



Expert Review of Cardiovascular Therapy

ISSN: 1477-9072 (Print) 1744-8344 (Online) Journal homepage: http://www.tandfonline.com/loi/ierk20

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To cite this article: Aghogho Odudu, Diana Vassallo & Philip A Kalra (2015): From anatomy to function: diagnosis of atherosclerotic renal artery stenosis, Expert Review of Cardiovascular Therapy, DOI: 10.1586/14779072.2015.1100077

To link to this article: http://dx.doi.org/10.1586/14779072.2015.1100077

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Published online: 19 Oct 2015.



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From anatomy to function: diagnosis of atherosclerotic renal artery stenosis

Expert Rev. Cardiovasc. Ther. Early online, 1–19 (2015)

Atherosclerotic renal artery stenosis (ARAS) affects 7% of the over 65 s and will be increasingly common with an ageing population. ARAS obstructs normal renal perfusion with adverse renal and cardiovascular consequences. Drug therapy is directed at reducing atherosclerotic risk. Two recent major trials of revascularization for ARAS showed that clinical outcomes were not improved beyond those offered by optimal drug therapy in most patients. This reflects experimental data showing that restoration of blood flow alone may not attenuate a cascade of tissue injury. A shift from anatomic to functional imaging of ARAS coupled to novel therapies might improve clinical outcomes in selected patients. This review outlines the case for separately assessing hemodynamic significance of arterial stenosis and functional reserve of renal parenchymal tissue. The authors consider current and emerging diagnostic techniques for ARAS and their potential to allow individualized and functionally directed treatments.

Keywords: atherosclerotic renal artery stenosis • diagnostic imaging • functional imaging • hypertension • oxygenation • perfusion • renovascular disease • review

The prevalence of atherosclerotic renal artery stenosis (ARAS) in a population-based cohort of individuals older than 65 years is around 7%,[1] increasing to 25–50% in comorbid Western populations with high atherosclerotic risk.[2] Study of Medicare claims data revealed a threefold increase in the incidence of ARAS between 1992 and 2004.[3] Whilst this might in part reflect increasing availability of diagnostic imaging, the burden of atherosclerosis in an aging population means that ARAS will be increasingly common.

ARAS is subclinical in the majority, whilst a few individuals have a high-risk phenotype of refractory hypertension, progressive renal functional loss or recurrent flash pulmonary edema. [4] Medical management of ARAS includes optimizing blood pressure control, renin– angiotensin blockade, smoking cessation and lipid-lowering with statin therapy. Despite their individual caveats, recent major randomized controlled trials have shown that restoring vessel patency by angioplasty or stenting does not confer any added benefit beyond

that achieved with current optimal medical therapy. [5,6] This reflects experimental data showing that restoration of blood flow alone may not attenuate a cascade of tissue injury.[7] In light of these data, the number of revascularization procedures performed has declined along with enthusiasm in pursuing the diagnosis. However, these trials still showed that a substantial minority of 16-22% developed substantial renal functional decline or end-stage kidney disease. Furthermore, those with highrisk phenotypes were typically excluded. Emerging novel therapies are directed at attenuating the ischemic injury that persists despite restoring blood flow.[8] It is increasingly important that the diagnosis of ARAS goes beyond assessment of its anatomy and quantifies functional viability. This may allow better selection for novel therapy trials or identification of those patients in whom revascularization will preserve kidney function whilst preventing harm in those who will not. The paradigm shifts in the epidemiology and current management of ARAS have been recently



¹Institute of Cardiovascular Sciences, University of Manchester, Manchester, UK ²Manchester Academic and Health Sciences Centre, Manchester, UK ³Salford Royal Hospitals National Health Service Foundation Trust, Salford, UK *Author for correspondence: Tel.: +44 161 206 4446 a. odudu@manchester.ac.uk summarized.[9,10] This review considers current and emerging diagnostic techniques for ARAS and their potential to allow individualized and functionally directed treatments.

Catheter angiography

Catheter angiography (CA) is now a rarely used reference-standard technique for diagnosis of significant ARAS due to its invasive nature. Even with preventative protocols, CA carries a small but important risk of contrast-induced nephropathy, cholesterol embolization, allergic contrast media reactions and arterial dissection. This procedure is now typically reserved for a planned endovascular intervention after noninvasive imaging. Several prospective clinical studies typically used a visually estimated stenosis of greater than 50% or 70% to determine hemodynamic significance. These biologically plausible criteria were supported by data demonstrating that the visually estimated percentage of stenosis was independently associated with worse survival.[10] It is now well recognized that such visual estimates have poor interobserver variability with a poor correlation to quantitative methods.[11] Further, even quantitative stenosis grading correlates poorly to functional severity as measured by pressure or flow changes.[12,13] Studies using latex casts and hemodynamic measurements indicate that measurable reductions in translessional pressures or blood flow only occur at a diameter stenosis of 70-80%. Reasons for such discrepancies include a 2D luminal view that ignores renal blood flow, vessel geometry, radiolucent atherosclerotic plaque, collateral circulation, microvascular resistance and parenchymal injury within the kidney downstream from the ARAS. Subgroup analysis of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial did not show any benefit in those with >80% stenosis by CA as estimated by individual study centers.[6] The 7% systemic overestimation of diameter stenosis between the core lab using quantitative software and the study centers [6] underscores just one aspect of the fundamental problem of estimating arterial flow based on 2D imaging, an issue not exclusive to the renal vasculature.[14]

Translesional pressure gradients

Indices derived from pressure-transducing guidewires are an established technique for assessing hemodynamic significance of coronary artery stenosis during coronary angiography.[14] These typically use maximal vasodilation with drugs such as adenosine or papaverine to allow a measure of vascular responsiveness independent of autoregulation termed coronary flow reserve. Normal coronary flow reserve is three- to fivefold the resting value. Values < 2 are typically associated with cardiac ischemia. This whole organ flow-derived measure represents the combined effect of contrary artery stenosis and microvascular dysfunction, but cannot distinguish the two. Such studies informed analogous techniques in renal arteries. Manoharan and coworkers measured renal hemodynamics in healthy volunteers modulated by a variety of vasodilators, determining that renal flow reserve was approximately twice the resting value.[15] Lower renal flow reserve compared to the heart is teleological as the kidney aims to maintain filtration pressure across a wide range of renal blood flow, whilst the heart aims to maintain adequate myocardial blood flow across a wide range of perfusion pressures.[16] Under maximal vasodilation, downstream resistance and venous pressure are negligible, and poststenotic blood flow becomes proportional to perfusion pressure and extent of stenosis. Fractional flow reserve (FFR) is a vessel-specific pressure-derived measure defined as the ratio of pressure distal and proximal to a stenosis under maximal vasodilation.[14,17] Normal maximum blood flow (Q^m) is

$$Q^{m} = Pa - Pv / R$$

where R is renal microvascular resistance at maximum vasodilation, Pa is mean aortic pressure and Pv is mean central venous pressure. Maximal blood flow (Q) in a stenotic artery can be represented as

$$Q = Pd - Pv / R$$

where Pd represents pressure distal to the stenosis. Under maximal vasodilation, renal microvascular resistance becomes negligible allowing renal FFR to be defined as

$$Q/Q^{m} = (Pd - Pv)/(Pa - Pv)$$

Assuming the central venous pressure to be negligible, this equation simplifies as

