Renovascular disease

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Abstract

In Western populations, fibromuscular disease accounts for around 10% of all cases of renal artery stenosis (RAS), usually presenting as hypertension in young people, most often women; there is often a successful response to angioplasty. Atherosclerotic renovascular disease (ARVD) accounts for the remaining 90% of cases of RAS. ARVD is a disease of ageing, frequently associated with hypertension and renal dysfunction. It is commonly accompanied by major atherosclerotic vascular disease in other parts of the body, such as coronary artery disease, peripheral vascular disease, cerebrovascular disease and aortic aneurysms. Clinical presentations include hypertension, chronic or acute kidney disease and heart failure, although many patients with ARVD are identified incidentally when being screened for extra-renal vascular disease. The mainstay of treatment involves general vascular protection centred on adequate blood pressure control, antiplatelet agents, renin–angiotensin blockade and statin therapy; however, a small proportion of patients gain benefit from percutaneous renal artery angioplasty and stenting. Two large prospective randomized controlled trials (ASTRAL, CORAL) have failed to show an overall benefit of intervention over optimal medical therapy in the trial setting, but higher risk patients contributed only a small proportion of subjects in these trials. However, observational evidence suggests that revascularization may play a role in the management of patients with high-risk phenotypes such as flash pulmonary oedema, rapidly deteriorating renal function or uncontrolled hypertension. Future research is needed to help identify those patients who will benefit from revascularization, while avoiding this procedure and its attendant risks in others.

Keywords ASTRAL trial; atherosclerotic renovascular disease; chronic kidney disease; fibromuscular disease; hypertension; MRCP; renal artery stenosis; renal revascularization

Key points

- The largest prospective randomized controlled trials in atherosclerotic renovascular disease, the ASTRAL and CORAL trials, have shown that unselected patients with RAS who undergo revascularization in addition to medical therapy do not have better clinical outcomes than patients given medical therapy alone
- However, these data refer to large groups of unselected trial patients and do not consider the phenotype of individual higher risk patients, many of whom were not included in the trials
- There is evidence that patients with certain high-risk presentations have better outcomes with revascularization, but further research is necessary to confirm this

Introduction

Renal artery stenosis (RAS) refers to narrowing of the renal arteries. It is a common condition that can cause, or be associated with, serious clinical abnormalities. Atherosclerotic renovascular disease (ARVD) accounts for >90% of RAS in Western populations, the rest resulting from fibromuscular disease (FMD). In the Indian subcontinent and Far East, vasculitis, such as Takayasu's arteritis, may be responsible for up to 60% of cases of RAS. The epidemiology and outcomes of FMD and ARVD differ markedly, so they are considered separately here, with greatest attention being directed to ARVD.

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Fibromuscular disease of the renal arteries

FMD accounts for up to 10% of cases of RAS. Studies of healthy renal donor populations (pre-transplantation) using catheter or computed tomography angiography (CTA) have shown a prevalence of 2.6–6.6%. It is less common in African and Asian populations. FMD involves the renal arteries in 60–75% of cases, but extra-renal FMD is more common than previously thought. Craniocervical arteries (e.g. carotid, vertebral) are involved in 75% of extra-renal cases. Two-thirds of cases of renal artery FMD have coexistent craniocervical involvement and vice versa. FMD can be seen in any small or medium sized arteries, including the lower-extremities (60%), mesentery (26%), upper extremities (16%) and, rarely, coronary arteries. Based on these data, guidelines now recommend that FMD found in any arterial bed should prompt screening for FMD elsewhere.[1]

Pathology

The aetiology of FMD is unknown. Given the large female preponderance, female hormones may be important, although genetics could also play a role. The most common pathological form of FMD is medial fibroplasia, which is typically found in women presenting in their fourth decade. Areas of intimal and medial thinning with loss of the elastic lamina occur in the vessel wall and lead to the formation of multiple small aneurysms. These areas alternate with localized regions of narrowing caused by fibrosis, giving a classical appearance at angiography resembling a 'string of beads' (Figure 1). FMD tends to affect the middle and distal part of the renal artery, as distinct from the ostial lesions commonly seen in ARVD.

