as pressure gradients and renal blood flow reductions vary with lesion geometry and residual renal function. Functional assessment using translesional pressure gradients, renal FFR, or hyperemia-based measurements may better identify clinically significant lesions.<sup>77</sup>

Physiologic and clinical data support the use of functional thresholds to define hemodynamic significance. In a porcine model of graded renal artery stenosis with a contralateral significant stenosis,

Drieghe et al. measured the ratio of distal renal artery pressure to aortic pressure as an index of the pressure actually delivered to the kidney. An index value of approximately 0.75 corresponded to a 25% reduction in distal renal perfusion pressure and was associated with a measurable decline in renal blood flow and a marked increase in renin secretion, indicating activation of the RAAS.<sup>79</sup> The recent FAIR prospective-randomized trial similarly demonstrated that patients with renal FFR values below 0.80 experienced meaningful reductions in ambulatory systolic BP and antihypertensive medication burden after stenting, whereas those with FFR  $\geq 0.80$  did not show measurable benefit. FAIR identified an optimal predictive threshold of 0.78 for BP improvement, closely aligned with the physiologic inflection point observed in the porcine model, supporting the role of functional assessment in identifying lesions that produce clinically relevant renal hypoperfusion.<sup>79,80</sup>

Computational fluid dynamics modeling using CT or MRI-derived vascular reconstructions offers a non-invasive method to estimate pressure gradients.<sup>77</sup> Additionally, AI-based imaging tools and advanced intravascular modalities such as IVUS and OCT are increasingly used to improve lesion characterization, stent optimization, and prediction of treatment response, reducing operator variability and enhancing precision in identifying patients with salvageable renal parenchyma.<sup>81</sup>

For most patients with ARAS, initial treatment focuses on comprehensive medical therapy, which includes aggressive BP control via RAAS inhibitors, calcium channel blockers, beta-blockers, and diuretics, along with lipid-lowering agents, antiplatelet therapy, and lifestyle modification to address atherosclerotic risk factors.<sup>35–38</sup> This approach has been shown to achieve durable BP control, preserve renal function, and reduce cardiovascular morbidity in the general ARAS population. Nonetheless, monitoring is essential, as high-risk symptoms such as recurrent flash pulmonary edema, rapid deterioration of renal function, or refractory HTN despite multiple agents may necessitate escalation to revascularization. The 2021 KDIGO consensus further highlights that many ARAS patients have concomitant CKD and elevated cardiovascular risk, recommending SGLT2 inhibitors for eligible patients to reduce CKD progression and heart failure hospitalizations independent of BP control.<sup>46</sup>

Endovascular revascularization remains important in selected high-risk scenarios, including patients with bilateral hemodynamically significant stenoses, severe stenosis to a solitary functioning kidney,

rapidly progressive CKD, or progressive cardio-renal deterioration due to ARAS. Patients with recurrent pulmonary edema, refractory HTN, or rapidly declining renal function may also experience clinically meaningful improvements in eGFR and BP following PTRAS, outcomes not captured in earlier RCTs.<sup>47,52,54,55,57,58,82</sup> Functional confirmation using translesional pressure gradients or renal FFR enhances patient selection, while imaging evidence of preserved renal parenchyma, such as adequate kidney size, low resistive index, and minimal proteinuria, is associated with better outcomes. Advanced intraprocedural imaging, careful preprocedural planning, and multidisciplinary evaluation further improve procedural success and long-term outcomes.<sup>37,39,51–53,62,81</sup> Figure 4 provides a practical clinical pathway for managing ARAS.