Renal FFR
$$= Pd/Pa$$

The renal FFR varies between 0 in a completely occluded artery and 1 in a normal renal artery. Limitations of FFR include the risks of administering vasodilators, assumptions of negligible central venous pressure, as well as the reliance on achieving maximal vasodilation. Failure to achieve maximal vasodilation will overestimate FFR. Several studies measured hemodynamic significance of ARAS using CA with pressuresensing guidewires using a range of translesional pressure gradients (Table 1). These generated a variety of thresholds to predict variably defined reductions in blood pressure with similar diagnostic performance. Using an elegant study design in stented ARAS, De Bruyne and coworkers demonstrated renin release was stimulated when the resting ratio between mean pressure distal and proximal to the stenosis (Pd, distal pressure; Pa, aortic pressure) fell below 0.9.[18] Thus, resting Pa/Pd ratio < 0.9 was proposed as a physiological definition of significant ARAS. Resting Pa/Pd ratio also did not require testing under vasodilation. Further studies established a poor correlation between 2D angiographic stenosis and translesional pressure gradients. Drieghe and coworkers measured renal artery FFR estimating that a threshold of >50% stenosis by CA, falsely identified hemodynamically significance in 38% of cases (Figure 1).[13] Expert consensus guidelines summarized these thresholds (see Box 1)[11]:

Robust validation of translessional gradients in large studies to predict clinical outcomes in ARAS remains an unmet need. The CORAL trial originally had angiographic eligibility criteria of 80–99% stenosis or 60–80% stenosis with a systolic pressure

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Jradient.	Authors'	ecommenaea hreshold to rredict BP esponse	lone	. MmHg >	IMG > 0 mmHg	ISG≥21 mmHg	(continued)
lesional pressure g	BP Outcome 🖌		No parameter N predicted BP or GFR change	SBP reduced by R 12 mmHg in group 2 with RMG > 22 mmHg versus 3 mmHg in group with RMG < 22 mmHg. RMG > 22 mmHg had best (albeit poor) prediction of BP response (sensitivity 50%, specificity 95% and accuracy 1%)	Dopamine-induced F HMG ≥20 mmHg 2 was best predictor of 3-month BP response (sensitivity 72%, specificity 82%)	HSG ≥21 mmHg was F best predictor of 12- month BP reduction (sensitivity 82%, specificity 84% and accuracy 84%)	
eline trans	Definition	or Br response	Not defined	Greater than the mean reduction of 5/ 2 mmHg observed for the whole group	24 h SBP > 20 mmHg (the mean for the overall group)	DBP < 90 mm Hg or reduced by ≥15 mm Hg and/or SBP < 140 mm Hg on same/ reduced reduced	
ion by base	Renal functional	tunctional change	None	None	None	None	
<u>ularizat</u>	Follow-	up (months)	Q	m	Μ	12	
se to revaso	Vasodilator		Papaverine	Dopamine	Papaverine Dopamine	Papaverine	
respon		ABPM	Yes	Yes	Yes	Ŷ	
functional		DBP	71 (62–79)	73 ± 10	81 ± 12	91 ± 13	
sure or renal		SBP	136 (126–147)	141 ± 14	162 ± 24	170 ± 12	
g blood pres	acteristics	Serum creatinine (mg/dl)	0.8 (0.7–1.0)	85 ± 27 ⁵	1.2 ± 0.5	1.2 ± 0.3	
s reporting	Baseline char	Visual diameter stenosis (%)	74 (67–80)	60 ± 12	58 ± 16	50-90%	
itudie			35	7e	23	62	
Table 1. 9	Study		Kądziela 2013 [68] and Kadziela 2015 [†] [69]	Protasiewicz 2013 [70]	Mangiacapra 2010 [71]	[72]	

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1	Authors'	threshold to predict BP response	FFR < 0.8	HSG > 20 mmHg
I	BP Outcome		3-month BP reduced in 86% with FFR < 0.8 vs. 30% with FFR > 0.8	SBP reduced by 33 ± 19 mmHg in 13 (59%) patients stented with HSG > 20 mmHg
I	Definition of BD	u br response	DBP < 90 mm Hg or reduced by ≥15 mm Hg and/or SBP < 140 mm Hg on same/ reduced reduced	Not defined
I	Renal	change	None	None
1	Follow-	up (months)	10 ± 2	1-5.5
I	Vasodilator		Papaverine	Acetylcholine
1		ABPM	Ŷ	°N N
I		DBP	8	76 ± 14
I		SBP	174	167 ± 24
I	Incteristics	Serum creatinine (mg/dl)	57*	1.3 ± 0.4
ued).	Baseline chara	Visual diameter stenosis (%)	£0-90%	55 ± 17
ontir			17	22
Table 1. (d	Study		Mitchell 2007 [73]	Jones 2006 [74]

⁺Kadziela 2013 and Kadziela 2015 report renal and BP outcomes for the same participants. [#]Estimated GFR m/min/1.73 m² using the Modification of Diet in Renal Disease formula. [§]Creatinine clearance (m/min). ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; DBP: Diastolic blood pressure; FFR: Fractional flow reserve; GFR: Glomerular filtration rate; HMG: Hyperemic mean gradient; HSG: Hyperemic systolic gradient; RMG: Resting mean gradient; SBP: Systolic blood pressure.



Figure 1. Example of angiography, ultrasound measurements and translesional pressure gradient in a right-sided ARAS. Angiography clearly demonstrates >50% stenosis. The left inset shows Doppler signals at the level of the stenosis (300 cm/s). Both suggest "significant" ARAS, while an invasive pressure gradient measurement only documents a very mild gradient (distal pressure/aortic pressure ratio 0.92, hence hemodynamically not significant). ARAS: Atherosclerotic renal artery stenosis.

