

Atherosclerotic renovascular disease – epidemiology, treatment and current challenges

Diana Vassallo, Philip A. Kalra

Department of Renal Medicine, Salford Royal NHS Foundation Trust, UK

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Abstract

The neutral results of recent large randomized controlled trials comparing renal revascularization with optimal medical therapy in patients with atherosclerotic renovascular disease (ARVD) have cast doubt on the role of revascularization in the management of unselected patients with this condition. However, these studies have strengthened the evidence base for the role of contemporary intensive medical vascular protection therapy and aggressive risk factor control in improving clinical outcomes in ARVD. Patients presenting with ‘high-risk’ clinical features such as uncontrolled hypertension, rapidly declining renal function or flash pulmonary oedema are underrepresented in these studies; hence these results may not be applicable to all patients with ARVD. In this ‘high-risk’ subgroup, conservative management may not be sufficient in preventing adverse events, and indeed, observational evidence suggests that this specific patient subgroup may gain benefit from timely renal revascularization. Current challenges include the development of novel diagnostic techniques to establish haemodynamic significance of a stenosis, patient risk stratification and prediction of post-revascularization outcomes to ultimately facilitate patient selection for revascularization. In this paper we describe the epidemiology of this condition and discuss treatment recommendations for this condition in light of the results of recent randomized controlled trials while highlighting important clinical unmet needs and challenges faced by clinicians managing this condition.

Key words: renal artery stenosis, revascularization, atherosclerosis, randomized controlled trials.

Introduction

Atherosclerotic renovascular disease (ARVD) refers to atheromatous stenoses of one or both renal arteries and, as expected, occurs more frequently with increasing age and in the presence of cardiovascular risk factors such as diabetes, smoking and hypertension. Although ARVD is very often asymptomatic and usually discovered incidentally during investigation for extrarenal atherosclerotic disease, in some patients it can present with florid symptoms of cardiovascular instability or rapidly deteriorating renal function, and is a frequent cause of significant morbidity and mortality [1].

The heterogeneous nature of this condition poses a significant diagnostic and management dilemma to the physician. Despite significant progress in imaging techniques, accurate determination of the functional significance of a stenosis remains difficult. In addition, percutaneous revascularization carries a risk of complications and does not guarantee improved outcomes. Recent large prospective trials in ARVD have shown that

revascularization does not confer any added benefit to optimal medical therapy in unselected populations and this has led to an overall decline in the number of revascularization procedures performed [2, 3]. However, there is observational evidence that subgroups of patients with a ‘high-risk’ phenotype, such as those patients presenting with recurrent flash pulmonary oedema, refractory hypertension or rapidly declining renal function, do benefit from revascularization [4]. Identifying these patients in a timely manner remains a considerable challenge.

Pathogenesis

Atherosclerotic renovascular disease typically occurs in the context of systemic atherosclerosis and the inflammatory milieu that accompanies this condition. As expected, risk factors for this condition include smoking, diabetes, hypertension and a genetic predisposition to atheromatous disease [5].

The exact degree of stenosis that defines significant renal artery stenosis (RAS) is still a matter of debate

Corresponding author:

Philip A. Kalra, Department of Renal Medicine, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, UK, phone: +44 1612060509, fax: +44 1612065713, e-mail: philip.kalra@srft.nhs.uk

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amongst clinicians. Historically, cross-sectional or two-dimensional RAS of more than 50% on invasive angiography was sufficient to establish a diagnosis of ARVD. Studies using latex casts and haemodynamic measurements however suggested that detectable hypoxia only occurs at a stenosis of 70–80% on two-dimensional invasive angiographic imaging [6]. This is in keeping with improved understanding of renal physiology; renal blood flow is in excess of the metabolic needs of the kidney and complex autoregulation mechanisms can support renal metabolism over a wide range of renal blood flow and perfusion pressures [7]. Both animal and human studies have in fact shown that a reduction in renal blood flow sufficient to cause activation of the renin-angiotensin system is still associated with well-preserved tissue oxygenation and stable cortico-medullary oxygen gradients [8, 9]. However, it is thought that more severe or prolonged vascular occlusion can overwhelm these adaptive mechanisms and activate an inflammatory cascade, which culminates in microvascular rarefaction and irreversible renal fibrosis [10]. Analysis of venous blood draining from stenosed kidneys reveals significantly higher levels of pro-inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), interferon- γ (IFN- γ), and tumour necrosis factor- α (TNF- α) compared to kidneys from patients with essential hypertension, despite similar blood pressure control and renin-angiotensin system blockade. These cytokines mediate ‘homing’ of inflammatory cells such as macrophages and B- and T-lymphocytes within the renal parenchyma, leading to matrix accumulation, collagen deposition, microvascular rarefaction and irreversible renal fibrosis. Blood from non-stenosed contralateral kidneys also demonstrates elevated cytokine levels although to a lesser extent than the stenosed side, suggesting that even in unilateral RAS, both kidneys are at risk of parenchymal inflammation and remodelling [11, 12].

