Nephrol Dial Transplant, 2023, **0**, 1–16
https://doi.org/10.1093/ndt/gfad095
Advance access publication date: 18 May 2023

SPECIAL REPORT

Atherosclerotic renovascular disease: a clinical practice document by the European Renal Best Practice (ERBP) board of the European Renal Association (ERA) and the Working Group Hypertension and the Kidney of the European Society of Hypertension (ESH)

Pantelis A. Sarafidis[1], Marieta Theodorakopoulou[1], Alberto Ortiz[2], Beatriz Fernandez-Fernández[2], Ionut Nistor[3,4], Roland Schmieder[5], Mustafa Arici[6], Athanasios Saratzis[7], Patricia Van der Niepen[8], Jean-Michel Halimi[9], Reinhold Kreutz[10], Andrzej Januszewicz[11], Alexandre Persu[12,†] and Mario Cozzolino[13,†]

[1]Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain
[3]Department of Internal Medicine, Nephrology and Geriatrics, Grigore T Popa University of Medicine and Pharmacy, Iasi, Romania
[4]Department of Nephrology, Dr C I Parhon University Hospital, Iasi, Romania
[5]Department of Nephrology and Hypertension, University Hospital Erlangen, Erlangen, Germany
[6]Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[7]Department of Cardiovascular Sciences & Leicester Vascular Institute, University Hospital Leicester, Leicester, UK
[8]Department of Nephrology & Hypertension, Universitair ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium
[9]Service de Néphrologie-Hypertension, Dialyses, Transplantation rénale, CHRU Tours, Tours, France and INSERM SPHERE U1246, Université Tours, Université de Nantes, Tours, France
[10]Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institut für Klinische Pharmakologie und Toxikologie, Berlin, Germany
[11]Department of Hypertension, National Institute of Cardiology, Warsaw, Poland
[12]Division of Cardiology, Cliniques Universitaires Saint-Luc and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium
[13]Renal Division, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy
Correspondence to: Pantelis A. Sarafidis; E-mail: psarafidis11@yahoo.gr
[†]These senior authors contributed equally to the manuscript.

ABSTRACT

Atherosclerotic renovascular disease (ARVD) is the most common type of renal artery stenosis. It represents a common health problem with clinical presentations relevant to many medical specialties and carries a high risk for future cardiovascular and renal events, as well as overall mortality. The available evidence regarding the management of ARVD is conflicting. Randomized controlled trials failed to demonstrate superiority of percutaneous transluminal renal artery angioplasty (PTRA) with or without stenting in addition to standard medical therapy compared with medical therapy alone in lowering blood pressure levels or preventing adverse renal and cardiovascular outcomes in patients with ARVD, but they carried several limitations and met important criticism. Observational studies showed that PTRA is associated with future cardiorenal benefits in patients presenting with high-risk ARVD phenotypes (i.e. flash pulmonary oedema, resistant hypertension or rapid loss of kidney function). This clinical practice document, prepared by experts from the European Renal Best Practice (ERBP) board of the European Renal Association (ERA) and from the Working Group on Hypertension and the Kidney of the European Society of Hypertension (ESH), summarizes current knowledge in epidemiology, pathophysiology and diagnostic assessment of ARVD and presents, following a systematic literature review, key evidence relevant to treatment, with an aim to support clinicians in decision making and everyday management of patients with this condition.

Keywords: angioplasty, atherosclerotic renovascular disease, epidemiology, renal artery stenosis, revascularization

Received: March 4, 2023; Editorial decision: May 15, 2023

INTRODUCTION

Atherosclerotic renovascular disease (ARVD) represents the most common type of renal artery stenosis (RAS), accounting for ≈90% of patients with RAS versus 10% of cases that are due to fibromuscular dysplasia (FMD) and other, more rare causes [1–4]. ARVD is commonly clustered with various comorbidities, including hypertension, chronic kidney disease (CKD), peripheral artery disease, coronary artery disease and heart failure (HF), and its overall prognosis is unfavourable [5]. Despite the fact that the pathophysiological basis of RAS was originally described almost 100 years ago [6, 7], the optimal treatment of ARVD is still highly controversial [8]. Preliminary observational evidence indicated the efficacy and safety of percutaneous transluminal renal artery angioplasty (PTRA) with or without stenting for the treatment of ARVD, but subsequent randomized controlled trials failed to demonstrate the superiority of revascularization in addition to standard medical therapy compared with medical therapy alone in lowering blood pressure (BP) levels or preventing adverse cardiovascular (CV) and renal outcomes in patients with ARVD [9–11]. However, these trials had several limitations in design or execution flaws and met important criticism [2]. Recent observational studies in ARVD patients with high-risk clinical presentations have demonstrated that successful restoration of blood flow is associated with the preservation of kidney function and decreased risk of CV events and death [8].

This document was prepared by experts from the European Renal Best Practice (ERBP) board of the European Renal Association (ERA) and from the Working Group on Hypertension and the Kidney of the European Society of Hypertension (ESH). It briefly summarizes current knowledge in epidemiology, pathophysiology and diagnostic assessment of ARVD and presents, following a systematic literature review, key evidence relevant to medical or interventional treatment, with an aim to support clinicians in decision -making and everyday management of patients with this condition.

Epidemiology

Prevalence

The prevalence of ARVD differs considerably among studied populations. In a population-based cohort of 870 participants >65 years of age, ARVD (defined as >60% stenosis) was identified by renal duplex sonography in 6.8% of patients, with equal frequency among White and Black participants [12]. Among hypertensives, the prevalence of ARVD is probably ≈1% in patients with mild hypertension [13], but may be as high as 14–24% in patients with severe or resistant hypertension [14–16]. Of note, among patients with hypertension, ARVD is considered the second most common cause of secondary hypertension [17].

The prevalence of ARVD is higher in individuals with atherosclerotic lesions in other vascular beds [18]. It has been documented that ARVD prevalence ranges from 12 to 45% of patients with peripheral artery disease (PAD) and from 5 to 30% in patients evaluated for coronary artery disease (CAD) [18, 19]. Studies in patients with abdominal aortic aneurysm (AAA) report prevalence rates of ARVD ranging from 2.6 to 30% depending on the criteria used for case definitions [18, 20, 21]. Finally, a relevant study reported that 54% of patients with HF and ejection fraction (EF) <40% had RAS of >50% of the luminal diameter as assessed by magnetic resonance angiography (MRA), while in the subgroup of patients with HF and CKD, the prevalence increased to 68% [22].

The association of ARVD with CKD is well described; the kidney disease resulting from stenotic lesions in the renal arteries is termed ischaemic nephropathy [23]. In middle-aged patients with advanced CKD, the prevalence of ARVD ranges from 5 to 22%, while in dialysis patients it can go as high as 40.8% [24–28]. A previous report from the US Renal Data System suggested a gradual increase in the diagnosis of ARVD from 9.2% to 11.2% in the 2-year period before dialysis initiation, based on relevant claims [29].

Prognosis

The overall prognosis of ARVD is poor. In an analysis of a 5% random sample of the US Medicare population, adverse event rates after incident diagnosis of ARVD greatly exceeded those in the general population, including atherosclerotic heart disease (303.9 versus 73.5 per 1000 patient-years), PAD (258.6 versus 52.2 per 1000 patient-years), congestive HF (CHF; 194.5 versus 56.3 per 1000 patient-years); cerebrovascular accident or transient ischaemic attack (175.5 versus 52.9 per 1000 patient-years), death (166.3 versus 63.3 per 1000 patient-years) and renal replacement therapy (28.8 versus 1.3 per 1000 patient-years) [30]. Patients with ARVD and pre-dialysis CKD have 1.5 times and those on dialysis 3.3 times higher mortality risk than patients with other causes of CKD [31]. RAS prognosis varies considerably depending on the underlying clinical presentation and comorbid conditions. A prospective cohort study in 467 patients with RAS >50% showed that among patients not treated with revascularization, those that present with flash pulmonary oedema have a markedly increased risk of death {hazard ratio [HR] 2.2 [95% confidence interval (CI) 1.4–3.5]} and CV events [HR 3.1 (95% CI 1.7–5.5)] compared with patients with low-risk phenotypes (i.e. those without flash pulmonary oedema, refractory hypertension or rapid loss of kidney function) [32].

Pathophysiology

The pathogenesis of BP rise in RAS was first described 90 years ago [7]. Currently it is widely accepted that ARVD with lumen stenosis >70% will cause a reduction of renal blood flow and hypoperfusion of the juxtaglomerular apparatus, which in turn stimulates the release of renin followed by increased production of angiotensin II and aldosterone [1, 2, 19, 33]. Stenoses of lesser degrees are suggested to have minimal haemodynamic effects due to the compensatory mechanisms of renal autoregulation [1, 19]. However, renal autoregulation may be compromised in several groups of individuals, including the elderly and those with diabetes mellitus or HF [34, 35], and thus it cannot be excluded that renal blood flow in such patient groups could be compromised in stenoses of lesser degrees. Furthermore, ischaemia of even a few nephrons can cause the full syndrome of renovascular hypertension, as shown in numerous cases of segmental RAS with excess unilateral renin release, striking hyperplasia of the juxtaglomerular apparatus of affected glomeruli and reversal of hypertension by partial nephrectomy or angiotensin-converting enzyme inhibitor (ACEI) use [36–38]. In unilateral RAS, the contralateral healthy kidney is expected to, at least partly, compensate for the above adverse effects of renin-dependent hypertension through pressure natriuresis. However, in the increasingly common cases of bilateral RAS, this compensation cannot be present, causing sodium/volume retention and leading to a volume-dependent hypertension phenotype and higher risk of 'flash' pulmonary oedema [39, 40].

The compensatory increase in renin–angiotensin–aldosterone system activity will have systemic effects, including increased sympathetic activity, arterial remodelling and vasoconstriction, activation of inflammatory and oxidative stress pathways and

Table 1: Clinical phenotypes of ARVD that should prompt investigations for this entity.