Clinical picture

The classical presentation of FMD is with hypertension and well-preserved renal function in young adults, but there are reports of individuals presenting in older age. The diagnosis must be

considered in young patients (e.g. <35 years old) who present with severe or accelerated-phase hypertension. An abdominal bruit may be detected, whereas neurological features, mesenteric angina or claudication can be manifestations of extra-renal FMD at other sites. Progressive narrowing of the renal arteries occurs in a third of patients but rarely progresses to occlusion.

Management

The management of patients with FMD is far clearer than that for atherosclerotic lesions. Percutaneous transluminal renal angioplasty (PTRA), usually without stenting, is the intervention of choice. Response rates are good, with 36% of patients cured of hypertension, and many of the remainder having improved blood pressure control and a reduced antihypertensive burden.[1]

Atheromatous renovascular disease

Over 90% of atheromatous RAS lesions are 'ostial', occurring within 1 cm of the origin of the renal artery (Figure 2). The lesions are bilateral in about 50% of cases.

Epidemiology

ARVD commonly occurs in the setting of generalized atherosclerotic disease such as coronary artery disease (CAD) or peripheral vascular disease. It is also more prevalent in older patients with associated cardiovascular risk factors such as smoking, diabetes mellitus and hypertension. Given that ARVD is usually asymptomatic, the true prevalence in the general population may be underreported. One American study found that 6.8% of healthy elderly people had incidental RAS (defined as >60% narrowing).

Only a few studies have focused on the incidence of ARVD and how this has changed over the years. Two studies of the US Medicare population aged >65 years have demonstrated that ARVD was diagnosed with an incidence of about four cases per 1000 patient−years, and that rates of diagnosis increased almost 4-fold between 1992 and 2004. This is thought to reflect improved imaging techniques rather than a truly increased incidence of ARVD.

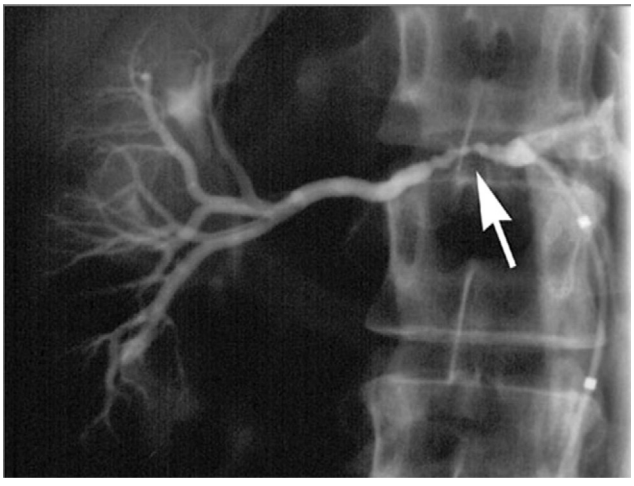


Figure 1 Fibromuscular RAS of the right renal artery. A 'string of beads' appearance characterizes the arterial narrowing (arrowed).

Clinical features

There is a strong association between ARVD and other atheromatous conditions, and in many patients asymptomatic ARVD is detected incidentally during investigation for extra-renal vascular disease. Hence, ARVD has been found in about 40% of patients with peripheral vascular disease (PVD), 15% with coronary artery disease (CAD), 30% with congestive heart failure, and about 30% of those undergoing investigation of aortic aneurysms. The association with cerebrovascular disease is significant if slightly less marked.

ARVD is found in about 2% of all cases of hypertension, whereas >95% of patients with ARVD are hypertensive. Causality is uncertain; in many cases, the essential hypertension probably contributes to the development of ARVD, rather than the latter being important in the pathophysiology of the hypertension. In ARVD, severe systolic hypertension resistant to medical therapy is often found, in keeping with ageing and vascular stiffness.