Irreversible renal parenchymal remodelling, in conjunction with target organ injury from systemic insults typically associated with ARVD, such as chronic hypertension, diabetes and increasing age, is thought to underpin the neutral results of randomized controlled trials (RCTs) [13]. Indeed, restoration of arterial patency was not associated with improved clinical outcomes in the majority of patients recruited to these studies [14, 15]. In contrast, revascularization leads to ‘cured’ hypertension or improved blood pressure control in up to 86% of patients with fibromuscular dysplasia [16]. These patients are characteristically younger, with few, if any, systemic co-morbidities; hence the post-stenotic renal parenchyma is usually relatively intact.

As described in more detail below, another potential reason for the lack of positive response to revascularization reported in RCTs is that a large proportion of recruited patients did not have haemodynamically significant stenoses. The actual haemodynamic and functional signifi-

cance of a stenosis is difficult to determine from two-dimensional visual estimation, as this does not take into account three-dimensional flow patterns, plaque geometry or collateral circulation. Invasive renal angiography is nowadays rarely used to diagnose or risk stratify ARVD [17] and patients almost invariably undergo non-invasive renal artery imaging, namely computed tomographic imaging (CTA) or magnetic resonance angiography (MRA). Although these imaging techniques are highly sensitive and specific, studies have shown that non-invasive two-dimensional imaging can overestimate the degree of stenosis [15, 18, 19]. Novel imaging techniques such as multi-parametric magnetic resonance imaging may potentially have a role in establishing functional significance in the future [19].

For the purpose of this thesis, we have considered the combination of the two-dimensional cut-off of > 70% RAS on CTA or MRA and clinical presentation with at least one ‘high-risk’ feature (uncontrolled hypertension, rapidly deteriorating renal function or flash pulmonary oedema) as diagnostic of haemodynamically significant ARVD. Expert consensus statements in fact recognize that revascularization may be ‘appropriate’ in these individuals, although stenosis severity was sometimes determined invasively in the studies underpinning these recommendations [17, 20]. None of the patients recruited into our observational studies underwent invasive physiological tests to determine haemodynamic significance of RAS, in keeping with routine clinical practice. Moreover, we believe that the definition of ‘clinically significant’ RAS cannot be limited to the degree of anatomical RAS. Atherosclerotic renovascular disease is a very complex condition that does not exist in isolation, and even RAS of 50% can be associated with a three-fold increased risk of death [21] and a four-fold-increased risk of cardiovascular events [22]; hence, as discussed below, there is a need for more accurate risk stratification for patients with this condition.

Epidemiology

The true incidence and prevalence of ARVD are unknown, due to variable definitions, use of different imaging modalities and fluctuating enthusiasm in investigation for this condition. Estimates of the prevalence of ARVD also vary depending on the type of population studied (Table 1) [23–53]. In a sub-study from the Cardiovascular Health Study from the US, up to 6.8% of healthy people aged over 65 years were found to have clinically silent ARVD [27]. However, the majority of epidemiological studies in ARVD have been carried out in populations enriched with documented systemic atherosclerosis or cardiovascular risk factors; prevalence rates in these patients are much higher, although the presence of ARVD does not imply functional significance and commonly represents an incidental finding in patients with widespread atherosclerosis. Indeed, incidental ARVD has been