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Box 1. Thresholds of translesional gradients for hemodynamically significant ARAS by intra-arterial pressure wire

- Resting mean gradient > 10 mm Hg
- Resting Pd/Pa < 0.9
- Hyperemic systolic gradient > 20 mm Hg
- FFR < 0.8

gradient of at least 20 mm Hg.[6] Translesional gradients were ultimately used in only 199 of 947 trial participants as the need for this investigation was considered to be a cause of delayed recruitment. Outcomes by FFR categories were not reported. Data on how frequently FFR is currently used in investigation of ARAS are not available. Efforts are being made to develop an international registry of ARAS interventional procedures to capture such data. Sufficient enthusiasm to recruit to an adequately sized FFR-directed clinical trial of revascularization might be unfeasible, unless combined with a novel adjunctive therapy. Whilst an advance from anatomically estimated stenosis, FFR and other pressure gradients focus on arterial hemodynamics ignoring the effects of poststenotic microvascular resistance or the contralateral kidney that may better represent tissue viability.

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Ultrasound

Duplex ultrasound is an inexpensive, repeatable, noninvasive and widely available technique that can determine the hemodynamic significance of ARAS. Disadvantages include angle dependency, high operator expertise, high interobserver variability and poor reproducibility (see Box 2). However, in expert hands, it is an excellent rule-out test and received the same Class I, evidence Level B recommendation for diagnostic screening as other established techniques.[19] Studies of duplex ultrasoundderived parameters have generated thresholds for significant ARAS with a variable correlation to diameter stenosis by CA (Table 2).[20] Commonly reported parameters that directly assess the pre-stenotic main renal artery include renal artery peak systolic velocity (PSV) or the renal to aortic ratio (RAR). The latter is the ratio of PSV in the renal artery to the aorta to eliminate the influence of cardiac output. End-diastolic velocities are less commonly reported. Several studies found a PSV > 200 cm/s and RAR > 3.5 corresponded to at least 60% diameter stenosis with sensitivity (71-98%) and specificity (62-98%).[21] A meta-analysis of 88 studies involving 8147 patients determined that PSV was the best predictor of ARAS > 50% by CA, with a sensitivity of 85% and a specificity of 92%. [20] Comparisons of direct ultrasound parameters to invasively measured translesional pressure gradients suggested that hemodynamically significant ARAS was associated with higher than

Box 2. Advantages and disadvantages of duplex ultrasound for diagnosis of renal artery stenosis

Advantages

- Inexpensive
- Noninvasive
- No contrast
- No radiation
- Repeatable
- Can assess a stented artery

Disadvantages

- Time consuming (>1 h)
- Operator dependent
- Lack of standardization in diagnosis of atherosclerotic renal artery stenosis
- Limited data on ability to grade stenosis >60%
- · Limited by abdominal adiposity or overlying gas
- Limited visualization of distal renal artery and accessory renal arteries
- Data cannot be acquired in up to 20% of patients

previously accepted thresholds (PSV > 318 cm/s, RAR > 3.74, Figure 1).[13]

Measuring direct parameters is technically challenging due to overlying bowel gas preventing access to the entire course of the renal artery, a challenge complicated if there are accessory vessels. Indirect duplex ultrasound parameters assess poststenotic segmental arteries within the renal parenchyma and include the resistance index (RI), acceleration time, acceleration index and the shape of the systolic peak. These parameters are easier to measure and less dependent on optimal Doppler angles. The RI is the most widely reported indirect parameter and is typically taken as a mean of three measurements calculated by (1 - end diastolic velocity)/PSV X 100). The RI is thought to reflect microcirculatory resistance. An RI value of 0.70 is accepted as the upper limit of normal in adults. A study of 58 patients showed that $RI \ge 0.65$ is associated with severe interstitial fibrosis and arteriosclerosis.[22] A difference in RI of >0.05 between kidneys correlated with >70% stenosis in a study of unilateral ARAS.[21] A landmark study showed that ARAS associated with RI > 0.8 predicted futility of revascularization. [23] However, increased RI is not specific to ARAS and is increased by other causes of chronic kidney disease (CKD), aging and extremes of heart rate. Other studies showed improved outcomes after revascularization amongst patients with RI > 0.8.[24] Some data suggest following an algorithm that combines direct and indirect parameters can improve diagnostic sensitivity and specificity (see Box 3).[21] Table 3 summarizes studies reporting the predictive ability of ultrasound parameters to predict a clinical response to revascularization.

Novel ultrasound techniques

Contrast-enhanced ultrasound involves slow intravenous injection of 1–3 ml of contrast media. The contrast is made of microbubbles with two parts; a biocompatible membrane shell surrounding a gas. The contrast enhancement lasts around 3 min after injection. Second-generation microbubbles are licensed that give more persistent contrast. The microbubbles remain in the vascular space and do not undergo glomerular filtration. The added value of contrast enhancement is in improving the proportion of patients with diagnostic images to determine hemodynamic significance as well as using the contrast kinetics to quantify regional perfusion. In a study of 120 patients with suspected ARAS, contrast-enhanced ultrasound identified all 38 cases confirmed by CA whilst only 33 were found by conventional duplex ultrasound.[25] These techniques are not yet widely available.

Radioisotope studies

Radioisotope studies remain a reference technique for measurement of glomerular filtration rate (GFR) with excellent correlation to the gold standard of inulin clearance.[26] Combining clearance studies with renal scintigraphy generates functional information that might be useful in the assessment of ARAS. The determination of single kidney (SK)-GFR uses 51Cr-ethylenediaminetetraacetic acid to assess global GFR and scintigraphy to apportion the filtration of each kidney by uptake of 99mTc-dimercaptosuccinic acid or mercaptoacetyltriglycine. Measuring tracer uptake at baseline and after a dose of captopril improves the ability to detect significant unilateral ARAS by an exaggerated transient reduction in GFR in the ipsilateral kidney due to a greater dependence on angiotensin-mediated efferent arteriolar resistance.[27] In a multicenter study population with ARAS detected by other methods, the technique was 83% sensitive and 93% specific for detecting unilateral ARAS > 70% by CA.[32] Captopril renography is currently rarely used as diagnostic accuracy is limited in bilateral ARAS or patients with CKD.[27] Metaanalyses report inferior diagnostic performance to angiography by computed tomography (CT) or magnetic resonance.[28]

CT angiography

In recent years, spiral CT angiography (CTA) has become a standard noninvasive technique for visualization of the renal vasculature. Rapid and accurate images are generated that are suitable for 3D reconstruction (Figure 2). Compared to magnetic resonance, CTA offers better spatial resolution and shorter exam times. Disadvantages of CTA include ionizing radiation, difficult interpretation in heavily calcified arteries and risk of contrast-induced kidney injury. Although modern nonionic contrast agents have a lower propensity to cause kidney injury than older ionic agents, the risk is still 2% in the general population and increases with declining GFR and comorbidity such as CKD or diabetes. Patients with a reduced intravascular volume are at a significantly greater risk. International