Acute kidney injury can complicate ARVD in patients with very severe bilateral RAS or occlusion, cholesterol atheroembolization (seen in patients with severe aortic atheroma who undergo angiographic procedures or anticoagulation) or damage caused by radiocontrast agents during angiography (contrast-induced nephropathy (CIN)). Acute kidney injury can also result from treatment with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which underpin renin−angiotensin blockade.

On starting renin−angiotensin blockade, a short-term and stable decline in glomerular filtration rate (GFR) is expected because of a reversible effect on renal blood flow. Clinical suspicion of underlying haemodynamically significant RAS (usually bilateral severe ARVD or RAS in a single functioning kidney) should be considered in individuals with significant functional deterioration (e.g. >30% increase in serum creatinine or >25% fall in estimated GFR from baseline) after initiation of these agents. In this situation, it is recommended that the drug should be stopped or its dose reduced, and haemodynamic stressors such as volume depletion or concurrent use of non-steroidal anti-inflammatory agents excluded. Renal vascular imaging should also be considered, as revascularization of significant RAS can be necessary to facilitate the safe reintroduction of these useful drugs.

Nevertheless, renin−angiotensin blockade should be considered to be the standard of care for most patients with ARVD as the frequent presence of cardiac structural abnormalities, renin-mediated hypertension and proteinuria is an indication for treatment. In addition, this therapy is tolerated by most individuals, even those with significant bilateral disease.

The most common presentation of ARVD is relatively stable chronic kidney disease (CKD) with hypertension. A small subgroup of patients have rapidly deteriorating renal function, usually with severe hypertension. Progression to end-stage kidney disease (ESKD) is recognized, but is uncommon (<2% per year) once the ARVD diagnosis has been made and basic vascular protective treatment initiated. Some reports suggest that around 10% of ESKD patients have ARVD, but this is usually an

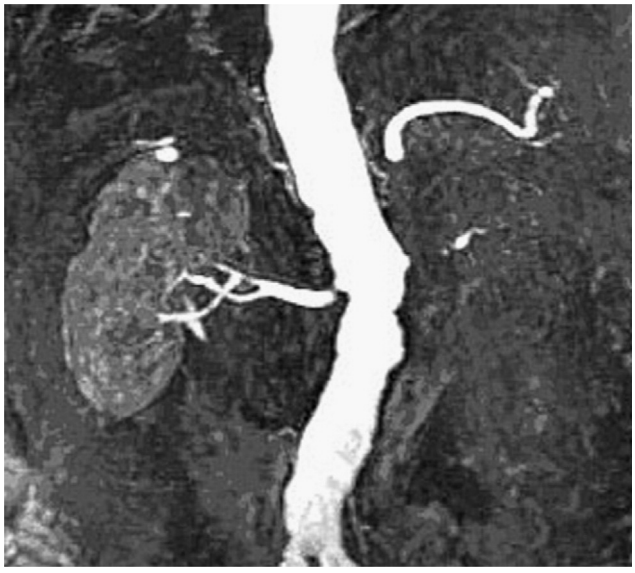


Figure 2 Renal MRA showing tight stenosis of the right renal artery and occlusion of the left renal artery.

associated finding rather than a cause. In most patients with ESKD, hypertension and intra-renal vascular damage (rather than RAS) are the dominant factors in the pathogenesis of CKD. This has implications for treatment and is reflected in the outcomes after renal revascularization procedures.

The importance of concomitant cardiac disease in ARVD is recognized, with >90% of patients having structural or functional abnormalities of the heart, such as left ventricular hypertrophy or diastolic dysfunction, at the time of diagnosis. The association with congestive heart failure has already been mentioned, but flash pulmonary oedema — the sudden onset of life-threatening heart failure — is an additional important clinical presentation affecting a minority of patients, usually in the presence of severe hypertension and significant bilateral ARVD.

Investigations

In most cases, ARVD is more often associated with rather than the cause of CKD. However, ARVD should be suspected in patients with hypertension and/or CKD and any of the following:

- audible vascular bruits (epigastric, renal, carotid, femoral)
- >1.5 cm disparity in bipolar renal length on ultrasonography
- unexplained pulmonary oedema
- unexplained CKD in individuals with evidence of other vascular disease
- significant deterioration of renal function in association with ACE inhibitors or ARB therapy.