Table 1. Major studies published since 2000 investigating the prevalence of ARVD in different patient groups (adapted from [23, 24])

| Risk category | Author, year | Study population | Age, mean \pm SD [years] | Diagnostic method | RAS definition | Prevalence RAS, N/Sample size (%) | Factors associated with presence of ARVD |
|-------------------|--------------------------|---|---|----------------------|--|---|---|
| Normal population | Lorenz, 2010 [25] | Potential living kidney donors | 43.0 \pm 12.0 | CTA | – | 103/1957 (5.3%) | – |
| | Tolkin, 2009 [26] | Consecutive patients undergoing abdominal CT for investigation of non-renal abdominal pathology | 61.0 \pm 13.0 | CTA | > 50% stenosis | 10/350 (2.9%) | Increasing age, male gender, hypertension and hypercholesterolaemia were strongly associated with renal artery calcification (RAC). The severity of RAC correlated significantly with the degree of RAS ($r = 0.7$) |
| Hypertension | Hansen, 2002 [27] | Healthy elderly volunteers | 77.0 \pm 5.0 | Doppler ultrasound | Renal peak systolic velocity > 1.8 m/s | 57/834 (6.8%) | Increasing age, increasing systolic blood pressure, decreased HDL-C |
| | Postma, 2012 [28] | Diabetes mellitus and hypertension | 59.0 \pm 8.5 | MRA | > 50% stenosis | 18/54 (33%) | Dyslipidaemia, baseline diastolic blood pressure, lower renal function at baseline |
| | Vasbinder, 2004 [29] | Diastolic blood pressure > 95 mm Hg and suspected RAS | 52.0 \pm 12.0 | DSA as gold standard | > 50% stenosis | 45/356 (12.6%) 12/356 (3.4%) – bilateral > 50% stenosis | – |
| | Van Jaarsveld, 2001 [30] | Therapy-resistant hypertension | 51.2 \pm 12.4 | DSA | > 50% stenosis | 89/439 (20.3%) 20/439 (4.6%) – bilateral > 50% stenosis | – |
| | Valabhji, 2000 [31] | Diabetes mellitus and hypertension (SBP > 160 mm Hg or DBP > 90 mm Hg or use of antihypertensive drugs) | 61 (56–65) | MRA | > 50% stenosis | 20/117 (17.1%) 1/117 (0.9%) – bilateral > 50% stenosis | Clinical features of atherosclerotic disease were not significantly associated with presence of RAS. Femoral bruit was predictive of RAS |
| | Courreges, 2000 [32] | Diabetes mellitus and severe hypertension (treatment with > 3 antihypertensive drugs) | N/a | Arteriography or MRA | > 70% stenosis | 34/208 (16.3%) | Male gender, smoking, insulin-requirement, decreased renal function, severe hypertension, extra-renal macrovascular disease |
| Heart disease | Ollivier, 2009 [33] | Consecutive patients undergoing CAG and renal angiography | 67.0 \pm 10.0 | Angiography | > 50% stenosis | 94/650 (14.5%) 20/650 (3.1%) – > 50% bilateral | Male sex, multi-vessel coronary artery disease, hypertension, renal insufficiency |
| | Dzelińska, 2007 [34] | CAG and hypertension (> 140/90 mm Hg or current anti-hypertensive medication) | 59.8 \pm 9.6 (RAS) 56.6 \pm 9.5 (no RAS) | Angiography | > 50% stenosis | 40/333 (12.0%) 8/333 (2.5%) – bilateral > 50% stenosis | Higher carotid intima-media thickness (IMT), more coronary arteries stenosed, higher serum creatinine concentration, lower BMI and more anti-hypertensive drugs |
| | De Silva, 2007 [35] | Chronic heart failure (ejection fraction < 40%) | 70.0 \pm 1.0 | MRA | > 50% stenosis | 73/135 (54.1%) 32/135 (23.7%) – bilateral > 50% stenosis | Higher doses of diuretics, lower doses of angiotensin converting enzyme inhibitors, prolonged hospital admission, admitted with heart failure exacerbations, higher mortality |

Table 1. Cont.