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Table 2. S	electe	ed studies co	mparing du	plex ultraso	und cr	iteria against cath	eter angiography.
Study	n	Duplex Criteria for diagnosis of RAS	Sensitivity (%)	Specificity (%)	AUC	Percentage diameter stenosis for catheter angiographic standard	Comments
AbuRahma 2012 [75]	313	PSV >285 cm/s	67	90	0.85	>60%	PSV > 285 cm/s or a RAR of 3.7 were the best parameters to detect RAS >
		RAR 3.7	69	91	0.82		60%
Drieghe 2008 [13]	47	PSV >318 cm/s	88	77	0.88	<0.90 [†]	RAR had the best AUC in ROC analysis
		EDV >70 cm/s	88	77	0.85		
		RAR > 3.74	75	97	0.94		
Staub 2007 49 PSV > 92 [76] 200 cm/s		92	81	NR	>50%	Mean translesional systolic pressure gradient was 24 mmHg at 50%	
		RAR > 2.5	92	79	NR		diameter stenosis and 23 mmHg at PSV
		dRI > 0.05	31	97	NR		200 cm/s criteria excluding RAS > 70% with 100% negative predictive value
Kawarada 2006 [77]	60	PSV > 219 cm/s	89	89	89	>20 mmHg [‡]	PSV correlated more strongly with translesional pressure gradients than percentage diameter stenosis, a gradient of 20 mmHg corresponded to 47% stenosis.
Conkbayir 2003 [78]	50	PSV 180–200 cm/ s and RAR > 3.0	92	88	0.95	>60%	Combination of direct parameters performed best at diagnosing RAS > 60%. There was no difference in performance between PSV 180 and 200 cm/s
Nchimi 2003 [79]	91	PSV > 180 cm/s or RAR > 3.5	91	97	96	>60%	Duplex ultrasound showed good interobserver agreement, however, is unreliable in detection of accessory arteries
de Haan 2002 [80]	78	PSV > 180 cm/s and RAR > 3.5	50	91	NR	>50%	The authors do not recommend using duplex ultrasound due to a wide range of sensitivities and specificities quoted in different studies
Zeller 2001 [81]	66	RAR > 3.5 and dRI > 0.05	76	97	NR	>70%	Although RAR detects the presence of RAS, dRI enables the diagnosis of hemodynamically significant RAS
		RAR > 3.5 and dRI < 0.05	100	60	NR		

⁺Ratio of poststenotic renal to aortic pressure < 0.9.

*Translesional systolic pressure gradient.

AUC: Area under the curve; dRI: Side-to-side difference in resistance index; EDV: End-diastolic velocity; NR: Not reported; PSV: Peak systolic velocity; RAR: Renal aortic ratio; RAS: Renal artery stenosis; ROC: Receiver operating characteristic.

guidelines recommend preventative protocols based on prehydration and stopping nephrotoxic drugs.[29]

Dynamic contrast-enhanced CT

Advances in CT technology allow renal physiological parameters to be derived from kinetic modeling of an injected bolus of iodinated contrast media. Kwon and coworkers recently

reported the largest comparison in 96 patients with essential (n = 56) or renovascular hypertension (n = 40).[30]Multidetector CT decay kinetics were used to derive SK perfusion, volume and GFR and compared to GFR by iothalamate clearance. GFR by CT correlated well with iothalamate GFR (r = 0.88), while Bland-Altman plots showed only moderate agreement with no systemic bias. GFR by CT is at an early stage

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Box 3. Diagnostic algorithm for using duplex ultrasound to determine hemodynamically significant ARAS proposed by Zeller and colleagues [21]

Unilateral ARAS

- 1. PSV > 200 and RAR >3.5
- 2. RI difference between stenotic and contralateral kidney >0.05

Bilateral ARAS

- 1. PSV > 200 and RAR >3.5
- 2. Acceleration time >0.07 s in relevant kidney

ARAS: Atherosclerotic renal artery stenosis; PSV: Peak systolic velocity; RAR: Renal to aortic ratio; RI: Resistance index.

of validation with reports confined to research studies in expert centers. Accuracy remains inferior to reference methods by radioisotope tracers and there is no multicenter validation.[24] A notable disadvantage to the technique is the significant additional dose of ionizing radiation incurred (26–27 mSv).[30]

Magnetic resonance angiography

Compared with CA, magnetic resonance angiography (MRA) is noninvasive and with multiplanar acquisition can generate 3D views. A meta-analysis demonstrated CTA and MRA have an almost equivalent performance to CA, with sensitivities and specificities > 90%.[28] The spatial resolution of MRA approaches that of CTA. The lack of ionizing radiation or nephrotoxic contrast media makes MRA a good choice both for screening and planning an intervention. MRA is typically performed using gadolinium-based contrast media (Gd). MRA has the ability to be combined with dynamic contrast imaging to determine blood flow, SK-GFR and other physiological information in a single investigation. Limitations include slower acquisition than CTA, patient intolerance due to claustrophobia, contraindications in patients with implanted ferromagnetic materials, flow-related artifacts and rare risk of nephrogenic systemic fibrosis in patients with advanced CKD. Multiple guidelines now advise avoidance of Gd contrast media in those with estimated GFR < 30 ml/min/ 1.73 m^2 to mitigate this risk, and no cases have been reported since their implementation.[31] Newer noncontrast MRA methods use time-of-flight techniques that are prone to signal loss with historically poor diagnostic accuracy compared to Gd-enhanced MRA. More recent data have demonstrated almost comparable accuracy with a sensitivity of 73-94% and a specificity of 82-98% to determine >50% ARAS by CA.[32,33] Where MRA was the screening technique for enrollment into the CORAL trial, only patients with specific criteria suggesting a greater likelihood of functionally significant ARAS were allowed to be enrolled.[6] For example, patients with >75% visually estimated stenosis on MRA were enrolled if there was spin dephasing or if the ipsilateral kidney was 1 cm smaller than, enhanced less or showed delayed Gd excretion compared to the contralateral kidney. Although the neutral

results of CORAL might argue against the need to evaluate functional significance of ARAS, the above MRA features have not been robustly validated.

Measuring hemodynamic significance by 4D flow MRI

Recent advances in MRI hardware and rapid acquisition techniques allow velocity-sensitive image acquisition in three dimensions with cardiac gating. This technique is known as 4D flow MRI. Such acquisitions can provide velocity, flow, shear wall stress and pressure gradients without contrast. They have shown excellent agreement with invasive pressure measurements in cardiac studies. Recently, the technique has been developed in renal arteries. Using experimentally induced ARAS in swine, a recent study reported excellent correlation between invasively measured systolic pressure gradient and the 4D-flow MRI estimate ($R^2 = 95\%$).[34] This technique potentially allows noninvasive assessment of translesional pressure gradients to complement routine MRA (Figure 3).