Hypertension	Sudden onset or worsening of existing hypertension Grade III hypertension (especially in the presence of other cardiovascular risk factors or atherosclerotic disease in other circulatory beds) Resistant hypertension
Kidney disease	Atrophic kidney or size difference >1.5 cm between kidneys Rapid, unexplained kidney function decline Decline in kidney function (eGFR) >30% after starting treatment with ACEIs/ARBs Increased albuminuria/proteinuria due to hypertensive damage in the non-stenotic kidney in unilateral RAS
Heart failure	Repeated hospital admissions for decompensated heart failure with preserved left ventricular function on echocardiography Sudden unexplained ('flash') pulmonary oedema

sodium and water retention. All the above would be added to the direct effects of glomerular hypoperfusion and adversely affect renal oxygenation and mitochondrial and microvascular function, leading to kidney fibrosis [1, 2, 19, 33]. In addition to the above, excess angiotensin II and aldosterone directly affect gene regulation in cardiac myocytes and fibroblasts, leading to excess inflammation and oxidative stress, upregulation of trophic factors and cytokines, myocardial cell hypertrophy, hyperplasia and apoptosis, extracellular matrix and collagen deposition and myocardial fibrosis [41–43]. Other adverse CV effects of ARVD include atheromatous plaque formation in the aortic arch, descending thoracic aorta [44] and carotid arteries [45]; increased macrophage influx and myocyte necrosis [46]; direct cardiac mitochondrial injury and impaired mitophagy [47]. All these pathways lead to adverse left ventricle (LV) remodelling/hypertrophy and diastolic dysfunction, which can be considerably reversed by renal revascularization [40, 48].

Clinical manifestations

Patients with ARVD may present with multiple clinical manifestations, ranging from asymptomatic disease to severe presentations, including malignant hypertension, flash pulmonary oedema and rapidly progressive kidney function decline. In some cases, ARVD may be identified as an incidental finding during imaging studies. Table 1 summarizes the most common clinical presentations and changes in common laboratory tests related to ARVD that should prompt clinicians to perform further investigations for this entity. The most common clinical presentations are resistant hypertension (defined as uncontrolled hypertension under office and ambulatory conditions despite appropriate lifestyle measures and optimal treatment with adequate doses of three or more antihypertensive drugs of different classes, including a diuretic, or controlled BP in the presence of adequate doses of more than four antihypertensive drugs) [49, 50] and ischaemic nephropathy, -CKD. Other clinical presentations of ARVD include a decline in glomerular filtration rate (GFR) >30% within the first weeks of initiating an ACEI or an angiotensin II receptor blocker (ARB), unexplained rapid decline in kidney function [acute kidney injury (AKI)] [51], 'flash' pulmonary oedema (known as Pickering syndrome) or repeated hospitalizations for decompensated HF with preserved EF, particularly in patients with hypertension and CKD [52, 53]. In unilateral RAS, the non-stenotic kidney can have damage associated with glomerular hypertension and hyperfiltration. Clinically, this can be associated with proteinuria that may reach nephrotic levels in some patients with severe hypertension [54], and can be reversed following BP reduction after revascularization by surgery or PTRA [55–57]. Histology in the non-stenotic kidney can reveal benign nephrosclerosis, focal and segmental glomerulosclerosis or relevant types of damage [54, 57, 58]. Increased albuminuria or proteinuria is a poor predictor of renal and cardiovascular outcome in patients with RAS [59].

Diagnosis

Duplex ultrasound is the most commonly used screening tool for ARVD due to its lower cost and non-invasive nature [19]. It provides waveform and velocity data [peak systolic velocity (PSV) and renal:aorta PSV ratio] [60], as well as data about kidney viability (resistive index) [61, 62]. A PSV >200 cm/sec is associated with 95% sensitivity and 90% specificity for >50% stenosis; a renal:aorta PSV ratio ≥3.5 has 92% sensitivity for 60% stenosis [63]. A renal-resistive index <0.8 indicates possible viability of renal parenchyma. However, the method is largely operator dependent and may be limited by the body habitus (obesity) and presence of bowel gas. Renal scintigraphy with and without captopril can offer useful information with regards to relevant blood flow in patients with unilateral RAS, but can be difficult to interpret in bilateral RAS and does not provide information on the degree of the stenosis [64].

Computed tomography angiography (CTA) or MRA are reliable methods for diagnosing RAS [19]. In older studies, the sensitivity and specificity of CTA and MRA were shown to be 64% and 92% and 62% and 84%, respectively [65]; however, with higher resolutions offered by newer devices and updated study protocols, the sensitivity and specificity is suggested to be improved, ranging between 90–96% and 90–92% with CTA and 94–97% and 85–93% with MRA [5, 19]. Both techniques are very useful for assessment of renal branching/orientation patterns and renal accessory arteries [19]. Contrast medium–induced nephropathy is considered the major limitation of CTA, although the risk is ≈5% even in individuals with stage 4 CKD [66, 67]. MRA is a reasonable alternative in these patients, since the risk of nephrogenic systemic fibrosis patients with CKD stage 4 or 5 receiving a group II gadolinium-based contrast agent was recently reported at <0.07% [68]. Apart from evaluating the actual stenosis degree, several preliminary studies suggest that the novel technique of blood oxygen level–dependent (BOLD) magnetic resonance imaging (MRI) can efficiently detect still viable 'hibernating' renal parenchyma and predict the positive renal functional response to renal artery revascularization [69–71]. Future developments in this area are awaited with interest.

Despite improvements in the diagnostic accuracy of CTA and MRA, invasive catheter angiography remains the gold standard method for RAS diagnosis and evaluation and it should guide the final decision to intervene. Catheter angiography additionally enables measurement of pre- and post-intervention pressure gradients to establish the haemodynamic severity of the stenosis and the possibility of treatment in the same setting and time [19]. By expert consensus and based on studies [72, 73], an angiographic RAS >70% lumen stenosis is considered severe or significant, and stenoses of 50–70% are considered moderately severe and of uncertain haemodynamic significance [74]. For moderately severe stenoses, confirmation of the haemodynamic sever-

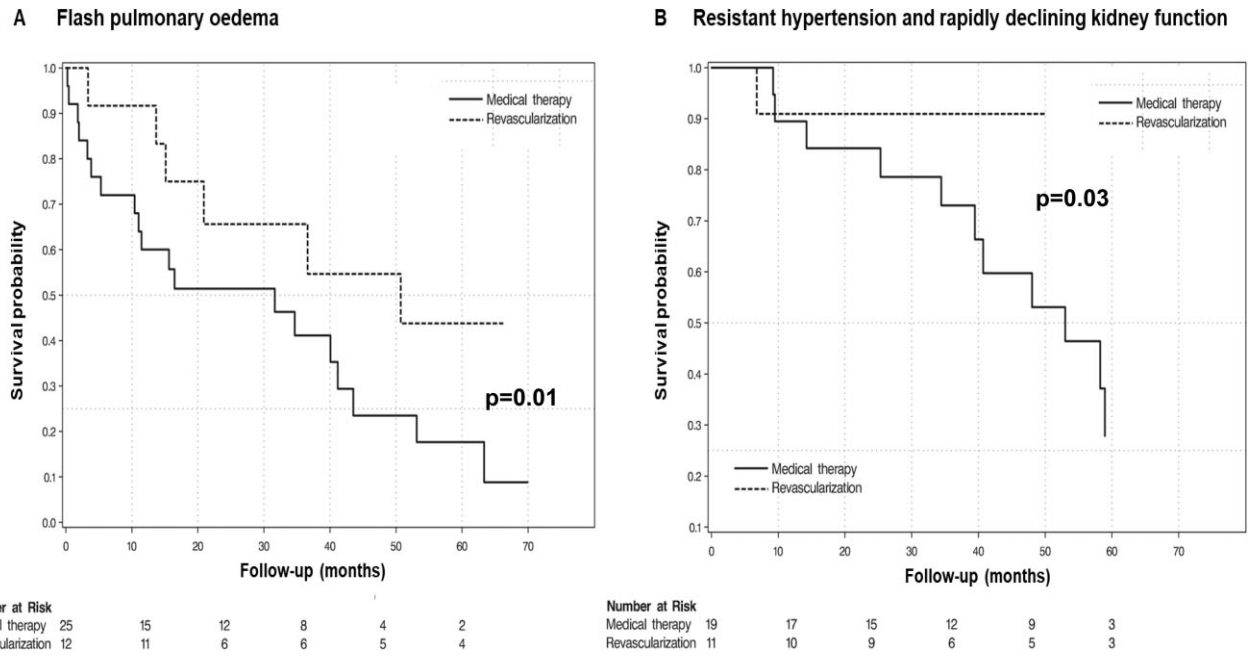

Figure 1: Kaplan–Meier curves for overall mortality in individuals with ARVD and high-risk clinical phenotypes (A: flash pulmonary oedema; B: resistant hypertension and rapidly declining kidney function). Groups compared are patients having received PTRA versus those receiving medical therapy only. Modified from Ritchie et al. (with permission) [32].

ity of the RAS is recommended prior to stenting [74]. A resting or hyperaemic translesional systolic gradient ≥20 mmHg, a resting or hyperaemic mean translesional gradient ≥10 mmHg or a renal fractional flow reserve (RFFR) ≤0.8 confirms haemodynamically severe RAS [74].

Management

ARVD management includes medical therapy with or without renal artery revascularization.