| Risk category | Author, year | Study population | Age, mean \pm SD [years] | Diagnostic method | RAS definition | Prevalence RAS, N/Sample size (%) | Factors associated with presence of ARVD |
|---------------|----------------------|---|---|-------------------|----------------------|---|---|
| | Cohen, 2005 [36] | Consecutive patients undergoing CAG and abdominal aortography | 64 (55–73) | Angiography | $\geq 75\%$ stenosis | 99/843 (11.7%) | Older age, higher creatinine levels, peripheral vascular disease, number of cardiovascular drugs, hypertension, female sex, three-vessel coronary artery disease or previous coronary artery bypass graft |
| | Rigatelli, 2005 [37] | CAG with one of the following criteria: at least one vessel CAD, severe or resistant HT, abnormal abdominal pulsation or murmur, unexplained kidney dysfunction, flushing pulmonary | 67.1 \pm 12.8 | Angiography | $\geq 50\%$ stenosis | 40/205 (19.5) 15/205 (7.3%) – bilateral $\geq 50\%$ stenosis | ≥ 3 vessel coronary artery disease, age > 65 years and ≥ 3 cardiac risk factors (hypercholesterolaemia, hypertension, diabetes, smoking) |
| | Buller, 2004 [38] | CAG with severe HT and/or unexplained renal dysfunction and/or acute pulmonary oedema and/or severe atherosclerosis | 67.9 \pm 9.9 | Angiography | $\geq 50\%$ stenosis | 120/837 (14.3%) 26/837 (3.1%) – bilateral $\geq 50\%$ stenosis 61/837 (7.3%) – $\geq 70\%$ stenosis 12/837 (1.4%) – $\geq 70\%$ stenosis bilaterally 8/837 (1%) – occlusion | Age, female gender, reduced creatinine clearance, increased systolic blood pressure, and peripheral or carotid artery disease |
| | Liu, 2004 [39] | Consecutive patients undergoing CAG | 66.4 \pm 7.8 (RAS) 60.3 \pm 5.7 (no RAS) | Angiography | $\geq 50\%$ stenosis | 24/141 (18.4%) 5/141 (3.5%) – bilateral $\geq 50\%$ stenosis | Three-vessel coronary artery disease, hypertension, renal impairment, hyperlipidaemia, hypokalaemia |
| | Park, 2004 [40] | Consecutive patients undergoing CAG | 63.2 \pm 8.5 (RAS) 59.2 \pm 9.9 (no RAS) | Angiography | $\geq 50\%$ stenosis | 158/1459 (10.8%) 24/1459 (1.6%) – bilateral $\geq 50\%$ stenosis | Extracranial carotid artery stenosis, peripheral artery disease, renal insufficiency, significant coronary artery disease, hypercholesterolemia, hypertension, increasing age |
| | Khosla, 2003 [41] | CAG with refractory HT (BP > 140/90 mm Hg on 2 drugs) or flash pulmonary oedema | 62.5 \pm 12.1 | Angiography | > 70% stenosis | 101/534 (18.9%) 26/534 (4.9%) – bilateral > 70% stenosis | – |
| | Aqel, 2003 [42] | CAG and hypertension (SBP > 135 mm Hg) | 65.3 \pm 9.4 | Angiography | $\geq 50\%$ stenosis | 25/90 (27.8%) 9/90 (10%) – bilateral $\geq 50\%$ stenosis 14/90 (16%) – unilateral $\geq 70\%$ stenosis 5/90 (6%) – bilateral $\geq 70\%$ stenosis | Age > 65 years and serum creatinine concentration > 1 mg/dl |

Table 1. Cont.