Dynamic contrast-enhanced MRI

Gd chelates produce contrast by shortening local T1 relaxation times and are freely filtered at the glomeruli without tubular secretion or reabsorption. After injecting an intravenous bolus of Gd, high-speed repetitive acquisition of T1-weighted images capture the bolus transit from the aorta into the renal arteries, then dispersing into the renal parenchyma and then collecting system. Mathematical modeling of the bolus transit generates estimates of SK-GFR, regional renal blood perfusion and tubular excretion. Dynamic contrast-enhanced (DCE)-MRI-based SK-GFR has a good correlation (r = 0.82-0.92) to isotopebased reference methods for SK-GFR using only 3-4 ml of Gd and adding little time to a routine MRA study.[35-38] Renal DCE-MRI has not yet penetrated into routine clinical practice due to reasons that include variation in the postprocessing, lesser accuracy than reference methods and a lack of multicenter validation.[39] The authors incorporated DCE-MRI into an investigation of the response to revascularization of ARAS. The authors reported predictors of GFR change in 15 patients with 22 kidneys stented for ARAS with paired assessment of SK-GFR by DCE-MRI and radioisotopes at baseline and 4 months post stenting.[40] Improved GFR was defined as >15% increase from baseline and at least >1 ml/min. DCE-MRI also produced measurements of blood flow, blood volume, extraction fraction, tubular transit time and functional volume (the area of Gd enhancement within the whole renal volume). A good correlation was found between SK-GFR values from DCE-MRI and radioisotopes (r = 0.91). Baseline predictors of GFR increase were lower extraction fraction, higher blood volume, longer tubular transit time and lower SK-GFR, as well as the ratio of renal parenchymal volume to SK-GFR (see below). Revascularization improved blood flow and blood volume in all groups but only increased functional volume in the group with improved GFR. As a result, the authors proposed that wellvascularized RAS kidneys with reduced extraction fractions are those most likely to benefit from revascularization and

Table 3. Stu	Idies	reporting	blood pres	sure or rer	nal functio	onal re	sponse to	revascularization by bas	seline duple	ex ultrasound parameters.
Study	c	Baseline ch	naracteristics				Follow-	Definition of BP response	Definition	Authors' recommended threshold
		Visual diameter stenosis (%)	Serum creatinine (mg/dl)	SBP	DBP	ABPM	up (months)		of renal response	to predict response
Fujihara 2015 [82]	49	>60	1.24 ± 0.5	154 ± 24	75 ± 15	2	12	>10 mmHg or >15 mmHg reduction where preprocedure SBP is 150–180 mmHg or >180 mmHg, respectively	eGFR increase > 10%	RI < 0.7 was associated with better response in the CKD group, although there was no overall improvement in renal function postrevascularization
Bruno 2014 [83]	158	>60	67 ± 29 [§]	162 ± 21	90 ± 14	2	12	DBP < 90 mmHg or reduced by ≥15 mm Hg and/or SBP < 140 mm Hg on same/reduced medication	eGFR increase > 20%	RI > 0.73 in the contralateral kidney predicts failed renal response but RI did not predict BP outcome
Cianci 2010 [84]	40	>70	2.0 ± 0.9	171 ± 20	89 ± 12	N	12	NR	NR	RI > 0.83 ± 0.2 averaged from both kidneys predicted renal functional decline and increased proteinuria
Santos 2010 [85]	106	>60	1.5	176	83	N	24	R	NR	RI < 0.8 was significantly associated with an improved BP (that was not defined) postrevascularization
Crutchley 2009 [86]	86	>1.8 ⁵	1.8 ± 1.1	183 ± 29	92 ± 17	6	58 ± 26	DBP reduced by ≥20 mm Hg on same/reduced medication if >95 mm Hg or reduced medication if DBP < 95 mm Hg	eGFR change >20%	RI > 0.8 predicted renal functional decline and death but not BP response
García-Criado	36	>60	NR	NR	NR	NR	23 ± 15	>15% reduction in BP on	>15%	RI > 0.8 predicted BP response but

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BP and renal function improved regardless of RI

>10% reduced

at

MAP reduction > 5 mmHg discharge after procedure

 27 ± 15

Yes

NR

NR

1.6[‡]

>70

241

Zeller 2003 [24]

2005 [87]

creatinine

serum

at 6 months

not renal functional change

reduced

same/reduced medication

serum

creatinine

Rl > 0.8 identifies those unlikely to improve postrevascularization

clearance

creatinine

increased

>10%

MAP reduction >10 mmHg on same/reduced medication

32 ± 21

Yes

16[‡] +I

86

 $157 \pm 22^{\pm}$

 $51 \pm 41^{\pm}$

70 ± 13

131

Radermacher 2001 [23]

⁺Creatinine clearance in ml/min. ^{*}Data were averaged where baseline characteristics were only reported for subgroups. ^{*}Feak systolic velocity by duplex ultrasound. ABPM: Ambulatory blood pressure monitoring: BP: Blood pressure; CKD: Chronic kidney disease; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; MAP: Mean arterial pressure; NR: Not reported; RI: Resistance index; SBP: Systolic blood pressure.



Figure 2. CT angiography with a 3D reconstruction. The arrow denotes a right-sided renal artery stenosis.

highlighted DCE-MRI as a complementary technique to routine MRA. The technique requires further refinement and validation before it can be recommended for routine clinical use.

Assessing renal functional reserve

One of the recent shifts in the understanding of ARAS is the need to assess the functional viability of the renal parenchyma that lies beyond the stenosis and in the contralateral kidney. This is conceptually equivalent to assessing the ischemic penumbra after a stroke or the area at risk or hibernation after myocardial infarction. These tissue regions are ischemic but not necrosed and retain the potential for restored function consequent to restored perfusion. Further, ARAS is histologically characterized by inflammation, oxidative stress, capillary rarefaction and fibrosis that might persist despite perfusion being restored.[8] Concepts of renal functional reserve have only been sparsely defined. This is in part because advanced imaging techniques have been confined to research settings.[41] However, there is also a more complex relation between perfusion, oxygenation and function in the kidney than other organs. To generate a filtration pressure, renal blood flow is in excess of the metabolic needs of that kidney and there is a steep oxygenation gradient between the cortex and the near hypoxic medulla. Compensatory arteriovenous shunting, tubuloglomerular feedback and neurohormonal inputs form part of complex autoregulatory interplay between perfusion, oxygenation and filtration.[42]

Blood-oxygen-level-dependent imaging

In vivo assessment of renal hemodynamics and tissue oxygenation is challenging. Blood-oxygen-level-dependent (BOLD) MRI was first described in human kidneys in 1996 and remains the most extensively studied noninvasive tool to assess regional renal oxygenation in humans.[41] BOLD imaging exploits the change in the weakly magnetic properties of hemoglobin as it converts from the deoxygenated to the oxygenated form, which in turn alters the magnetic field in the vicinity of adjacent water molecules to increase signal intensity in T2*-weighted images. The relationship between BOLD signal intensity denoted by $R2^*$ ($R2^* = 1/T2^*$) and renal tissue oxygenation has been validated against implanted oxygen-sensitive microelectrodes in animal studies.[43] However, the nature of the R2* signal is complex as it can be influenced by nonoxygen-related factors including hydration status, sodium avidity, vessel geometry and local temperature. Thus, repeated measures of R2* within patients under physiological challenge are inherently more sensitive to oxygenation changes than single measurements between patients by effectively controlling for confounders. The R2* response to furosemide is most frequently reported. Furosemide inhibits sodium transport in the thick ascending loop of Henle, reducing medullary oxygen consumption with a consequently increased medullary oxygenation and decreased medullary R2*.