The degree of haemodynamic compromise caused by a stenosis diagnosed by imaging may not reflect its full functional effects on the kidney. Studies using latex casts and haemodynamic measurements indicate that measurable hypoxia only occurs when RAS is 70–80% by angiographic assessment. Animal studies have shown that this haemodynamic compromise is initially potentially reversible but triggers an inflammatory cascade that leads to irreversible renal parenchymal damage. Restoring blood flow to such kidneys will not help improve function, and this could explain why randomized controlled trials (RCTs) such as ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) and CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) (see below) have failed to show improved outcomes after revascularization compared with medical therapy. There is now scepticism regarding the value of detecting the condition in otherwise asymptomatic patients, other than for the purpose of risk stratification.

Magnetic resonance angiography (***MRA***) is non-invasive, and its sensitivity/specificity for detecting RAS exceeds 90%. MRA can, however, overestimate the degree of RAS. Caution should be used when ordering contrast MRA in patients whose GFR is <30 ml/minute/1.73 m^2 because of the risk of nephrogenic systemic fibrosis, a syndrome associated with the use of gadolinium chelates as contrast agents.

CTA has similar sensitivity/specificity to MRA for detecting RAS but does not provide a functional assessment of the severity of stenosis. Its main drawbacks are the use of ionizing radiation, and the risk of CIN in patients with advanced CKD. A GFR <30 ml/minute is a threshold worth remembering: in these patients, the use of intravenous fluid infusion can be considered to prevent CIN.

Duplex ultrasonography is sensitive for detecting RAS, and the Doppler waveforms can provide information on intra-renal vascular resistance. The technique can be limited by patient body habitus and is operator-dependent, but it is completely risk-free and certainly the best screening tool for use in patients with advanced CKD.

Renal angiography (usually intra-arterial digital subtraction angiography (IA-DSA)) is usually employed only to confirm the presence of RAS at the time of revascularization procedures, or in the diagnosis of more complicated/uncertain cases. It provides only two-dimensional images and no functional information, it is invasive, and it exposes the patient to the risks of ionizing radiation and CIN.

Management

Medical treatment: ARVD is part of a diffuse vascular atheromatous disease process, and extra-renal vascular pathology is the major contributor to the poor outcome in ARVD patients. Despite the lack of specific trials investigating vascular protection, smoking cessation, optimization of glycaemic control in diabetic patients, and administration of antiplatelet therapy, statins, β-adrenoceptor blockers and renin–angiotensin blockade are strongly advised. There is some evidence that statins can slow progression or even induce regression of atherosclerotic renal artery lesions. It is advisable to optimize blood pressure control (target <130/80 mmHg), which can require multiple drugs in combination.

As mentioned previously, ACE inhibitors and ARBs are sensible drug choices for most patients with ARVD, especially those with proteinuria (indicative of chronic renal parenchymal injury) and those with coexisting CAD and cardiac dysfunction. Careful monitoring of renal function is required, especially with significant bilateral RAS, or RAS affecting a solitary kidney, and patients should be warned to stop these medications temporarily during intercurrent illnesses that result in hypovolaemic stress.

Renal revascularization: until the mid-2000s, it was thought that reversal of the haemodynamic compromise caused by RAS would prevent progression to occlusion and renal atrophy, as well as deterioration of renal function, and improve blood pressure control. Renal revascularization originally involved a surgical reconstructive procedure that carried a high in-hospital mortality rate, but this was eventually replaced by less invasive, percutaneous endovascular techniques (PTRA, usually with stenting). Even PTRA has a complication rate of around 5–7%, but complications are usually minor (e.g. groin haematoma) or resolve rapidly (e.g. CIN). More serious complications such as irreversible cholesterol embolization, arterial rupture or thrombosis are fortunately less common, but affect up to 2% of patients.