| Risk category | Author, year | Study population | Age, mean ± SD [years] | Diagnostic method | RAS definition | Prevalence RAS, N/Sample size (%) | Factors associated with presence of ARVD |
|---------------------------------------|------------------------|--|---|-------------------|----------------|--|--|
| Aortic or peripheral arterial disease | Wang, 2003 [43] | CAG in patients with confirmed coronary artery disease | 65.1 ± 10.2 | Angiography | ≥ 50% stenosis | 34/230 (14.8%) 6/230 (2.6%) – bilateral ≥ 50% stenosis | Increasing age and multi-vessel coronary artery disease |
| | Rihal, 2002 [44] | CAG and HT (treatment with ≥ 1 antihypertensive drug of BP > 140/90 mm Hg) | 64.9 ± 10.2 | Angiography | > 50% stenosis | 57/297 (19.2%) 11/297 (3.7%) – bilateral > 50% stenosis 21/297 (7.0%) – unilateral RAS > 70% | Systolic blood pressure, CVA/TIA, cancer |
| | Weber-Mzell, 2002 [45] | Consecutive patients undergoing CAG | 67.0 ± 8.0 (RAS) 61.0 ± 11.0 (no RAS) | Angiography | > 50% stenosis | 19/177 (10.7%) 5/177 (2.8%) – bilateral > 50% stenosis | Low glomerular filtration rate and extent of coronary artery disease |
| | Yamashita, 2002 [46] | Consecutive patients undergoing CAG | 65.8 ± 10.6 | Angiography | > 50% stenosis | 21/289 (7.3%) 3/289 (1.0%) – bilateral > 50% stenosis | Hypertension and coronary artery disease especially three-vessel disease |
| | Conlon, 2001 [47] | Consecutive patients undergoing CAG | 61 (52–69) | Angiography | > 50% stenosis | 362/3987 (9.1%) 33/3987 (0.8%) – bilateral > 50% stenosis | Female sex, increasing age, hypertension, CCF, increased creatinine |
| | Song, 2000 [48] | Consecutive patients undergoing CAG | 59.2 ± 10.3 | Angiography | ≥ 50% stenosis | 24/427 (5.6%) 6/427 (1.4%) – bilateral ≥ 50% stenosis | Increasing age, hypertension, peripheral vascular disease |
| | Amighi, 2009 [49] | Consecutive patients undergoing revascularization of symptomatic peripheral arterial disease | 71 (63–79) | Angiography | ≥ 60% stenosis | 76/487 (15.6%) | Increased risk of major adverse events (composite of death, myocardial infarction, stroke, percutaneous coronary intervention, coronary bypass surgery, amputation and kidney failure) and increased risk of death |
| | Androes, 2007 [50] | Consecutive patients undergoing peripheral angiography for symptomatic PAD | 70.1 ± 10.3 (RAS) 62.1 ± 12.3 (no RAS) | Angiography | > 50% stenosis | 24/200 (12%) | Hypertension, coronary artery disease, female, diabetic, aorto-iliac disease, age, > 60 years, multiple levels of PVD |
| | Leertouwer, 2001 [51] | Consecutive patients who underwent angiography for suspected ischaemic PAD | 68.8 ± 9.8 (RAS) 61.5 ± 11.6 (no RAS) | Angiography | ≥ 50% stenosis | 126/386 (32.6%) 88/386 (22.8%) – bilateral | – |
| | Iglesias, 2000 [52] | Consecutive patients who underwent angiography for aortoiliac disease | 73.0 ± 10.0 (RAS) 69.0 ± 11.0 (no RAS) | Angiography | > 50% stenosis | 53/201 (26.4%) | History of coronary artery disease |
| End-stage kidney disease | Van Ampting, 2003 [53] | Consecutive patients starting renal replacement therapy | 61.0 ± 9.4 | CTA | ≥ 50% stenosis | 20/49 (40.8%) 6/49 (12.2%) – bilateral ≥ 50% stenosis | – |

reported in up to a quarter of patients with peripheral vascular disease and in a third of patients with abdominal aortic aneurysms [23]. As expected, patients with ARVD usually have evidence of other macrovascular disease such as coronary (67%), peripheral arterial (56%) and cerebrovascular atherosclerotic disease (37%) [5].

Although there is a paucity of modern epidemiological studies in ARVD, there is a strong suggestion that the incidence and prevalence of this condition have evolved significantly over the past few years. Administrative insurance claims data report a three-fold increase in diagnosis between 1992 and 2004; this may reflect both an increasingly ageing population with a greater atherosclerotic burden and increased accessibility to non-invasive imaging in the more recent years [54]. In contrast, the advent of intensive, multi-targeted vascular protection therapy (e.g. statins, renin-angiotensin blockade) and tight cardiovascular risk factor control (e.g. lower blood pressure targets, smoking cessation campaigns) may have led to a change in the natural history of this condition. A retrospective study performed at our centre based on the analysis of at least 2 renal angiograms performed over a 3-year period in 79 patients showed that the incidence of progression of ARVD over this period was around 6% compared to 30% in the pre-statin era. Disease regression was also reported in 14 renal arteries from 12 (15%) patients and a greater proportion of these patients were on a statin (10 (83%) patients on a statin vs. 2 (17%) patients not on a statin, $p = 0.001$) [55]. Recent trials also reported a lower rate of adverse renal events (16–22% over 40 months) or progression to end-stage kidney disease (ESKD) (2–8% over 40 months) in comparison to much higher rates of adverse renal events (41% over 44 months) reported in historical literature [14, 15, 56]. Nonetheless, the presence of ARVD is still undeniably strongly associated with mortality and this should not be overlooked; the risk of death has indeed been reported to be up to six times that of developing ESKD (incidence of death of 166 per 1000 patient years compared to 29 per 1000 patient years for ESKD) [22].