Medical therapy

Medical management of ARVD should aim to reduce CV risk and protect kidney function. Hypertension control is a prominent goal. Since no clinical studies examining different BP targets have been performed in patients with RAS, the general recommendations should be followed [17]. With regards to antihypertensive classes, ACEIs and ARBs are considered first-line options, as observational studies suggest that these agents can reduce mortality risk in patients with ARVD [75–77]. However, these agents should be initiated with particular care, and an estimated GFR (eGFR) decline of >30% should prompt further evaluation of the patient for revascularization, as discussed below. In cases of bilateral RAS or RAS in solitary kidneys, ACEIs and ARBs should generally be avoided and the patient evaluated directly for revascularization, as they may significantly compromise renal function and there is no relevant evidence in support of their use. Most often, several antihypertensive agents are needed to achieve the BP targets, selection of which should follow the general guidelines and include dihydropyridine calcium channel blockers (CCBs), diuretics of appropriate class and dose, β-blockers and second-line agents [17]. Lipid-lowering agents are needed to achieve cholesterol targets depending on total CV risk [78]. The role of antiplatelet therapy in mitigating adverse CV outcomes in patients with ARVD has not been tested in clinical trials, but its role is established in patients with atherosclerotic coronary or peripheral artery disease [79], and observational studies have shown that the use of low-dose aspirin is associated with reduced mortality risk in patients with ARVD [80]. Additional measures to help BP control and CV risk reduction include smoking cessation, weight loss, regular physical exercise and reduced sodium consumption [17, 19, 81]; for all these measures, no hard evidence from randomized controlled trials (RCTs) in patients with ARVD is available.

Renal artery revascularization

The evolution of evidence in the field of revascularization for ARVD has gone through different phases [8]. During the early 1990s, a relative enthusiasm towards the benefit of revascularization occurred, following observational data showing significant BP reductions and stabilization of kidney function in many individuals. In later years, a few RCTs attempted to properly test the superiority of standard medical therapy plus PTRA with or without stenting compared with medical therapy alone in lowering BP levels or preventing adverse renal and CV outcomes in patients with ARVD. They largely showed that PTRA had no additional benefit on BP control, renal function and adverse CV or renal outcomes when compared with medical therapy alone [2, 8, 82]. However, these trials met severe criticism due to numerous limitations in study design, methodology and execution, as discussed in detail below. To this end, a second round of observational cohort studies examined whether PTRA would be of benefit for patients with clinical presentation highly suggestive of functionally critical ARVD, such as those with flash pulmonary oedema, refractory hypertension or rapid loss of kidney function, and helped to establish a clearer picture for current recommendations.

Observational studies

Preliminary studies of surgical revascularization for ARVD showed significant BP reductions and stabilization of kidney function in some individuals [83–86]. With the expansion of endovascular revascularization procedures, PTRA with stent implantation was subsequently widely applied for ARVD, allowing treatment of individuals deemed to be at high surgical risk [2, 86]. Several prospective observational studies published in the late 1990s

showed that PTRA with or without stenting was effective for BP reduction, with decreases in systolic BP (SBP) levels of 20–25 mmHg [87–89], and for stabilization or improvement of kidney function [87, 88, 90]. In an international registry of 265 consecutive patients with ARVD (≥50% stenosis) treated with PTRA with stenting, BP levels were reduced from 160/86 mmHg to 135/75 mmHg after a median follow-up of 23.8 months. In addition, eGFR improved in 53.9% of patients, remained unchanged in 15.5% and continued to deteriorate in 30.6%. Patients whose eGFR or BP improved or stabilized had lower pre-procedural SBP and more severe stenotic lesions at baseline (longer lesion and/or higher stenosis degree) compared with patients with worsening renal function [91].

In addition to the above, several reports of individual cases and cohorts showed that patients with high-risk presentations of AVRD (flash pulmonary oedema, refractory hypertension or rapid loss of kidney function) were those that benefit the most from revascularization. These patients often have nearly occluded renal arteries or bilateral RAS or single RAS with a solitary kidney, and revascularization had immediate beneficial effects with substantial decreases in BP and significant improvement in kidney function [2]. Following the publications of relevant RCTs that almost entirely excluded patients with ARVD and high-risk clinical presentations, as discussed in detail below, several observational cohort studies examined whether PTRA with stenting might be beneficial for these individuals.

A previous prospective cohort study evaluated 467 individuals with RAS >50% who received either medical treatment or medical treatment plus PTRA with stenting in UK, and examined future CV events and mortality depending on the clinical presentation, as well as the relevant treatment. Among patients receiving only medical treatment, those who presented with flash pulmonary oedema had a markedly increased risk of death [HR 2.2 (95% CI 1.4–3.5)] and CV events [HR 3.1 (95% CI 1.7–5.5)] compared with patients with low-risk phenotypes (i.e. those without flash pulmonary oedema, refractory hypertension or rapid loss of kidney function) [32]. In the same study, PTRA with stenting compared with medical treatment was associated with large reductions in the risk of death [HR 0.15 (95% CI 0.02–0.9)] and CV events [HR 0.23 (95% CI 0.1–0.6)] in patients with high-risk presentations (Fig. 1), but no apparent benefit was observed in patients without the above high-risk presentations [HR 0.8 (95% CI 0.7–1.2) and 1.0 (95% CI 0.8–1.2), respectively]. A recent prospective cohort study investigating the effects of PTRA with stenting on ambulatory BP levels, eGFR and HF recurrence in a group of well-defined patients with severe ARVD (defined as RAS >70% in CTA or MRA and at least one of the following: resistant hypertension confirmed by 24-hour ABPM, reduction in eGFR >5 ml/min/1.73 m^2/year or hospitalization for acute decompensated HF with no obvious explanation) demonstrated that PTRA was associated with better ambulatory BP levels [24-hour SBP change from baseline: −25.7 mmHg (95% CI −30.8 to −20.6)] and BP control [change in the number of antihypertensive drugs: −0.9 (95% CI −1.3 to −0.5)], improved kidney function [eGFR change: +7.2 ml/min (95% CI 3.2–11.2)] at the 24-month evaluation and reduced hospital admissions for HF/flash pulmonary oedema (of 17 patients with a history of hypertensive HF, 14 patients had no new episodes after PTRA with stenting) [92].

RCTs

The major RCTs in the field of revascularization of ARVD are summarized in Table 2. A systematic literature search in four major databases (PubMed/MEDLINE, Cochrane/CENTRAL, Scopus and Web of Science) up to February 2023 was conducted using various combinations of the following keywords: 'randomized controlled trial', 'atherosclerosis', 'atherosclerotic', 'renal artery stenosis', 'endovascular', 'angioplasty', 'surgical intervention', 'revascularization', 'stent'. An example of the search strategy used is presented in Supplementary Table 1. In addition, a reference search was carried out to identify additional publications by screening reference lists. Eligible studies were RCTs including adult patients with ARVD randomized to either PTRA (with or without stenting) or medical therapy. Non-randomized comparisons, observational studies or trials comparing surgical interventions with either PTRA or medical therapy were excluded. Two authors (M.T. and P.S.) independently screened the records by title, abstract and full text to identify eligible publications. The flow diagram of the study selection process is depicted in Supplementary Fig. 1.

In the Dutch Renal Artery Stenosis (DRASTIC) study, 106 patients with ARVD (defined as lumen stenosis ≥50%) with normal or mildly impaired renal function were randomly assigned to PTRA or medical therapy [93]. No significant between-group differences in BP levels were detected at 3 and 12 months. However, almost half of the patients from the medical therapy group crossed over to the intervention group after 3 months due to uncontrolled BP despite treatment with three or more drugs or due to deterioration in renal function [2, 8]. In the Essai Multicentrique Medicaments vs Angioplastie (EMMA) [94] and the Scottish and Newcastle Renal Artery Stenosis Collaborative Group studies [95], no additional benefit from PTRA in addition to medical therapy in terms of BP control was shown, although in EMMA a lower number of antihypertensive medications was required in the active group and PTRA was associated with lower BP levels in patients with bilateral ARVD. These studies also had significant limitations, mainly relevant to a properly followed patient inclusion process. In EMMA, 27 of 76 originally eligible patients were excluded because of unexplained 'physician refusal' [94], while in the Scottish and Newcastle study, only 55 of the initial 135 eligible patients considered were finally randomized in the study protocol; the remaining subjects were not randomised because of unclarified 'critical renal status', 'unstable BP' or unexplained 'multiple medical problems' [95]. The Nephropathy Ischemic Therapy (NITER) trial [96] included patients with hypertension, GFR ≥30 ml/min and RAS ≥70%. It prematurely terminated with only 51 patients being enrolled (of 80 participants that were initially planned) due to slow enrolment and reported no primary results. A post hoc analysis [97] stratified patients into two groups according to median urinary albumin levels (≤0.04 g/24 h or >0.04 g/24 h) and showed no differences between PTRA with stenting and medical treatment alone in the composite of all-cause mortality, dialysis and CV events in the high albuminuria group, but event-free survival rates of 83% versus 45%, respectively, in the low albuminuria group.

A decade later, two multicentre studies compared PTRA with stenting plus medical therapy versus medical treatment alone for the prevention of kidney disease progression in patients with ARVD. The Stent Placement for Atherosclerotic Stenosis of Renal Artery (STAR) trial randomly assigned 140 patients with ARVD (defined as a reduction in the luminal diameter of the renal artery ≥50%), normal or impaired renal function (estimated creatinine clearance <80 but >15 ml/min/1.73 m^2) and controlled BP while receiving a stable medication dosage in the month before inclusion [9]. The primary outcome was a 20% decrease in creatinine clearance during a 2-year follow-up. There was no difference between the two groups in the primary and several secondary endpoints, including changes in BP, incidence of refractory or malignant hypertension, pulmonary oedema, CV

Table 2: Major RCTs of PTRA with and without stenting versus medical therapy in ARVD.