Gloviczki and coworkers reported R2* in 24 patients with essential hypertension, 13 with moderate ARAS and preserved renal volume and 17 with severe ARAS and reduced renal volume.[44] Cortical R2* values were increased in severe ARAS but preserved in moderate ARAS. Whilst baseline medullary R2* values did not differ between groups, the medullary R2* response to furosemide was attenuated in moderate and severe ARAS. Textor and coworkers reported R2* response to furosemide in 25 subjects with suspected ARAS.[45] Furosemide induced a normal decrease in R2* in 21 kidneys without ARAS. In kidneys with severe ARAS but preserved volume, R2* was elevated at baseline with the R2* response to furosemide maintained. In kidneys with severe ARAS and reduced volume, the basal R2* was paradoxically low (reflecting increased oxygenation) but with no change in response to furosemide. Gloviczki and coworkers reported R2*, blood flow and SK-GFR in 14 patients with unilateral ARAS and 14 control patients with essential hypertension.[46] Within the ARAS group, stenosed kidneys had increased renal vein renin levels, reduced blood flow, reduced GFR but preserved oxygenation by basal R2* compared to contralateral kidneys. The stenosed kidneys had an attenuated R2* response to furosemide compared to the hypertensive group. Increased renal venous oxygenation invasively sampled from stenosed kidneys was interpreted as an adaptive reduction in oxygen consumption.[46]

In summary, basal cortical R2* may be increased in severe ARAS. The lack of a medullary R2* decrease in response to furosemide might reflect adaptive reduction in oxygenation consumption or reduced renal oxygenation reserve. Quantifying the magnitude of the furosemide R2* response to



Figure 3. Swine model of ARAS with unenhanced 4D flow MRI. (A) Catheter angiography image shows two endovascular pressure-sensing guidewires across a moderate left ARAS (solid arrow). Pressure sensors are located at the end of each wire (open arrows). (B) Reconstruction of the complex difference signal obtained from 4D flow MRI shows stenosis (arrow). (C) Velocity map shows increased velocities (open arrow, color coded in gold and red) distal to ARAS (solid arrow). (D) Corresponding pressure map shows a pressure gradient across the stenosis (arrow). ARAS: Atherosclerotic renal artery stenosis. Reproduced with permission from [34].

predict clinical outcomes showed promise in a swine model of

ARAS, but to date there are no data in humans.[47]

Other noninvasive MRI tissue characterization techniques

Combining renal volume with functional measurements The length of a kidney has long been used as a surrogate to predict functional severity of ARAS, with a severe unilateral ARAS being classically associated with a small atrophied kidney. ARAS may also cause glomerular microangiopathy in the contralateral kidney.[16] This results in reduced volume in the stenotic kidney, with the contralateral kidney showing early compensatory hypertrophy then late volume loss.[48] In 65 patients with ARAS, we showed that 3D renal volume measured by MRI was better correlated to isotopic SK-GFR (r = 0.86; p < 0.001) than 2D measures including length and cortical thickness (r = 0.6-0.78; p < 0.001).[49] We also found a greater ratio of volume to SK-GFR in the kidneys with the largest increases in GFR following revascularization, proposing the ratio as a measure of functional reserve or "hibernation" in ARAS.[49] The concept of assessing functional reserve to predict treatment response was evolved in a pilot study of 28 patients investigated for ARAS (16 with ARAS > 50% and 12 controls).[50] We showed that whilst R2* alone had only 40% sensitivity, the ratio of R2* to isotopic SK-GFR was 67% sensitive and 86% specific in predicting a 15% increase in GFR four months after stenting of ARAS.[50]

Other noninvasive MRI-based techniques might hold promise in assessment of renal functional reserve. Magnetic resonance elastography uses an external mechanical vibration source and velocity-encoded MRI to characterize wave propagation. Stiffer tissues generate higher wavelengths allowing 3D maps of tissue stiffness that showed good correlation to fibrosis in a swine model of ARAS.[51]

Diffusion tensor imaging can describe tissue microstructure by quantifying the degree of restriction of water molecule diffusion by cell membranes in multiple directions. Preliminary studies in the setting of CKD and renal allografts have shown diffusion measures correlate to histopathological fibrosis scores, but there are no data in the context of ARAS.[52]

Arterial spin labeling uses magnetic labeling of water in blood across an artery as an endogenous tracer to generate perfusion maps by kinetic modeling.[41] Fenchel and coworkers reported promising initial data in 18 patients [53]; severe ARAS > 70% showed reduced perfusion values (Figure 4). Combining arterial spin labeling with BOLD to estimate blood flow and oxygenation would have advantages in the assessment of ARAS, allowing serial studies and obviating the need for exogenous contrast or ionizing radiation.



Figure 4. Arterial-spin labeling magnetic resonance showing mild (30%) left RAS and severe (90%) right RAS in a 70-year-old man. Perfusion-weighted map shows differences in perfusion between right (191 ml/100 g/min) and left (270 ml/100 g/min) kidneys. Color bar represents perfusion, in milliliters per 100 g per minute. RAS: Renal artery stenosis. Reproduced with permission from [53].

Serum and urine biomarkers

A few studies have reported inflammatory and cardiovascular biomarkers for ARAS. Studies using nonspecific inflammatory or cardiovascular biomarkers such as C-reactive protein have limited value as levels correlate to general atherosclerotic risk and comorbidities that are associated with ARAS. Another nonspecific marker is the level of urinary protein that reflects parenchymal microangiopathy and was correlated to poor renal functional and blood pressure outcomes after revascularization. [54] Plasma renin activity is a marker for activation of the renin-angiotensin-aldosterone system and was historically used to identify patients with renovascular hypertension that would benefit from surgical revascularization. However, serum values showed poor sensitivity and specificity and studies were prone to reporting bias.[55] A recent study explored potential novel biomarkers sampled peripherally and from renal veins in matched groups with ARAS and essential hypertension.[56,57] Higher systemic and stenotic renal vein levels of neutrophil gelatinase-associated lipocalin, plasminogen activator inhibitor-1 and soluble urokinase-type plasminogen activator receptor were noted in ARAS.[56,57] Metabolite profiling by LC-MS on renal venous samples from 16 patients with ARAS and 16 with essential hypertension demonstrated a clear separation of profiles between groups but not between stenotic and contralateral kidneys.[58] These findings are consistent with the kidney's ability to adapt to ARAS but also reflect that the contralateral kidney is subject to similar inflammatory and pressor responses initiated in the stenotic kidney. Currently, these biomarkers lack the specificity required to inform clinical practice.