Management of atherosclerotic renovascular disease

Medical treatment

Atherosclerotic renovascular disease is invariably associated with systemic atherosclerosis. In view of this, tight atherosclerotic risk factor control, such as smoking cessation and target-level driven control of blood pressure and glycaemic levels in diabetic patients, together with intensive multi-targeted vascular protective therapy, should form the mainstay of treatment for all patients with this condition. The role of vascular protective therapy in mitigating adverse outcomes in patients with ARVD is not as well validated as in the cardiovascular population, but evidence from observational studies has

persistently pointed towards important benefits. The pleiotropic effects of statins extend beyond reduction in lipid levels and they have been shown to be associated with better patient survival (HR = 0.131 (0.039–0.438), $p = 0.001$) and renal survival (HR = 0.211 (0.070–0.637), $p = 0.006$) [57], together with reduced risk of disease progression (RR = 0.28 (0.10–0.77)) [55]. As mentioned above, concerns about the risk of AKI with the use of renin-angiotensin blockade in patients with ARVD have led to underutilization of this important medication in this patient cohort. Evidence from two separate observational studies shows that renin-angiotensin blockade is associated with reduced risk of death (HR = 0.61 (0.40–0.91), $p = 0.02$) [58] and improved survival (HR = 0.24 (0.08–0.71), $p = 0.0098$) [59]. Renin-angiotensin blockade helps mitigate intra-renal parenchymal injury, decrease degree of proteinuria and improve renal outcomes while conferring important cardio-protection in a patient population that is particularly enriched with cardiovascular disease. Data published previously from our Salford Renovascular Study has also revealed a reduced risk of death with antiplatelet agents (RR = 0.52 (0.31–0.89), $p = 0.02$) and β -blockers (RR = 0.45 (0.21–0.97), $p = 0.04$) [60].

Renal revascularization

A number of studies have been carried out over the past decades to determine whether restoration of renal artery patency by renal revascularization confers any added benefit to medical therapy. A meta-analysis of 3 small RCTs included 210 patients randomized to either percutaneous transluminal angioplasty (mostly without stenting) or medical therapy, with change in blood pressure control as the primary end-point. The results showed that revascularization did not improve blood pressure or renal function outcomes, although there was a suggestion that patients with bilateral disease had better blood pressure control post-intervention [61–63]. Only a minority of these patients underwent stenting, which has been shown to be a technically superior intervention to angioplasty on its own [64]. A subsequent study, the STAR trial, randomized 140 patients to either medical therapy only or in conjunction with angioplasty and stenting. The primary end-point was change in creatinine clearance over 24 months. This study again showed that revascularization did not exert any further benefit when compared to medical therapy [18]. It is noteworthy that all these studies highlighted the considerable risks that are associated with revascularization. The STAR trial quoted a periprocedural mortality rate of 3% and the prevalence of more commonly occurring complications in contemporary clinical practice is around 0.5–10% (Table II) [65, 66].

These small studies were followed by two large, landmark RCTs which provide the most robust data regarding the role of renal revascularization in the management of patients with ARVD.

The UK-based Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with ARVD to either medical therapy alone or in conjunction with revascularization. The primary end-point was change in renal function from baseline. Patients were included in the trial if they had ‘substantial’ renal artery stenosis on at least one side and the managing clinician was ‘uncertain’ whether revascularization would provide benefit. This inclusion criterion was the main point of criticism as there were no clear criteria for revascularization and the haemodynamic significance of the stenoses was not assessed. Indeed, out of the study population, 40% were found to have low-grade stenosis (50–70%) at angiography and 17% of patients randomized to stenting did not receive the intervention as there was no identifiable stenosis. After a median follow-up of 34 months, the results showed that revascularization had no impact on decline in renal function or on blood pressure control, incidence of cardiovascular events or mortality (secondary end-points). Revascularization was also associated with a complication rate of 6.8% [14]. More recently, the results of a cardiac magnetic resonance sub-study performed in 44 patients recruited into ASTRAL have been published. Cardiac magnetic resonance was performed at recruitment and before revascularization in the intervention group ($n = 22$) and compared with repeat CMR after 12 months. Over this period, there was improvement in left ventricular structural parameters in both arms, possibly due to the effect of modern cardioprotective therapy, but there was no significant difference between the two treatment arms [67]. These results echo those of a previous Italian study which investigated the effect of revascularization on left ventricular mass index (LVMI) using serial echocardiography in 84 patients with both ARVD and coronary artery disease over the same period. There was overall improvement in LVMI in both arms, but revascularization did not exert any added benefit [68]. Patients with severe ARVD or those with acute heart failure were not recruited to either of these studies.