Study ID	Design	N	Endpoints	Results
EMMA Plouin *et al.*, 1998	Multicentre RCT No blinding of intervention Standardized medical treatment FU: 6 months	49	Primary: mean 24-h BP Secondary: number and DDD of antihypertensive drugs, creatinine clearance, rate of occluded arteries, complications	No significant difference in ambulatory BP PTRA: fewer antihypertensive drugs (1.0 versus 1.78; $P < .01$), higher complication rate
SNRASCG Webster *et al.*, 1998	Multicentre RCT No blinding of intervention Standardized medical treatment FU: 6 months	55	Primary: office BP, serum creatinine Secondary: number antihypertensive drugs, complications	PTRA: significant BP reduction only if bilateral RAS; no significant difference in CV events or renal function 20% participants assigned to PTRA had a surgery
DRASTIC Van Jaarsveld *et al.*, 2000	Multicentre RCT No blinding of intervention FU: 12 months	106	Primary: mean office BP Secondary: number and DDD of antihypertensive drugs, serum creatinine, restenosis, complications	No significant difference in SBP and DBP PTRA: fewer antihypertensive drugs (1.9 versus 2.4; $P < .01$) 44% of participants assigned to medical therapy underwent revascularization at 3 months if DBP >95 mmHg despite three or more antihypertensive drugs Only 3.6% stenting
NITER Scarpioni *et al.*, 2005 *from post hoc analysis published in 2018	Multicentre RCT, prematurely terminated	51	Primary: composite of all-cause mortality, CV events, dialysis	Low albuminuria group ($n = 26$): event-free survival 83% in PTRA versus 45% in medical therapy ($P = .501$) High-albuminuria group ($n = 25$): event-free survival 64% in PTRA versus 52% in medical therapy ($P = .644$)
STAR Bax *et al.*, 2009	Multicentre RCT No blinding of intervention FU: 24 months	140	Primary: worsening of renal function (>20% decline in eCrCl with Cockcroft–Gault formula) Secondary: office BP, incidence of refractory or malignant hypertension, pulmonary oedema, CV morbidity, CV mortality, total mortality	No significant difference in renal function, BP, CV mortality and morbidity 28% of participants allocated to PTRA did not undergo revascularization, mainly due to minimal stenosis 1.3% crossover
ASTRAL *Wheatley et al.*, 2009	Multicentre RCT No blinding of intervention Medical treatment was not standardized Median FU: 34 months	806	Primary: renal outcome (reciprocal of serum creatinine) Secondary: office BP, time to renal and major CV events and mortality, complications	No significant difference in renal function, BP, CV events and mortality 17% of participants allocated to PTRA, did not undergo revascularization 6% crossover
RASCAD Marcantoni *et al.*, 2012	Single-centre RCT Single-blinded Standardized medical treatment FU: 12 months	84	Primary: change in echocardiographic LVMI Secondary: LV function, CV events and mortality, BP control, kidney function	No significant difference in change in LVMI, BP, eGFR, CV events and mortality
CORAL Cooper *et al.*, 2014	Multicentre RCT No blinding of intervention Standardized medical treatment Median FU: 43 months	947	Primary: composite of adverse fatal and non-fatal CV and renal events Secondary: all-cause mortality, SBP, restenosis, renal resistance index, QOL, cost-effectiveness	No significant difference in primary composite endpoint, any of individual components of primary endpoint or all-cause mortality Almost 17% of participants either withdrew or were lost to follow-up 5.4% of participants allocated to PTRA did not undergo revascularization 4% of participants allocated to medical therapy crossed over
RADAR Zeller *et al.*, 2017	Multicentre RCT No blinding of intervention Standardized medical treatment FU: 3 years Prematurely terminated	86	Primary: change in eGFR at 12 months Secondary: technical/procedural success, LVMI, BP, renal resistance index, kidney length, restenosis, QOL, NYHA classification, CV events and mortality, renal events and mortality, revascularization	Non-significant between-group differences in eGFR change at 12 months and the secondary endpoints At 3 years, 29.4% from the medical group underwent revascularization (versus 3.0% in the PTRA group)

DDD: daily defined dose; eCrCl: estimated creatinine clearance; FU: follow-up; LVMI: left ventricular mass index; NYHA: New York Heart Association; QOL: quality of life.

events and all-cause mortality. Again, however, almost one-third of the patients in the intervention group had a stenosis <50% at the time of angiography and were not eventually treated. Further, 30% of patients included in the medical therapy group and 44% in the stent group had arterial occlusion to a small or shrunken kidney, or both, although renal size <8 cm was an exclusion criterion [2, 9].

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial assigned 806 patients with evidence of renovascular disease and 'substantial' anatomical atherosclerotic stenosis (degree of stenosis not predefined) in at least one renal artery to revascularization plus medical therapy or to medical therapy alone [10]. The primary outcome was renal function, as measured by the reciprocal of the serum creatinine level (a measure that has a linear relationship with creatinine clearance). After 5 years of follow-up, there were no significant improvements in BP or reductions in the incidence of renal or CV events or mortality in the revascularization group and the benefits in terms of renal function were not clinically significant. However, the ASTRAL trial did not answer the question of intervention in severe ARVD. Patients were enrolled if there was a stenosis of >70% by non-invasive evaluation only 'if the physician was uncertain if there would be benefit' [10]. Thus patients considered likely to benefit from revascularization were excluded [2, 8]. In this context, <50% of the participants met current criteria for resistant hypertension. Moreover, 40% of the patients at angiography did not meet entry criteria for severe RAS. The average degree of stenosis was 76% (range 40–100) and 75% (range 20–99) in the revascularization and the medical treatment groups, respectively [10].

In the Renal Artery Stenosis in Coronary Artery Disease (RASCAD) trial [98], 84 patients undergoing cardiac catheterization for ischaemic heart disease and who had renal artery stenosis >50% but ≤80% were randomized to revascularization plus standard medical therapy versus medical therapy alone. After 1 year, there was no significant difference in the primary outcome between groups, i.e. change in echocardiographic left ventricular mass index. The study had no inclusion criterion relevant to hypertension or other ARVD phenotypes, had slow enrolment rates and a final population that was half of that planned.

The multicentre Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study [11] originally aimed to enrol 947 patients with ARVD and either uncontrolled systolic hypertension while taking two or more antihypertensive drugs or CKD and RAS >80% but <100% of the diameter or RAS >60% but <80% with a systolic pressure gradient >20 mmHg. The primary endpoint was a composite of death from CV or renal causes, myocardial infarction, stroke and hospitalization for CHF, progressive renal insufficiency or the need for renal replacement therapy. The CORAL study replicated the findings of the STAR and ASTRAL trials and also showed no additional benefit in the composite primary endpoint when compared with medical therapy alone. However, again, several methodological issues appeared. Similar to the other clinical trials, patients with a presentation suggestive of critical RAS (flash pulmonary oedema, refractory hypertension or rapid loss of kidney function after ACEI/ARB use) were excluded. Several protocol modifications to expand the inclusion criteria were made due to very slow enrolment. Uncontrolled hypertension was no longer required and >25% of patients were already at goal. Angiographically documented stenosis was no longer an inclusion criterion and in one out of four patients the diagnosis was based only on renal ultrasound.

Table 3: Major limitations of RCTs in the field of ARVD.

- Non-standardized inclusion criteria
- Inclusion of patients with mild/asymptomatic RAS, mild hypertension or advanced CKD
- Exclusion of patients with clinical presentation suggestive of critical RAS (recurrent flash pulmonary oedema, resistant hypertension, progressive renal function decline)
- Great variability between and within study protocols in imaging techniques of RAS diagnosis and evaluation, often resulting in overestimation of the degree of stenosis
- Enrolment delays
- Protocol revisions during the trial
- High crossover rates between treatment arms
- Low event rates of major outcomes

As such, although a stenosis >70% was an inclusion criterion, the CORAL cohort had a mean RAS of 67%, with <50% of patients having severe disease (>80% stenosis). Lastly, the more recently published RADAR trial [99], including 86 patients with 'hemodynamically relevant' RAS and a follow-up period of 3 years, showed no significant differences between PTRA with stenting plus best medical treatment versus medical treatment alone in all studied outcomes. However, this trial was also terminated due to very slow enrolment (86 of the 300 initially scheduled participants) and had high crossover rates (29.4% of patients in the medical group underwent revascularization).

Major limitations of RCTs in the field and evolution of treatment practices

The aforementioned RCTs attempted to properly examine whether revascularization of the renal artery is superior or not to medical treatment alone in ARVD. An objective reader should note that investigators of more recent trials tried to avoid the limitations of early RCTs; this is exemplified in the original design of the CORAL trial, which included a large population, a clinically relevant cardiorenal primary endpoint and required both resistant hypertension and angiographically documented severe RAS [11]. However, the complexity of the disease under study led to very slow recruitment and protocol amendments that introduced bias. Overall, a set of major limitations are common for these RCTs [2, 32, 100–102] (Table 3). All of them had non-standardized inclusion criteria, resulting in enrolment of large numbers of patients with mild/asymptomatic RAS, mild hypertension or advanced CKD with small kidneys, i.e. individuals with almost certain absence of benefit from RAS revascularization. The presence of systematic biases in radiological assessment of RAS and poor laboratory proof of critical RAS is also highly possible, as there was large variability not only between, but also within study protocols in imaging techniques used for RAS diagnosis and evaluation, often resulting in overestimation of the degree of stenosis. Additional methodological limitations include a large number of patients fulfilling the inclusion criteria that were not randomized based on investigators' judgment without specific justification. Large enrolment delays were present for all major trials and led to protocol amendments during the trial that greatly changed the composition of the studied population. Further, high crossover rates between the study arms and low event rates for major outcomes were present in several cases [2, 32, 100–102].

Overall, the diverse trials also demonstrated the difficulties encountered in performing trials in subjects with ARVD, even before

accounting for additional issues such as the potential variability in the level of expertise of physicians performing the procedures. In this regard, the few additional clinical trials examining possible benefits of revascularization in the field of ARVD identified in a systematic search of databases of clinical trials (Supplementary Table 2) appear to have been terminated without publishing results. As such, no major input in the field from major trials can be anticipated in near future.

The most important problem arising from the aforementioned RCTs is a large misinterpretation of their results by the medical community. As discussed, they have almost entirely excluded patients with clinical presentations highly suggestive of functionally important RAS, such as those with flash pulmonary oedema, refractory hypertension or rapid loss of kidney function after use of an ACEI or ARB. Although that this was a conscious and ethical choice, on the basis that the investigators truly considered these individuals to have a clear indication for revascularization, the fact that their results cannot be extrapolated to these specific subsets of patients with high-risk phenotypes was not properly emphasized. Thus these publications rather gave rise to widespread doubt of the utility of PTRA and many selected patients that could have significantly benefited, were deprived of the procedure [2, 8, 82]. To this end, several guideline and consensus documents in recent years have provided detailed recommendations against this nihilistic view of PTRA, indicating that revascularization should be performed in specific patient groups [19, 74, 103–106], as discussed in detail below.