The role of revascularization in the management of ARVD has become more controversial with the advent of improved medical management and recent experimental research that has shed light on the progressive irreversible intraparenchymal injury that occurs in the post-stenotic kidney. Six RCTs have been performed to date to investigate outcomes of intervention in patients with ARVD. The first three were small and published almost 10 years ago; a meta-analysis of these showed that angioplasty at best only slightly improved systolic blood pressure control. A Dutch study (STAR) reported on 140 ARVD patients in 2009 but was underpowered, and a high proportion of the patients randomized to revascularization did not undergo the procedure. Another study looking specifically at the effect of revascularization on cardiac status showed that intervention had no impact on the degree of left ventricular hypertrophy, whereas optimal medical therapy was shown to improve it. The largest and the most recent RCTs were the ASTRAL and CORAL trials.

The UK-led ASTRAL trial randomized 806 patients with significant atherosclerotic RAS to medical therapy or medical therapy plus percutaneous revascularization. After a median follow-up of 34 months, revascularization had resulted in no worthwhile reduction in the deterioration of renal function (the primary outcome; Figure 3), and no improvement in blood pressure control or reduction in renal or cardiovascular events or mortality (secondary outcomes). However, the serious adverse event rate complicating revascularization was almost 7%.[2]

The US-led CORAL study was the largest and most recent RCT in ARVD; in this, 947 patients were randomly assigned to stenting and medical therapy or medical therapy alone. The primary outcome of this study investigated whether renal revascularization led to an improvement in a composite clinical outcome of major cardiovascular events: need for dialysis and mortality. No difference in outcomes between the two groups of patients was noted after a median follow-up of 43 months (Figure 4).[3]

The major limitation of these trials was the inadequate representation in the study cohorts of patients with a high-risk clinical phenotype, in whom medical management on its own is believed to be insufficient. Indeed, according to the American Heart Association guidelines, revascularization is advised in the following situations:

- recurrent acute heart failure or flash pulmonary oedema
- declining kidney function in the context of bilateral RAS, or RAS affecting a solitary functioning kidney
- refractory hypertension.

These guidelines were based on consensus and data derived from case-series rather than robust studies.

A single-centre retrospective study from our department included 237 patients with >50% RAS and one or more of the high-risk phenotypes defined by the American Heart Association. One-quarter (24%) of these patients underwent revascularization and their outcomes were compared with those in patients who were treated medically. Revascularization was associated with improved survival in patients with flash pulmonary oedema, but not in those with a history of cardiovascular events or ESKD. Revascularization was also beneficial in terms of reduced mortality and cardiovascular events in patients with the combination of rapid deterioration of kidney function and refractory hypertension, but not with either of these presentations in isolation.[4]

This study was followed by another observational study focused on ARVD patients with more severe, haemodynamically significant RAS (≥70% RAS unilaterally or bilaterally) and at least one high-risk clinical presentation. Revascularization was found to benefit a subgroup of patients with rapidly deteriorating renal function in the context of either critical stenosis (≥70% bilaterally) or <1 g/day baseline proteinuria, a surrogate marker of well-preserved renal parenchyma.[5]

Previous work from our research group forged the concept of 'hibernating parenchyma' – viable renal parenchyma that has not yet undergone the irreversible changes associated with chronic or severe ARVD and hence retains the possibility to recover function after revascularization. These kidneys have been shown to exhibit a higher ratio of renal volume to isotopic GFR than kidneys that do not respond positively to revascularization, implying that the former have more functioning tissue available once a stenosis has been corrected.

This research highlights the fact that ARVD is a heterogeneous condition and treatment needs to be patient-specific. It is unlikely that another RCT comparing revascularization with medical therapy alone will be carried out in the near future, although further research is required to help accurately identify patients who are more likely to benefit from revascularization, and to ensure timely referral for revascularization.