The US-based Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial randomized 947 patients to either stenting and best medical therapy or best medical therapy alone. The primary end-point was a composite of major cardiovascular events, progressive deterioration in renal function and death from cardiovascular or renal causes. The initial design of CORAL aimed to overcome the flaws observed in ASTRAL; only patients with haemodynamically confirmed severe renal artery stenosis and a systolic BP of 155 mm Hg or higher despite use of at least 2 antihypertensive agents were originally intended to be recruited. The degree of stenosis was standardized by means of an angiographic ‘core lab’ evaluation and trans-lesional gradient measurement, and severe stenosis was defined as either at least 80% but less than 100% angiographic stenosis or 60–80% ste-

Table II. Complications after endovascular renal revascularization [65, 66]

- Groin haematoma
- Renal artery dissection
- Cholesterol embolization
- Renal artery rupture
- Contrast medium induced nephropathy
- Aortic dissection

nosis with a trans-lesional systolic pressure gradient of at least 20 mm Hg. However, these inclusion criteria had to be relaxed due to slow patient recruitment, but core laboratory criteria were maintained for patient inclusion. By the end of the study average angiographic stenosis was 67%, similar to that in ASTRAL, and only 20% of patients had > 80% stenosis. After a median follow-up of 43 months, revascularization did not confer any clinical benefit over medical therapy on its own [15].

Current challenges

All patients with ARVD should receive adequate multi-targeted vascular protective treatment

Given the reduction in revascularization procedures performed worldwide following the results of recent RCTs [3], the focus of management of ARVD has shifted onto medical therapy. The multi-targeted treatment regimen used in the CORAL study, consisting of an angiotensin-receptor blocker, statin, antiplatelet agent and goal-oriented treatment of hypertension and diabetes, led to surprisingly good cardiovascular and renal outcomes despite the participants’ advanced age and significant burden of co-morbidities [15]. However, the ‘optimal’ medical therapy regime for patients with ARVD remains to date undefined, and recent data from CORAL confirms that there is still a lot of geographical variability in prescribing tendencies [69]. There also appears to be a ‘treatment bias’ as patients who are already known to have documented coronary or cerebrovascular atherosclerotic disease are more likely to be established on adequate vascular protective treatment compared to patients with ARVD who do not have documented extra-renal atherosclerosis. An observational study comparing two prospective cohorts of patients with ARVD, one based in the UK and the other one in Germany, revealed that prescription of statins and renin-angiotensin blockade was much higher in the German cohort, as this cohort was mostly composed of patients who were referred for renal artery imaging following diagnosis of concurrent or suspected coronary artery disease [70]. Data from this thesis show that although there is increased awareness about the importance of vascular protection in patients with systemic atherosclerosis, more effort is required to ensure that all patients with ARVD are uniformly prescribed this important therapy.