Clinical phenotypes of ARVD that may benefit from revascularization

Based on the totality of the available evidence, there are several clinical phenotypes of ARVD that may benefit from revascularization: resistant hypertension, HF, patients with rapid deterioration of renal function and kidney transplant recipients (KTRs).

Resistant hypertension

Resistant hypertension is associated with increased risk of CV events and mortality and is most often due to secondary types of hypertension [17, 40]. The prevalence of ARVD is estimated to be 14–24% in patients with severe or resistant hypertension [14–16], but no RCT in the field included solely patients with properly defined resistant hypertension. Multiple prospective and retrospective studies of patients with ARVD and resistant hypertension who underwent PTRA indicate that BP levels and antihypertensive pill burden were significantly reduced after revascularization [2]. In a retrospective uncontrolled single-centre study in 72 patients with ARVD and resistant hypertension, PTRA with or without stenting significantly decreased ambulatory BP levels by 14.0 ± 17.3/6.4 ± 8.7 mmHg and the number of antihypertensive drugs (from 4.0 ± 1.0 to 3.6 ± 1.4) [107]. In an international registry (2001–2009) including 265 consecutive patients with ARVD (≥50% *de novo* stenosis) and at least one of the following: mean SBP ≥160 mmHg on at least three anti-hypertensive medications including a diuretic, eGFR <60 ml/min/1.73 m^2, or unexplained CHF or recurrent acute pulmonary oedema that was treated by PTRA with stenting [91], BP was reduced from 160/86 mmHg to 135/75 mmHg. Finally, in the aforementioned study of 467 patients from Ritchie *et al.* [32], revascularization was associated with improved survival in patients with the combination of rapidly declining renal function and refractory hypertension [HR for death 0.15 (95% CI 0.02–0.9), $P = .04$].

HF

ARVD is highly prevalent in HF, occurring in 54% of outpatient individuals with HF with reduced EF [108] and in 34% of patients >70 years of age with hospitalization for acute systolic HF [108]. Two small secondary analyses of ASTRAL showed no difference between groups in cardiac structure and function, assessed either by echocardiography or MRI [109, 110]. However, as discussed above, HF was underrepresented in the large RCTs [2] and no imaging RCTs including solely patients with HF and RAS are available. Several case reports reported significant improvements in cardiac morphology and function after renal artery revascularization in patients with severe bilateral renal artery stenosis presenting with flash pulmonary oedema [111, 112]. Another observational analysis from the UK in 611 patients with RAS >50% (of which 152 patients had coexisting HF without previous pulmonary oedema) showed a large difference in mortality risk between PTRA and standard medical therapy for those with HF [HR 0.6 (95% CI 0.3–0.9)] and non-significant reductions for those without [HR 0.8 (95% CI 0.5–1.1)] [113]. Furthermore, the HR for hospital admission for HF overall in revascularised patients was 0.2 (95% CI 0.0–1.1, $P = .06$). In 152 patients with HF but without previous acute pulmonary oedema, the HR for death after revascularization compared with medical therapy was 0.76 (95% CI 0.58–0.99) [114]. In another observational study in 163 patients, PTRA with stenting was associated with a significant decrease in the New York Heart Association functional class (1.9 ± 0.8 versus 2.6 ± 1.0; $P < .04$) and a 5-fold reduction in the number of hospitalizations compared with medical treatment [53]. These data suggest that revascularization of RAS in HF is associated with a substantial reduction in all-cause mortality and hospital admission and call for an RCT of renal artery revascularization versus medical therapy in patients with RAS and HF. Until such evidence is available, on the basis of existing observational data and expert opinion, recurrent hospitalizations for HF and/or pulmonary oedema with severe ARVD are considered indications for PTRA. Of note, all this published experience preceded the introduction of several newer agents that constitute the current standard of therapy for HF, such as sacubitril–valsartan or sodium–glucose cotransporter-2 inhibitors [115, 116].

Patients with rapid deterioration of kidney function

Patients with rapid deterioration of kidney function and ARVD may benefit from revascularization, as has been shown by several small studies, case series and case reports [100, 117–120]. In selected patients with advanced CKD or recent initiation of dialysis, revascularization can also be beneficial in stabilization or significant recovery of kidney function [100, 118, 120–122]. Of note, participants who presented improved kidney function after PTRA with stenting have a lower risk of death and multiple CV and renal complications, as recently demonstrated in a subgroup analysis of the CORAL trial [123]. Most reports of salvage of renal function apply to patients with renovascular disease affecting the total functional mass (e.g. a solitary functioning kidney or high-grade bilateral disease) [90, 124]. Some patients continue to have relative preservation of renal size despite high-grade vascular occlusion. Preservation of volume may be related to the presence of collateral vessels that develop to replace a minimum level of perfusion, but most commonly indicate a stenosis that has recently become severe and functionally critical. As such, the reversibility of damage is time dependent and, regarding the patients who were receiving dialysis, there is a consensus to avoid revascularization in those on dialysis for >3 months [19].

KTRs

The occurrence of transplant RAS ranges from 1 to 23% and is associated with poor graft and patient survival [125, 126]. Endovascular treatment of transplant RAS is effective. Long-term graft and patient survival after endovascular correction of transplant RAS were similar to those without transplant RAS and most patients avoided returning to dialysis [127]. In a study from 1999, the incidence of transplant RAS was 6.6%, the technical success of angioplasty was 92.3% and restenosis occurred in 23.1%; revascularization resulted in improved BP control and improved renal function. The 8-year patient (100% versus 98.6%, respectively) and graft (88.1% versus 88.9%, respectively) survival rates were similar in patients with and without transplant RAS [128]. In a recent single-centre study including 62 patients undergoing PTRA for transplant RAS, the patency rates were 85% at 1 year and allograft survival rates were 97% at 1 year, 89% at 5 years and 85% at 10 years [129]. In a recent study, 65 cases of RAS were identified from 1072 patients who underwent kidney transplantation. One-year clinical success according to renal outcome and BP reduction was 78.5% and 49.2%, respectively. Both renal outcome (79.4% versus 77.4%; $P = .845$) and BP reduction (40.6% versus 58.1%; $P = .166$) at 1 year were similar between the PTRA and PTRA with stenting groups. Event-free survival for composite of kidney transplant graft failure or transplant renal artery restenosis was significantly higher in PTRA with stenting at 1 year, but similar between groups at 10 years [130].

Antithrombotic therapy following PTRA

The type and duration of antithrombotic therapy after renal artery PTRA has not been studied in specific RCTs. In the aforementioned trials comparing PTRA with stenting to medical treatment, different types of antithrombotics were used in most (but not all) patients included in the intervention arm, such as low-dose aspirin monotherapy [9] or combinations of low-dose aspirin with clopidogrel or ticagrelor [11, 99]. One observational study reported a trend towards fewer secondary procedures for revascularization failure if the initial stenting was followed by dual antiplatelet therapy [131]. Of note, the various stent devices (bare metal, drug eluting etc.) require different types and duration of antiplatelet treatment and the majority of patients with ARVD have additional atherosclerotic lesions on other vascular beds (coronary, carotid or peripheral arteries) that could have been previously treated with intravascular or open surgical procedures and require antithrombotic therapy [104]. In the absence of trials directly assessing the effects of dual versus single antiplatelet therapy after renal PTRA with stenting, antithrombotic therapy should be chosen in collaboration of the interventionists and the treating nephrologists and cardiologists on an individualized basis, taking into account all the patient's comorbidities, as well as the thrombotic and bleeding risk. In everyday clinical practice, a combination of clopidogrel and low-dose aspirin is empirically prescribed in most centres, typically from 1 to 3 months, prolonged in some cases up to 1 year, after which single antiplatelet therapy is used [104].

Complications of PTRA

With technical improvements in recent decades, complication rates of PTRA have decreased and occur in ≈5% of patients [132]. Most complications are minor and related with the vascular access site, usually the femoral artery (i.e. haematoma). Catastrophic events such as atheroemboli, dissection, renal artery rupture and thrombosis are rare [132]. Atheroembolism represents a common complication of any patient with atherosclerotic disease and may occur spontaneously irrespective of PTRA [133]; however, any catheter manipulation during the procedure increases the relative risk. Some studies have demonstrated that atheroemboli can be prevented by using embolic prevention [134–138]. The only prospective and randomized trial testing embolic prevention device (EPD) efficacy showed no differences in kidney function between renal artery stenting alone, stenting with EPD and stenting with glycoprotein IIb/IIIa inhibitors [139]. Arterial dissection and arterial perforation or rupture are rare complications that usually are successfully treated with an additional stent or a covered stent graft, respectively, without requiring surgery [132]. Finally, contrast medium–induced nephropathy occurs in <5% of patients undergoing PTRA; regular prevention measures with normal saline hydration should be incorporated if the patient is not fluid overloaded [140–142].

Surgical revascularization

High-quality evidence on the use of surgical revascularization for ARVD is scarce, since all major RCTs examined the efficacy and safety of PTRA [19]. A previous meta-analysis included 47 studies comparing open surgical revascularization versus PTRA for ARVD and showed a higher rate of improvement in kidney function with surgery but a 3.1% higher perioperative mortality [143]. In agreement with interventions in other vascular beds, open surgical revascularization should be limited to patients with recurrent stenosis after percutaneous interventions (as discussed below), patients not suitable for PTRA as a result of complex anatomy [144] or patients undergoing scheduled open repair for other diseases, most commonly with an abdominal aortic aneurysm [145].