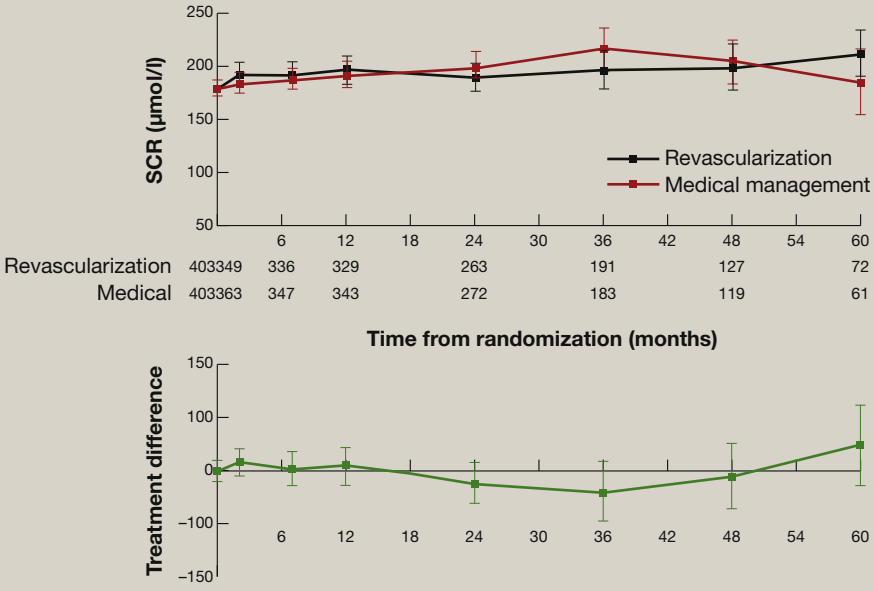
Novel functional magnetic resonance imaging (MRI) techniques such as blood oxygen-dependent MRI can estimate the degree of intra-renal hypoxia and thus help identify critically ischaemic or 'hibernating' kidneys. MRI has also been used to determine the haemodynamic significance of a stenosis and to measure single-kidney GFR and other perfusion parameters that could correspond to the functional status of the post-stenotic kidney.

Experimental therapeutic approaches have focused on developing novel adjuncts to revascularization or conservative medical therapy that aim to attenuate ischaemia–reperfusion injury and post-ischaemic inflammatory injury in the post-stenotic kidney even after successful revascularization. Strategies include: targeting mitochondrial injury, which appears to play a major role in mediating both renal and cardiac remodelling in ARVD; and infusion of vascular growth factors, endothelial progenitor cells or mesenchymal stem cells to stimulate angiogenesis and modulate the inflammatory milieu.

Prognosis

Many patients with ARVD have CKD, but only a minority eventually require dialysis; in a cohort of patients with >50% RAS, the rate of decline of kidney function was only 2 ml/minute/1.73

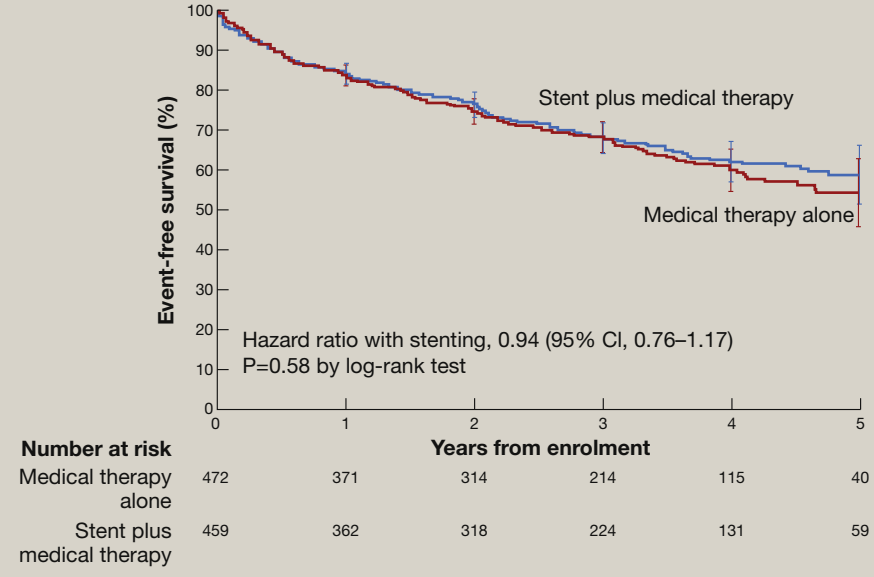
Renal functional outcome after renal revascularization in the ASTRAL trial



Adapted from ASTRAL investigators, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009; **361**: 1953-62.