Novel strategies seek to address limitations inherent in conventional revascularization, particularly incomplete renal recovery after stenting. Drug-eluting stents have shown enhanced patency in small-diameter accessory renal arteries (3–5 mm) by eluting agents such as sirolimus to inhibit neointimal hyperplasia, while mesenchymal stem cell embolization may mitigate microvascular damage caused by atheroembolism and reperfusion injury.<sup>83</sup> Preclinical models indicate that intra-arterial delivery of mesenchymal stem cells during renal angioplasty can improve cardiac function, microvascular density, and ventricular remodeling.<sup>83</sup> Future directions also include robot-assisted interventions, bioresorbable scaffolds, drug-coated balloons, and AI-driven prediction models to optimize patient selection and procedural planning.<sup>81</sup>

Surgical revascularization has become increasingly rare but remains indicated for anatomically complex lesions unsuitable for stenting, cases of failed endovascular intervention, or when concurrent aortic surgery is planned.<sup>39</sup> Techniques such as aortorenal bypass, transaortic endarterectomy, and *ex vivo* repair offer durable results, while nephrectomy may be warranted for a non-functioning kidney contributing to refractory HTN.<sup>67–76</sup> Uncommon reconstructive approaches, including splenorenal transposition, have been described for challenging anatomy.<sup>75,76</sup> Structured, multidisciplinary team evaluation improves identification of surgical candidates and optimizes outcomes, particularly in patients with complex anatomy or treatment-resistant HTN.<sup>65,66</sup>

The management of ARAS should follow a strategy that begins with accurate diagnosis using advanced imaging, progression to comprehensive medical therapy, and careful selection of high-risk