Follow-up after revascularization

The initial clinical response to PTRA should be evaluated within the first week after the intervention [146]. Antihypertensive medications, kidney function and/or cardiac symptoms should be reassessed at follow-up and screening for restenosis should be considered in case of unexplained BP increase, kidney function decline, episode of pulmonary oedema or other symptoms/signs suggestive of renovascular stenosis. Restenosis is one of the major complications that can occur at any time after PTRA. The incidence rates of restenosis are not clear and range from 6 to 60% [147]. Despite initial reports suggesting that in-stent stenosis occurs early after PTRA, studies with longer follow-up periods showed that rates of restenosis within 1 year and within 5 years were 20% and 32%, respectively [148]. A number of clinical (i.e. smoking, obesity, non-adherence to standard medical therapy, female sex), technical (i.e. stent type, mismatched stent and lesion, high residual stenosis) and vessel-related (i.e. vessels with a diameter <5 mm, long lesion/stent, fibrosis/plaque adjacent to stent) risk factors have been identified [147]. Surveillance with renal artery duplex ultrasound is suggested in all patients with renal artery stents to assess patency. The presence of risk factors for in-stent stenosis can guide the timing and frequency of screening. Previous ungraded recommendations suggest that all patients should undergo duplex ultrasonography soon as after PTRA is performed, to establish baseline parameters and patency; surveillance studies at 6 months and 1 year, then at least yearly thereafter, are suggested [147]. For patients in whom duplex ultrasonography does not provide accurate data regarding vessel patency, CTA or angiography could be considered when clinical questions on restenosis arise.

Table 4: Evaluation of the possible viability of the kidney with ARVD following revascularization.

Variable	Likely to benefit	Unlikely to benefit
RAS degree	>70%	<50%
Kidney length (cm)	>8 cm[a]	<7 cm
Renal resistive index	<0.8	>0.8
Cortical thickness	Cortex distinct, e.g. >0.5 cm	Loss of corticomedullary differentiation, no cortex

[a]The suggested kidney length thresholds are relevant to individuals with average body habitus (i.e. body surface area ≈1.73 m^2). For patients with very high or very low body mass, possibly consider the ratio of kidney length to the patient's body mass index or body surface area to approximate kidney size in relation to patient's body habitus.

Table 5: Indications of PTRA in patients with ARVD.

Strong indications
- High-grade (>70%) RAS in association with one of the following criteria:
  - Resistant hypertension
  - New-onset or recently uncontrolled hypertension
  - Acute pulmonary oedema or acute decompensated HF
  - Rapid decline of eGFR (bilateral stenosis or solitary kidney)
  - ACEI or ARB intolerance (≥30% eGFR reduction)
  - Renal replacement treatment (with possibly viable renal parenchyma) if stenosis detected <3 months after renal replacement treatment or if uncontrolled hypertension with multiple (five or more) antihypertensive agents
- AKI due to acute renal artery occlusion or high-grade stenosis
- Kidney transplant with RAS

Moderately strong indications
- High-grade (>70%) RAS in association with one of the following criteria:
  - Chronic HF
  - Asymptomatic but either bilateral or supplying a solitary kidney with viable renal parenchyma (non-atrophic kidney, distinct renal cortex)

Table 6: Areas for further clinical research in the field of ARVD

- RCTs enrolling patients with haemodynamically significant ARVD and high-risk clinical presentations, with true renovascular hypertension rather than patients with primary hypertension and incidental RAS through a wider and more systematic use of the translesional pressure gradient
- Studies testing the impact of functional non-invasive imaging, such as BOLD MRI, to identify patients more likely to benefit from revascularization
- Studies examining the efficacy of PTRA on moderate versus advanced CKD
- Studies establishing the optimal timeline of revascularization to avoid delay-related ineffectiveness
- Studies identifying predictors of PTRA benefit
- Studies evaluating the efficacy of PTRA in combination with novel therapeutic strategies (e.g. targeting inflammation-related pathways, mesenchymal stem cells or angiogenic/growth factors)

Clinical practice recommendations

As discussed above, in view of the results and the possible limitations of RCTs in the field, as well as several pieces of observational data showing that PTRA is associated with renal and CV benefits in patients presenting with high-risk ARVD phenotypes, a progressive shift in relevant recommendations from different bodies has occurred in recent years [8]. The present group of experts suggests a careful evaluation of the degree of the stenosis and the viability of the renal parenchyma of the stenotic kidney in candidates for revascularization, as described in Table 4. In addition, we suggest a personalized approach to select patients who will benefit from revascularization based on the strong and moderately strong indications described in Table 5. Additional parameters that should be taken into account to estimate overall renal and cardiovascular benefit should include the patient's age, duration of hypertension, presence of proteinuria and presence of comorbid conditions from other organs.

CONCLUSIONS AND FUTURE PERSPECTIVES

ARVD is a common clinical problem with clinical presentations relevant to many medical specialties and important prognostic associations. In contrast to previous RCTs, several pieces of observational data showed that PTRA in addition to medical therapy is associated with future renal and CV benefits in patients presenting with high-risk ARVD phenotypes. As such, based on the best available evidence, PTRA should be offered in selected individuals after careful evaluation. Future studies in the field should focus on several issues requiring further investigation that include but are not limited to those presented in Table 6.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

The ERBP is an official body of the European Renal Association.

FUNDING

A.O. and B.F.F. are supported by FIS/Fondos FEDER (PI20/00744, PI22/00050, Instituto de Salud Carlos III (ISCIII) RICORS program to RICORS2040 (RD21/0005/0001) funded by European Union–NextGenerationEU, Mecanismo para la Recuperación y la Resiliencia (MRR).

CONFLICT OF INTEREST STATEMENT

B.F.F. has received grants from Esteve and Mundipharma and consultancy or speaker fees or travel support from Springer, AstraZeneca, Bayer, Menarini, Novo Nordisk, Boehringer Ingelheim and Mundipharma and is Editor for *Nefrologia* Editorial Board (Nefroplus). M.A. has received payment or honoraria for lectures, presentations, speakers' bureaus, publication writing or educational events from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, MSD, Novo Nordisk, Sandoz and

Sanofi. A.S. has received honoraria, lecture fees, research funding, training fees and consultancy fees from Abbott, Shockwave, Amgen and Boston Scientific and proctoring fees from Abbott and Bentley. The other authors disclose that they do not have any financial or other relationships that might lead to a conflict of interest regarding this article.

REFERENCES

1. Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001;**344**:431–42. https://doi.org/10.1056/NEJM200102083440607
2. Van der Niepen P, Rossignol P, Lengelé J-P *et al.* Renal artery stenosis in patients with resistant hypertension: stent it or not? *Curr Hypertens Rep* 2017;**19**:5. https://doi.org/10.1007/s11906-017-0703-8
3. Gornik HL, Persu A, Adlam D *et al.* First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens* 2019;**37**:229–52. https://doi.org/10.1097/HJH.0000000000002019
4. Persu A, Canning C, Prejbisz A *et al.* Beyond atherosclerosis and fibromuscular dysplasia: rare causes of renovascular hypertension. *Hypertension* 2021;**78**:898–911. https://doi.org/10.1161/HYPERTENSIONAHA.121.17004
5. Prince M, Tafur JD, White CJ. When and how should we revascularize patients with atherosclerotic renal artery stenosis? *JACC Cardiovasc Interv* 2019;**12**:505–17. https://doi.org/10.1016/j.jcin.2018.10.023
6. Goldblatt H, Lynch J, Hanzal RF *et al.* Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934;**59**:347–79. https://doi.org/10.1084/jem.59.3.347
7. Goldblatt H. Renovascular hypertension due to renal ischemia. *Circulation* 1965;**32**:1–4. https://doi.org/10.1161/01.CIR.32.1.1
8. Theodorakopoulou MP, Karagiannidis AG, Ferro CJ *et al.* Renal artery stenting in the correct patients with atherosclerotic renovascular disease: time for a proper renal and cardiovascular outcome study? *Clin Kidney J* 2023;**16**:201–4. https://doi.org/10.1093/ckj/sfac140
9. Bax L, Woittiez A-JJ, Kouwenberg HJ *et al.* Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function. *Ann Intern Med* 2009;**150**:840–8. https://doi.org/10.7326/0003-4819-150-12-200906160-00119
10. Investigators ASTRAL, Wheatley K, Ives N *et al.* Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953–62.
11. Cooper CJ, Murphy TP, Cutlip DE *et al.* Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**:13–22. https://doi.org/10.1056/NEJMoa1310753
12. Hansen KJ, Edwards MS, Craven TE *et al.* Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg* 2002;**36**:443–51. https://doi.org/10.1067/mva.2002.127351
13. Berglund G, Andersson O, Wilhelmsen L. Prevalence of primary and secondary hypertension: studies in a random population sample. *BMJ* 1976;**2**:554–6. https://doi.org/10.1136/bmj.2.6035.554
14. Khosla S, Kunjummen B, Manda R *et al.* Prevalence of renal artery stenosis requiring revascularization in patients initially referred for coronary angiography. *Catheter Cardiovasc Interv* 2003;**58**:400–3. https://doi.org/10.1002/ccd.10387
15. Buller CE, Nogareda JG, Ramanathan K *et al.* The profile of cardiac patients with renal artery stenosis. *J Am Coll Cardiol* 2004;**43**:1606–13. https://doi.org/10.1016/j.jacc.2003.11.050
16. Benjamin MM, Fazel P, Filardo G *et al.* Prevalence of and risk factors of renal artery stenosis in patients with resistant hypertension. *Am J Cardiol* 2014;**113**:687–90. https://doi.org/10.1016/j.amjcard.2013.10.046
17. Williams B, Mancia G, Spiering W *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.
18. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens* 2009;**27**:1333–40. https://doi.org/10.1097/HJH.0b013e328329bbf4
19. Hicks CW, Clark TWI, Cooper CJ *et al.* Atherosclerotic renovascular disease: a KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference. *Am J Kidney Dis* 2022;**79**:289–301. https://doi.org/10.1053/j.ajkd.2021.06.025
20. Studzińska D, Rudel B, Polok K *et al.* Infrarenal versus suprarenal abdominal aortic aneurysms: comparison of associated aneurysms and renal artery stenosis. *Ann Vasc Surg* 2019;**58**:248–254.e1. https://doi.org/10.1016/j.avsg.2018.10.044
21. Sarafidis P, Martens S, Saratzis A *et al.* Diseases of the aorta and kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Cardiovasc Res* 2022;**118**:2582–95. https://doi.org/10.1093/cvr/cvab287
22. de Silva R, Loh H, Rigby AS *et al.* Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. *Am J Cardiol* 2007;**100**:273–9. https://doi.org/10.1016/j.amjcard.2007.02.098
23. Jacobson HR. Ischemic renal disease: an overlooked clinical entity? *Kidney Int* 1988;**34**:729–43. https://doi.org/10.1038/ki.1988.240
24. Appel RG, Bleyer AJ, Reavis S *et al.* Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int* 1995;**48**:171–6. https://doi.org/10.1038/ki.1995.281
25. Baboolal K, Evans C, Moore R. Incidence of end-stage renal disease in medically treated patients with severe bilateral atherosclerotic renovascular disease. *Am J Kidney Dis* 1998;**31**:971–7. https://doi.org/10.1053/ajkd.1998.v31.pm9631841
26. Leertouwer TC, Pattynama PMT, Van Den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int* 2001;**59**:1480–3. https://doi.org/10.1046/j.1523-1755.2001.0590041480.x
27. Mailloux LU, Napolitano B, Bellucci AG *et al.* Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis* 1994;**24**:622–9. https://doi.org/10.1016/S0272-6386(12)80223-X
28. van Ampting JMA, Penne EL, Beek FJA *et al.* Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. *Nephrol Dial Transplant* 2003;**18**:1147–51. https://doi.org/10.1093/ndt/gfg121
29. Guo H, Kalra PA, Gilbertson DT *et al.* Atherosclerotic renovascular disease in older US patients starting dialysis, 1996 to 2001. *Circulation* 2007;**115**:50–8. https://doi.org/10.1161/CIRCULATIONAHA.106.637751
30. Kalra PA, Guo H, Kausz AT *et al.* Atherosclerotic renovascular disease in United States patients aged 67 years or