Clinical risk scores and phenotypes

ARAS frequently coexists with extrarenal atherosclerosis and is a common incidental finding during coronary angiographic procedures.[59] Many of the diagnostic techniques we have outlined have small but important hazards, and there has been interest in developing clinical risk scores that improve the pretest probability or diagnostic yield of such tests. A summary of these studies is outlined in Table 4. As a practical illustration, Cohen and coworkers described a clinical risk score predicting that a 56-year-old man with hypertension, treated with two cardiovascular drugs, a creatinine level of 1.4 mg/dl and three-vessel coronary disease has an estimated 19% probability of ARAS with >75% stenosis by CA.[60] A valid critique of such scores is that they merely capture general atherosclerotic risk and lack the specificity to inform clinical decisions.

A recent single-center study described 237 patients with >50% ARAS and one or more high-risk phenotypes including flash pulmonary edema, rapid decline in kidney function and refractory hypertension (Table 2).[4] This study showed that revascularization led to improved outcomes in patients with flash pulmonary edema or a combination of rapid decline in kidney function and refractory hypertension. Crucially, it is these high risk patient subgroups that are emphasized in consensus guidelines (Table 5) and scarcely represented in major randomized trials. Identification of high-risk phenotypes might inform shared decision-making around the investigation and management of ARAS.

Expert commentary

In view of neutral results of randomized controlled trials, the value of screening for ARAS is less clear. An important subgroup of patients with high-risk clinical features that will benefit from revascularization remains and the challenge lies in identifying patients with functionally significant stenosis and viable renal tissue. Advances in imaging techniques have shifted the focus from anatomical towards functional imaging. CA and captopril renography are no longer recommended for diagnosis, but CA with translesional pressures can determine hemodynamic significance. Duplex ultrasound shows promise for non-invasive measurement of hemodynamic significance, but remains limited by operator dependency and the inability to distinguish stenosis beyond 60%. It is likely best used in conjunction with CTA or MRA. Although we have summarized small observational cohorts using functional measures to determine hemodynamic significance of ARAS, no randomized trials selecting only by these criteria have been successfully conducted.

The most commonly used diagnostic techniques are CTA and MRA with similar diagnostic accuracy (Table 6). Their use is limited in patients with estimated GFR < 30 ml/min due to the respective risks of contrast-induced nephropathy and nephrogenic systemic fibrosis. However risks are acceptable by following preventive protocols. As it does not require ionizing radiation, functional MRI with techniques such as velocity-encoded and BOLD imaging show the greatest promise for

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Table 4	. Sen	sitivity and specificit	y of I	putative diagno	sstic risk prediction sco	ores for sign	nificant unila	ateral ARAS.		
Study	Deriv	ation cohort	Valid	ation cohort	Factors contributing	Reference	Sensitivity	Specificity	AUC	Comments
	c	Characteristics	c	Characteristics		ARAS by CA (%)	(%)	(0/)		
Ma 2015 [88]	257	Coronary angiography for myocardial infarction, concurrent renal angiography	86	lschemic heart failure⁺ ARAS > 60% by Duplex ultrasound	Age, hypertension, stroke, intermittent claudication, serum creatinine	>60	85	31	0.72	The score predominantly predicts atherosclerotic risk rather than ARAS per se
Cohen 2005 [60]	843	Coronary angiography, concurrent abdominal aortography, 10% unilateral ARAS	843	The derivation cohort was internally validated by bootstrapping	Age, sex, serum creatinine, peripheral vascular disease, number of cardiovascular drugs, hypertension, three-vessel coronary artery disease or previous coronary bypass surgery	>75	76	71	0.80 ⁺	The score predominantly predicts atherosclerotic risk rather than ARAS per se. Using a score of ≥11 in clinical practice could reduce the proportion of patients receiving abdominal aortography to 34%
Krijnen 2005 [89]	460	Refractory hypertension despite a standardized two-drug regime or significant rise in creatinine on commencing ACE- inhibitor, serum creatinine < 200 µmol/l	180	Refractory hypertension, serum creatinine < 200 µmol/l	Age, sex, vascular disease, recent onset of hypertension, smoking, body mass index, abdominal bruit, serum creatinine, and hypercholesterolemia	>50	6	X	0.71	Discriminative ability was limited by a high proportion of nonatherosclerotic stenosis due to 37% fibromuscular dysplasia in the derivation cohort. The score would reduce imaging referrals by 20% at the expense of 9% false negatives
[†] New York [‡] Concordai ACE: Angic	Heart C nce inde: tensin-c	assification stage II–IV due to cr (equivalent to AUC for dichott onverting enzyme; ARAS: Ather	oronary omous v oscleroti	artery disease and left v ariables). c renal artery stenosis; /	entricular ejection fraction < 50%. AUC: Area under receiver-operator	characteristic cun	/e; CA: Catheter ar	ngiography; NR: No	ot reported	Ť

Table 5. Reasonable indications for percutaneous revascularization of ARAS from ACCF/AHA Guidelines.

- 1. Hemodynamically significant ARAS with unexplained recurrent congestive heart failure or flash pulmonary edema
- 2. Stent placement for ostial ARAS associated with an appropriate clinical syndrome
- Class Ila
- 1. Hemodynamically significant ARAS with accelerated/resistant/malignant hypertension
- 2. Hemodynamically significant ARAS with unstable angina
- 3. ARAS and progressive CKD with bilateral stenosis or a solitary functioning kidney

Class IIb

- 1. Hemodynamically significant ARAS with asymptomatic bilateral stenosis or a solitary functioning kidney
- 2. Unilateral ARAS with CKD

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ARAS: Atherosclerotic renal artery stenosis; CKD: Chronic kidney disease. Reproduced with permission from [93].