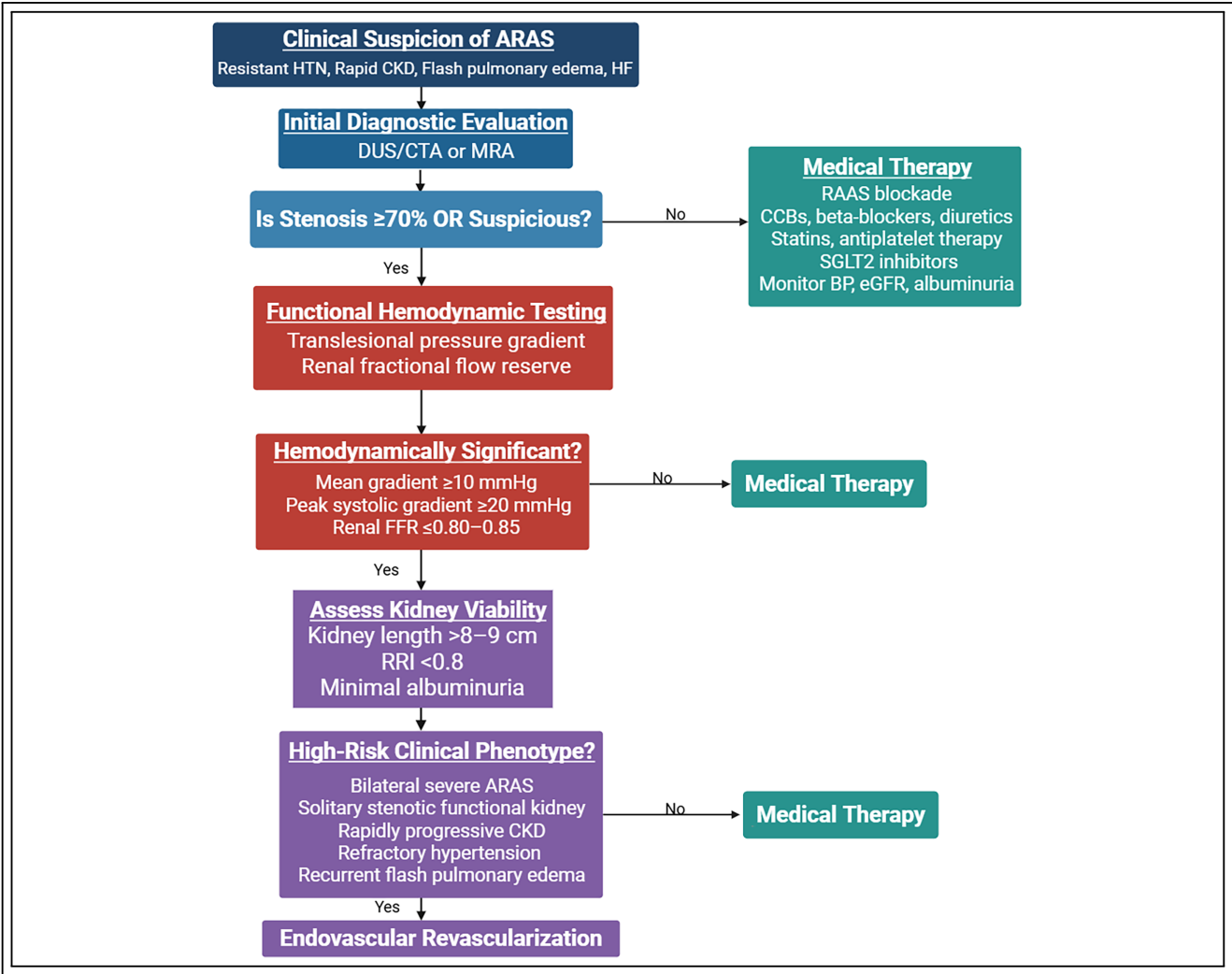


**FIGURE 4.** Clinical pathway for atherosclerotic renal artery stenosis (ARAS) management. Structured decision framework outlining diagnostic evaluation, medical therapy, and selection of high-risk patients for revascularization

patients for revascularization. Surgical intervention remains a fallback for anatomically unsuitable or technically failed endovascular cases. Advancing understanding of these invasive approaches will require robust, multicenter trials focused on high-risk cohorts, incorporating standardized, imaging-based functional criteria, strict definitions for significant lesions, rigorous BP and renal function endpoints, and long-term renal and cardiovascular outcomes. Precision-based frameworks integrating AI-driven imaging, functional hemodynamic assessment, computational modeling, and biomarkers such as albuminuria may reconcile discrepancies between RCTs and real-world outcomes, ensuring

revascularization is directed toward patients with the greatest potential for clinical benefit.<sup>62,77,81</sup>

Limitations

This review has limitations that warrant consideration. Much of the available evidence derives from randomized trials such as CORAL, ASTRAL, and STAR, which underrepresented high-risk clinical presentations and therefore may underestimate the benefit of revascularization in patients with hemodynamically significant disease. Definitions of hemodynamic significance vary across studies, and reliance on angiographic severity alone does not



reliably reflect physiological impairment, limiting comparability. Evidence supporting revascularization in high-risk phenotypes is largely observational and therefore subject to biases. Diagnostic modalities also have limitations, DUS is operator dependent, whereas CTA and MRA are susceptible to artifacts that may misclassify stenosis severity. Emerging diagnostic and treatment approaches require further validation. As a narrative review, this work did not follow a systematic methodology and may be subject to selection bias.

## Conclusions

ARAS remains a challenging condition in which optimal medical therapy is appropriate for most patients, while selective revascularization or surgery benefits carefully defined high-risk groups. Major trials such as CORAL, STAR, and ASTRAL did not show benefit for routine stenting, but these studies enrolled heterogeneous populations with preserved renal function and controlled blood pressure, often excluding patients with rapidly progressive disease or recurrent heart failure. Evidence from observational studies, prospective cohorts, and subgroup analyses demonstrates that endovascular treatment can improve blood pressure, renal function, and clinical outcomes in patients with hemodynamically significant stenosis, resistant hypertension, flash pulmonary edema, or progressive renal decline. Accurate diagnosis, functional assessment, and individualized patient selection remain critical to identify those most likely to benefit from intervention, while surgical management is reserved for complex or treatment-resistant cases.

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## Author Contributions

Yujiang Fang initiated the idea and supervised the whole process. Ahnaf J. Ahmed, Austin J. Marrah, Trenton G. Mayberry and Braydon C. Cowan wrote the draft. Yujiang Fang and Mark R. Wakefield made critical revisions to the draft. All authors reviewed and approved the final version of the manuscript.

## Availability of Data and Materials

Not applicable. This article does not involve the generation or analysis of datasets, and therefore no data are available.

## Ethics Approval

Not applicable. This study did not involve human participants, animal subjects, or identifiable personal data, and therefore did not require institutional ethics approval.

## Conflicts of Interest

The authors declare no conflicts of interest.

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