Development of non-invasive techniques for risk stratification

The interest in diagnostic imaging in ARVD has shifted from simple anatomical evaluation of stenosis severity to a more functional approach, which aims to determine the haemodynamic significance of a stenosis and the viability of the post-stenotic renal parenchyma. Although none of the randomized controlled trials have shown that revascularization plays a beneficial role in the management of ARVD, these studies have recruited a large proportion of relatively stable patients, many with well-preserved kidney function (e.g. average eGFR at recruitment in CORAL was 58 ml/min/1.73 m²), leading to under-representation of patients with uncontrolled hypertension, rapidly deteriorating renal function or recurrent flash pulmonary oedema. Patients with these ‘high-risk’ features are more likely to have underlying ‘critical’ or haemodynamically significant ARVD. A recent observational retrospective study conducted at our research centre looked at 237 patients with at least 50% RAS and one or more of the above ‘high-risk’ features. Around one-quarter (24%) of these patients underwent revascularization, and clinical outcomes for this subset of patients were compared to those of similar patients who were treated exclusively medically. The results showed that revascularization was associated with improved outcomes in patients with either flash pulmonary oedema or in those with a combination of rapidly declining kidney function and uncontrolled hypertension [4]. Previous work from our research group forged the concept of ‘hibernating parenchyma’, that is, viable renal parenchyma that has not yet undergone the irreversible changes associated with ARVD and hence retains the possibility to recover function after revascularization. These kidneys have been shown to exhibit a higher magnetic resonance-measured renal volume to isotopic glomerular filtration rate ratio than kidneys that do not respond positively to revascularization [71].

The heterogeneous nature of ARVD demands accurate risk stratification of patients to allow a more patient-centred approach to treatment. It is hoped that the novel functional imaging techniques will enable characterization of the functional significance of RAS and renal parenchyma; however, these modalities are still in an experimental phase, so there is an urgent need for clinical risk prediction scores based on easily obtainable parameters to help identify patients who may gain benefit from revascularization in a timely manner.

The role of novel therapeutic strategies

It is important to note that despite the overall improved clinical outcomes in patients with ARVD that have occurred in recent years, probably a product of tighter cardiovascular risk control and optimized medical therapy, 16–22% of patients in both ASTRAL and CORAL still

suffered adverse renal end-points irrespective of treatment arm [1]. As explained above, chronic activation of the renin-angiotensin system, oxidative stress and the co-existent atherosclerotic inflammatory milieu that characterize ARVD can overwhelm the kidneys’ adaptive response to hypoperfusion, leading to irreversible endothelial injury, microvascular rarefaction, and renal fibrosis [72, 73]. In addition, persistent activation of these pro-inflammatory and pro-fibrotic pathways also leads to myocardial injury and remodelling, leading to poor cardiovascular outcomes in these patients [74].

Besides adding further weight to the importance of administering renin-angiotensin blockade and statins in patients with ARVD, given their potential to attenuate these inflammatory pathways, these research findings highlight the need for development of novel adjuncts to revascularization or conservative medical therapy that may help mitigate irreversible tissue injury and optimize clinical outcomes [12]. Some experimental 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 [74–77].

Creation of an international ARVD registry

In light of the neutral results of recent large RCTs, it is unlikely that further RCTs evaluating the role of revascularization in the management of ARVD will be carried out in the near future, exacerbating the declining interest in this intervention. Nonetheless, it is anticipated that the prevalence of ARVD will continue to rise in parallel with the increasing population age and burden of atherosclerotic co-morbidities. While conservative management may be the appropriate approach for the majority of patients with ARVD, reduced interest in establishing the diagnosis of ARVD and referral for revascularization may lead to a risk of missing the opportunity of successful revascularization in the small subgroup of patients who present with the ‘high-risk’ features mentioned above. It is also likely that revascularization may be of benefit in other patient subgroups that were also underrepresented in large RCTs, such as those with chronic heart failure [78–81] or bilateral severe ARVD [62, 63].

These issues highlight the need for an international ARVD registry. This would encourage active collaboration between clinicians and researchers to help address important unanswered questions relating to management of ARVD. Patient recruitment to a registry is not affected by restrictive inclusion or exclusion criteria and clinicians are not bound to adhere to a single treatment protocol; hence a registry would provide an opportunity to evaluate the ‘real-world’ outcomes of an intervention. Indeed, the creation of an international ARVD registry would in-

crease the knowledge base about the natural history of this condition while shedding more light on the clinical and cost-effectiveness of revascularization in specific patient subgroups [82].

Conclusions

Atherosclerotic renovascular disease is a heterogeneous condition with variable clinical outcomes in different patients. While optimized medical vascular therapy remains the undeniable cornerstone of management of this condition, new information about the complex pathophysiology of this condition highlights the importance of a more individualized and patient-centred approach. It is hoped that novel diagnostic and risk stratification techniques will help identify patients who may potentially benefit from revascularization whilst avoiding this potentially hazardous intervention in others.

Conflict of interest

The authors declare no conflict of interest.

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