Table 6	Pros	pective studies co	omparing dif	ferent imagi	ing modaliti	es performed over the past 10 years.
Study	n	Reference standard ARAS (%)	Modalities studied	Sensitivity (%)	Specificity (%)	Comments
Eriksson	47	>50% by CTA	MRA	81	79	CTA and MRA are superior to DUS and CR in
2010			DUS	70	89	diagnosing ARAS but DUS suits patient screening
[90]			CR	40	100	
Rountas	58	>50% by CA	CTA	94	93	Authors suggest individualized algorithms involving
2007			MRA	90	94	use of DUS screening, especially in younger patients,
[]]			DUS	75	90	
Eklof	58	Resting	СТА	94	62	Prior consensus DUS thresholds were poorly
2006		translesional	MRA	93	91	correlated to hemodynamic significance by
[92]		15 mmHg	CR	52	63	recommended for evaluating ARAS.
		-	DUS	73	71	

ARAS: Atherosclerotic renal artery stenosis; CA: Catheter angiography; CR: Captopril renography; CTA: Computed tomographic angiography; DUS: Duplex ultrasound; MRA: Magnetic resonance angiography.

characterizing functionally viable tissue. Their combination with MRA allows a single visit assessment of vascular anatomy, functional significance of ARAS and viability of parenchymal tissue. Whilst pilot studies show promise, they remain at the early phase of validation that would be required to justify adoption in routine practice.

Although serum and urine biomarkers have been investigated in ARAS, data are sparse and are presently of limited diagnostic value. Few studies have described risk prediction scores that might prevent unnecessary investigation particularly in patients who do not align to high-risk phenotypes. These scores are currently too crude to recommend for use.

Five-year view

After the initial enthusiasm for revascularization of ARAS, recent neutral trial outcomes have shown that restoring vessel

patency alone does not recover kidney function in most patients selected by conventional criteria.[61] There are novel cellular protective treatments on the horizon that are natural adjuncts to revascularization.[62] Thus, the imperative is greater than ever for diagnostic methods in ARAS that can identify those who might benefit from targeted therapies whilst avoiding harm in those who will not. When benchmarked to a developmental pathway of comprehensive validation [63], even established techniques such as CTA and MRA are inadequate for the purpose of improving patient outcomes (see Box 4). Therefore, we believe that the shift from anatomical to functional or physiological imaging will continue to occur. A clear separation should be made between assessing hemodynamic significance of arterial stenosis and functional reserve of renal parenchymal tissue. MRI has advantages over CT with unrealized potential for assessing both hemodynamic significance and tissue viability, mostly without using Gd

Box 4. Developmental framework of incremental steps required for comprehensive validation of diagnostic methods of atherosclerotic renal artery stenosis

Each step is harder to fulfill. No current test in development achieves more than 7 of these 15 steps and many whole imaging modalities have never achieved the final step.

- 1. Technical development and theoretical basis of test.
- 2. Direct comparison (animal models and then human autopsy material).
- 3. Detection of changes in established disease compared with normal subjects.
- 4. Correlation with known markers of impaired perfusion (e.g., reduced glomerular filtration).
- 5. Correlation with known biomarkers of reduced perfusion or filtration (e.g., cystatin).
- 6. Demonstration of the test in more than one clinical scenario.
- 7. Demonstration of test sensitivity (early disease or with age).
- 8. Demonstration of the ability to track change (with time, after treatment).
- 9. Demonstration of predictive or prognostic value of the test.
- 10. Standardization of the test (reproducibility, different equipment, nonresearch settings, quality control, limitations of test).
- 11. Development of robust age/ethnic normal reference ranges.
- 12. Changes in biomarker remain tied to the disease after treatment.
- 13. Demonstration of the test as a surrogate trial endpoint.
- 14. Clinical use and regulatory approval of the test.
- 15. Proof that test use improves clinical outcomes.

Adapted with permission from [63].

contrast media. Some MRI techniques such as BOLD imaging are technically established but not validated. A recent study proposed a method of BOLD R2* values to determine fractional tissue hypoxia, a measure that is reproducible and that might form a surrogate outcome or selection criteria for a future clinical trial.[64] A recent proof-of-concept study reported that arterial-spin labeling might allow measurement of SK-GFR without contrast media and further developments in this area are expected.[65] 4D flow MRI will allow noninvasive measures of translesional gradients to complement anatomical MRA. SK-GFR with DCE-MRI and low-dose Gd is being developed to further improve accuracy against reference standards. The experience in functional brain imaging has demonstrated that a coordinated research effort to harmonize protocols between research centers and MRI vendors can accelerate technique development and validation. [66] Efforts are being made to establish a similar international network in renal functional MRI. CT perfusion and GFR measurements will continue to develop with methods to reduce the radiation burden. A current phase 2a clinical trial is assessing the effects of a cell-based therapy as an adjunct to renal revascularization to minimize ischemia reperfusion injury (ClinicalTrials.gov identifier: NCT01755858). This study uses iothalamate GFR as the primary outcome complemented by SK-GFR, perfusion by CT and inflammatory biomarkers. Duplex ultrasound techniques continue to improve and the wider use of microbubble contrast enhancement may start to bridge the gap to CTA and MRA at least in research settings. Recent advances may see microbubbles used not for diagnosis but as targeted delivery of novel cellular protective therapies for ARAS.[67] The imperative to deliver individualized and functionally directed treatments whilst avoiding harms will accelerate development and validation of these diagnostic techniques.

Financial & competing interests disclosure

A. Odudu acknowledges financial support of a National Institute for Health Research Clinical Lectureship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Two recent major trials of angioplasty and stenting for atherosclerotic renal artery stenosis (ARAS) did not show improved clinical outcomes compared to optimal drug therapy. However, the trials were limited by reliance on anatomically estimated disease severity and a lack of higher-risk patients.
- There has been a shift in focus from anatomical to functional imaging of ARAS to assess hemodynamic significance and the functional reserve of the renal parenchyma.
- ARAS can be diagnosed by several techniques. None are perfect, with respect to a balance of accuracy versus risk.
- Catheter angiography with translesional pressure assessment is the reference standard technique, but this is invasive and reserved for planned intervention. Despite promising data, translesional pressure gradients require robust validation against clinically important outcomes.
- Duplex ultrasound is inexpensive, repeatable and noninvasive with potential to determine hemodynamic significance. However, it is the least accurate and most operator dependent. Advances in contrast-enhanced ultrasound may improve accuracy, but to date only preliminary data are available.
- CT angiography and magnetic resonance angiography are the current mainstay of diagnostic techniques and they have equivalent accuracy.
- Renal functional MRI shows great promise. Techniques such as velocity-encoding, blood-oxygen-level-dependent imaging, volumetry and single-kidney glomerular filtration rate (SK-GFR) by dynamic contrast-enhanced MRI allow a comprehensive evaluation of renal artery hemodynamics and tissue viability. However, standardized protocols in multicenter studies are required to enable the evidence base to mature.
- In research centers, novel CT methods allow the estimation of SK-GFR and perfusion with the tradeoff of greater ionizing radiation exposure.
- Captopril renography is rarely used, but radioisotope studies to determine SK-GFR remain the reference standard technique for measured GFR.
- Soluble biomarkers and clinical prediction scores are currently nonspecific adding little to diagnostic imaging.

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