older: risk factors, revascularization, and prognosis. *Kidney Int* 2005;**68**:293–301. https://doi.org/10.1111/j.1523-1755.2005.00406.x
31. Ritchie J, Green D, Alderson HV *et al.* Risks for mortality and renal replacement therapy in atherosclerotic renovascular disease compared with other causes of chronic kidney disease. *Nephrology* 2015;**20**:688–96. https://doi.org/10.1111/nep.12501
32. Ritchie J, Green D, Chrysochou C *et al.* High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis* 2014;**63**:186–97. https://doi.org/10.1053/j.ajkd.2013.07.020
33. Textor SC, Lerman LO. Paradigm shifts in atherosclerotic renovascular disease: where are we now? *J Am Soc Nephrol* 2015;**26**:2074–80. https://doi.org/10.1681/ASN.2014121274
34. Hill GS, Heudes D, Bariéty J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. *Kidney Int* 2003;**63**:1027–36. https://doi.org/10.1046/j.1523-1755.2003.00831.x
35. Christensen PK, Hansen HP, Parving HH. Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. *Kidney Int* 1997;**52**:1369–74. https://doi.org/10.1038/ki.1997.463
36. Lee SM, Drach GW. Renovascular hypertension from segmental renal artery stenosis: importance of segmental renal vein renin sampling. *J Urol* 1980;**124**:704–6. https://doi.org/10.1016/S0022-5347(17)55618-9
37. Aoi W, Akahoshi M, Seto S *et al.* Correction of hypertension by partial nephrectomy in segmental renal artery stenosis and electron microscopic studies of renin. *Jpn Heart J* 1981;**22**:679–87. https://doi.org/10.1536/ihj.22.679
38. Sarafidis PA, Georgianos PI, Germanidis G *et al.* Hypertension and symptomatic hypokalemia in a patient with simultaneous unilateral stenoses of intrarenal arteries and mesangioproliferative glomerulonephritis. *Am J Kidney Dis* 2012;**59**:434–8. https://doi.org/10.1053/j.ajkd.2011.11.001
39. Kawarada O, Yasuda S, Noguchi T *et al.* Renovascular heart failure: heart failure in patients with atherosclerotic renal artery disease. *Cardiovasc Interv Ther* 2016;**31**:171–82. https://doi.org/10.1007/s12928-016-0392-2
40. Januszewicz A, Mulatero P, Dobrowolski P *et al.* Cardiac phenotypes in secondary hypertension: JACC state-of-the-art review. *J Am Coll Cardiol* 2022;**80**:1480–97. https://doi.org/10.1016/j.jacc.2022.08.714
41. Brilla CG. Renin-angiotensin-aldosterone system and myocardial fibrosis. *Cardiovasc Res* 2000;**47**:1–3. https://doi.org/10.1016/S0008-6363(00)00092-4
42. Díaz HS, Toledo C, Andrade DC *et al.* Neuroinflammation in heart failure: new insights for an old disease. *J Physiol* 2020;**598**:33–59. https://doi.org/10.1113/JP278864
43. Alexandrou M-E, Theodorakopoulou MP, Kanbay M *et al.* Mineralocorticoid receptor antagonists for cardioprotection in chronic kidney disease: a step into the future. *J Hum Hypertens* 2022;**36**:695–704. https://doi.org/10.1038/s41371-021-00641-1
44. Pathak AS, Huang J, Rojas M *et al.* Effects of restoration of blood flow on the development of aortic atherosclerosis in ApoE-/- mice with unilateral renal artery stenosis. *J Am Heart Assoc* 2016;**5**:e002953. https://doi.org/10.1161/JAHA.115.002953
45. Stouffer GA, Pathak A, Rojas M. Unilateral renal artery stenosis causes a chronic vascular inflammatory response in ApoE$^{-/-}$ mice. *Trans Am Clin Climatol Assoc* 2010;**121**:252–66.
46. Kashyap S, Warner G, Hu Z *et al.* Cardiovascular phenotype in Smad3 deficient mice with renovascular hypertension. *PLoS One* 2017;**12**:e0187062. https://doi.org/10.1371/journal.pone.0187062
47. Nargesi AA, Farah MC, Zhu X-Y *et al.* Renovascular hypertension induces myocardial mitochondrial damage, contributing to cardiac injury and dysfunction in pigs with metabolic syndrome. *Am J Hypertens* 2021;**34**:172–82. https://doi.org/10.1093/ajh/hpaa202
48. Farahani RA, Yu S, Ferguson CM *et al.* Renal revascularization attenuates myocardial mitochondrial damage and improves diastolic function in pigs with metabolic syndrome and renovascular hypertension. *J Cardiovasc Transl Res* 2022;**15**:15–26. https://doi.org/10.1007/s12265-021-10155-3
49. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension—its identification and epidemiology. *Nat Rev Nephrol* 2013;**9**:51–8. https://doi.org/10.1038/nrneph.2012.260
50. Lazaridis AA, Sarafidis PA, Ruilope LM. Ambulatory blood pressure monitoring in the diagnosis, prognosis, and management of resistant hypertension: still a matter of our resistance? *Curr Hypertens Rep* 2015;**17**:78. https://doi.org/10.1007/s11906-015-0590-9
51. Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann Intern Med* 1993;**118**:712–9. https://doi.org/10.7326/0003-4819-118-9-199305010-00010
52. Messerli FH, Bangalore S, Makani H *et al.* Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *Eur Heart J* 2011;**32**:2231–5. https://doi.org/10.1093/eurheartj/ehr056
53. Kane GC, Xu N, Mistrik E *et al.* Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrol Dial Transplant* 2010;**25**:813–20. https://doi.org/10.1093/ndt/gfp393
54. Halimi JM, Ribstein J, Du Cailar G *et al.* Nephrotic-range proteinuria in patients with renovascular disease. *Am J Med* 2000;**108**:120–6. https://doi.org/10.1016/S0002-9343(99)00411-8
55. Eiser AR, Katz SM, Swartz C. Reversible nephrotic range proteinuria with renal artery stenosis: a clinical example of renin-associated proteinuria. *Nephron* 1982;**30**:374–7. https://doi.org/10.1159/000182521
56. Ben-Chitrit S, Korzets Z, Podjarny E *et al.* Reversal of the nephrotic syndrome due to renovascular hypertension by successful percutaneous angioplasty and stenting. *Nephrol Dial Transplant* 1995;**10**:1460–1.
57. Ubara Y, Hara S, Katori H *et al.* Renovascular hypertension may cause nephrotic range proteinuria and focal glomerulosclerosis in contralateral kidney. *Clin Nephrol* 1997;**48**:220–3.
58. Gephardt GN, Tubbs RR, Novick AC *et al.* Renal artery stenosis, nephrotic-range proteinuria, and focal and segmental glomerulosclerosis. *Cleve Clin J Med* 1984;**51**:371–6. https://doi.org/10.3949/ccjm.51.2.371
59. Halimi JM, Ribstein J, Du Cailar G *et al.* Albuminuria predicts renal functional outcome after intervention in atheromatous renovascular disease. *J Hypertens* 1995;**13**:1335–42. https://doi.org/10.1097/00004872-199511000-00016
60. Williams GJ, Macaskill P, Chan SF *et al.* Comparative accuracy of renal duplex sonographic parameters in the diagnosis of renal artery stenosis: paired and unpaired analysis. *Am J Roentgenol* 2007;**188**:798–811. https://doi.org/10.2214/AJR.06.0355
61. Davies MG, Saad WE, Bismuth J *et al.* Renal parenchymal preservation after percutaneous renal angioplasty and stenting. *J Vasc Surg* 2010;**51**:1222–9. https://doi.org/10.1016/j.jvs.2009.09.050
62. Soulez G, Therasse E, Qanadli SD *et al.* Prediction of clinical response after renal angioplasty: respective value of