Figure 3

Survival curves for stent and medical therapy versus medical therapy alone in the CORAL trial



Reproduced from Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014; **370(1)**: 13–22, with kind permission from Massachusetts Medical Society

Figure 4

m^2 per year. In a study of the US Medicare population undertaken over a decade ago, the risk of death was almost six times that of developing ESKD, and the rate of progression to the latter only 2% per year, the same figure found in the ASTRAL trial. The poor survival is due largely to the effects of co-morbid cardiovascular disease and the degree of CKD, as shown in historical single-centre studies. In 148 ARVD patients with RAS and CKD, overall 5-year survival was 52%, but those with ESKD had a 30-fold mortality risk compared with patients with well-preserved function. Nevertheless, there is evidence that current medical therapy could be improving outcomes, as the annual mortality rate of 8% in ASTRAL was approximately half that seen in the Medicare study referred to above, and cardiovascular mortality in CORAL was only 2–3% per year. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 70-year-old man presented with deterioration of renal function. Two weeks previously, an angiotensin receptor blocker had been added to his antihypertensive treatment of a diuretic, an α-adrenoceptor blocker and a calcium antagonist, with instructions to have repeat blood tests in 2 weeks. As well as hypertension, he had a history of intermittent claudication and myocardial infarction. He had a 30 pack–year smoking history.

Investigations

- Creatinine 270 micromol/litre (60–110 micromol/litre) (previously 150 micromol/litre)
- Estimated glomerular filtration rate 21 ml/minute/1.73 m^2 (>60 ml/minute/1.73 m^2) (previously 43 ml/minute/1.73 m^2)

What is the most appropriate next investigation?

A. Direct intra-arterial angiography
B. Renography with captopril provocation
C. Contrast-free magnetic resonance angiography
D. Computed tomography angiography
E. Duplex ultrasound of the renal arteries

Question 2

A 68-year-old man presented with high blood pressure that was difficult to control with three classes of drugs including a calcium channel blocker, a β-adrenoreceptor blocker and a diuretic. He had a past history of a transient ischaemic attack.

Investigations

- Contrast-free magnetic resonance angiography showed a completely occluded right renal artery and ≥70% stenosis at the origin of the left renal artery

What is the most appropriate management plan?

A. Percutaneous transluminal renal angioplasty (PTRA) with stenting of the right renal artery
B. PTRA with stenting of the left renal artery
C. PTRA without stenting of the left renal artery
D. PTRA with stenting of both renal arteries
E. Close monitoring of renal function with repeat imaging in 6 months

Question 3

A 59-year-old woman presented for review. She had stable chronic kidney disease stage 3b and long-standing hypertension

and hypercholesterolaemia. She was taking an angiotensin-converting enzyme inhibitor, a calcium channel blocker, aspirin and a statin. On clinical examination she was euvolaemic BP 165/90 mmHg. Besides routine investigations, she had also undergone magnetic resonance angiography (MRA) of the renal arteries due to the strong clinical suspicion of underlying renovascular disease contributing to her poorly controlled blood pressure.

Investigations:

- Serum creatinine 196 micromol/litre (60–100)
- Serum cholesterol 5.8 mmol/litre (<5.2 mmol/litre)
- eGFR 33 ml/minute/1.73 m^2
- MRA – 60% bilateral renal artery stenosis

What does best evidence suggest would be the result of an attempt at revascularization of the kidneys?

A. Improvement in eGFR
B. Improvement in patient survival
C. Improvement in blood pressure control
D. No change
E. Reduction in resistive index of both kidneys