renal doppler sonography and scintigraphy. *Am J Roentgenol* 2003;**181**:1029–35. https://doi.org/10.2214/ajr.181.4.1811029
63. Soares GM, Murphy TP, Singha MS *et al.* Renal artery duplex ultrasonography as a screening and surveillance tool to detect Renal artery stenosis. *J Ultrasound Med* 2006;**25**:293–8. https://doi.org/10.7863/jum.2006.25.3.293
64. van Jaarsveld BC, Krijnen P, Derkx FH *et al.* The place of renal scintigraphy in the diagnosis of renal artery stenosis. Fifteen years of clinical experience. *Arch Intern Med* 1997;**157**:1226–34. https://doi.org/10.1001/archinte.1997.00440320128012
65. Vasbinder GBC, Nelemans PJ, Kessels AGH *et al.* Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. *Ann Intern Med* 2004;**141**:674–82. https://doi.org/10.7326/0003-4819-141-9-200411020-00007
66. Davenport MS, Khalatbari S, Dillman JR *et al.* Contrast material–induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. *Radiology* 2013;**267**:94–105. https://doi.org/10.1148/radiol.12121394
67. McDonald JS, McDonald RJ, Carter RE *et al.* Risk of intravenous contrast material–mediated acute kidney injury: a propensity score–matched study stratified by baseline-estimated glomerular filtration rate. *Radiology* 2014;**271**:65–73. https://doi.org/10.1148/radiol.13130775
68. Woolen SA, Shankar PR, Gagnier JJ *et al.* Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis. *JAMA Intern Med* 2020;**180**:223–30. https://doi.org/10.1001/jamainternmed.2019.5284
69. Chrysochou C, Mendichovszky IA, Buckley DL *et al.* BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;**27**:1013–9. https://doi.org/10.1093/ndt/gfr392
70. Gloviczki ML, Saad A, Textor SC. Blood oxygen level-dependent (BOLD) MRI analysis in atherosclerotic renal artery stenosis. *Curr Opin Nephrol Hypertens* 2013;**22**:519–24. https://doi.org/10.1097/MNH.0b013e32836400b2
71. Pruijm M, Mendichovszky IA, Liss P *et al.* Renal blood oxygenation level-dependent magnetic resonance imaging to measure renal tissue oxygenation: a statement paper and systematic review. *Nephrol Dial Transplant* 2018;**33**:ii22–8. https://doi.org/10.1093/ndt/gfy243
72. May AG, De Weese JA, Rob CG. Hemodynamic effects of arterial stenosis. *Surgery* 1963;**53**:513–24.
73. Imanishi M, Akabane S, Takamiya M *et al.* Critical degree of renal arterial stenosis that causes hypertension in dogs. *Angiology* 1992;**43**:833–42. https://doi.org/10.1177/000331979204301006
74. Klein AJ, Jaff MR, Gray BH *et al.* SCAI appropriate use criteria for peripheral arterial interventions: an update. *Catheter Cardiovasc Interv* 2017;**90**:E90–110. https://doi.org/10.1002/ccd.27141
75. Losito A, Gaburri M, Errico R *et al.* Survival of patients with renovascular disease and ACE inhibition. *Clin Nephrol* 1999;**52**:339–43.
76. Hackam DG, Duong-Hua ML, Mamdani M *et al.* Angiotensin inhibition in renovascular disease: a population-based cohort study. *Am Heart J* 2008;**156**:549–55. https://doi.org/10.1016/j.ahj.2008.05.013
77. Chrysochou C, Foley RN, Young JF *et al.* Dispelling the myth: the use of renin–angiotensin blockade in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;**27**:1403–9. https://doi.org/10.1093/ndt/gfr496
78. Sun D, Chen Z, Eirin A *et al.* Hypercholesterolemia impairs nonstenotic kidney outcomes after reversal of experimental renovascular hypertension. *Am J Hypertens* 2016;**29**:853–9. https://doi.org/10.1093/ajh/hpv222
79. Visseren FLJ, Mach F, Smulders YM *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. https://doi.org/10.1093/eurheartj/ehab484
80. Ritchie J, Green D, Alderson HV *et al.* Associations of antiplatelet therapy and beta blockade with patient outcomes in atherosclerotic renovascular disease. *J Am Soc Hypertens* 2016;**10**:149–158.e3. https://doi.org/10.1016/j.jash.2015.12.002
81. Bhalla V, Textor SC, Beckman JA *et al.* Revascularization for renovascular disease: a scientific statement from the American Heart Association. *Hypertension* 2022;**79**:e128–43. https://doi.org/10.1161/HYP.0000000000000217
82. Pappaccogli M, Robberechts T, Lengelé J-P *et al.* Endovascular versus medical management of atherosclerotic renovascular disease: update and emerging concepts. *Hypertension* 2023;**80**:1150–61. https://doi.org/10.1161/HYPERTENSIONAHA.122.17965.
83. Steinbach F, Novick AC, Campbell S *et al.* Long-term survival after surgical revascularization for atherosclerotic renal artery disease. *J Urol* 1997;**158**:38–41. https://doi.org/10.1097/00005392-199707000-00011
84. Hansen KJ, Cherr GS, Craven TE *et al.* Management of ischemic nephropathy: dialysis-free survival after surgical repair. *J Vasc Surg* 2000;**32**:472–82. https://doi.org/10.1067/mva.2000.108637
85. Cambria RP, Brewster DC, L'Italien GJ *et al.* Renal artery reconstruction for the preservation of renal function. *J Vasc Surg* 1996;**24**:371–380; discussion 371–82. https://doi.org/10.1016/S0741-5214(96)70193-3
86. Weibull H, Bergqvist D, Bergentz SE *et al.* Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. *J Vasc Surg* 1993;**18**:841–50; discussion 850–852. https://doi.org/10.1016/0741-5214(93)90340-R
87. Burket MW, Cooper CJ, Kennedy DJ *et al.* Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am Heart J* 2000;**139**:64–71. https://doi.org/10.1016/S0002-8703(00)90310-7
88. Harden PN, MacLeod MJ, Rodger RS *et al.* Effect of renal-artery stenting on progression of renovascular renal failure. *Lancet* 1997;**349**:1133–6. https://doi.org/10.1016/S0140-6736(96)10093-3
89. Blum U, Krumme B, Flügel P *et al.* Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. *N Engl J Med* 1997;**336**:459–65. https://doi.org/10.1056/NEJM199702133360702
90. Watson PS, Hadjipetrou P, Cox SV *et al.* Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. *Circulation* 2000;**102**:1671–7. https://doi.org/10.1161/01.CIR.102.14.1671
91. Milewski K, Fil W, Buszman P *et al.* Renal artery stenting associated with improvement in renal function and blood pressure control in long-term follow-up. *Kidney Blood Press Res* 2016;**41**:278–87. https://doi.org/10.1159/000443423
92. Reinhard M, Schousboe K, Andersen UB *et al.* Renal artery stenting in consecutive high-risk patients with atherosclerotic renovascular disease: a prospective 2-center cohort study. *J Am*

Heart Assoc 2022;**11**:e024421. https://doi.org/10.1161/JAHA.121.024421

93. van Jaarsveld BC, Krijnen P, Pieterman H *et al.* The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med* 2000;**342**:1007–14. https://doi.org/10.1056/NEJM200004063421403
94. Plouin PF, Chatellier G, Darné B *et al.* Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension* 1998;**31**:823–9. https://doi.org/10.1161/01.HYP.31.3.823
95. Webster J, Marshall F, Abdalla M *et al.* Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *J Hum Hypertens* 1998;**12**:329–35. https://doi.org/10.1038/sj.jhh.1000599
96. Scarpioni R, Michieletti E, Cristinelli L *et al.* Atherosclerotic renovascular disease: medical therapy versus medical therapy plus renal artery stenting in preventing renal failure progression: the rationale and study design of a prospective, multicenter and randomized trial (NITER). *J Nephrol* 2005;**18**:423–8.
97. Siddiqui EU, Murphy TP, Naeem SS *et al.* Interaction between albuminuria and treatment group outcomes for patients with renal artery stenosis: the NITER study. *J Vasc Interv Radiol* 2018;**29**:966–70. https://doi.org/10.1016/j.jvir.2018.03.003
98. Marcantoni C, Zanoli L, Rastelli S *et al.* Effect of renal artery stenting on left ventricular mass: a randomized clinical trial. *Am J Kidney Dis* 2012;**60**:39–46. https://doi.org/10.1053/j.ajkd.2012.01.022
99. Zeller T, Krankenberg H, Erglis A *et al.* A randomized, multicenter, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis (RADAR) – one-year results of a pre-maturely terminated study. *Trials* 2017;**18**:380.
100. Sarafidis PA, Stavridis KC, Loutradis CN *et al.* To intervene or not? A man with multidrug-resistant hypertension, endovascular abdominal aneurysm repair, bilateral renal artery stenosis and end-stage renal disease salvaged with renal artery stenting. *Blood Press* 2016;**25**:123–8. https://doi.org/10.3109/08037051.2015.1110926
101. Messina LM, Zelenock GB, Yao KA *et al.* Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. *J Vasc Surg* 1992;**15**:73–80; discussion 80–82. https://doi.org/10.1016/0741-5214(92)70015-D
102. Murphy TP, Cooper CJ, Cutlip DE *et al.* Roll-in experience from the Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study. *J Vasc Interv Radiol* 2014;**25**:511–20. https://doi.org/10.1016/j.jvir.2013.09.018
103. Whelton PK, Carey RM, Aronow WS *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *Hypertension* 2018;**71**:e13–115.
104. Aboyans V, Ricco J-B, Bartelink M-LEL *et al.* 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018;**39**:763–816.
105. Umemura S, Arima H, Arima S *et al.* The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res* 2019;**42**:1235–481. https://doi.org/10.1038/s41440-019-0284-9
106. Johansen KL, Garimella PS, Hicks CW *et al.* Central and peripheral arterial diseases in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2021;**100**:35–48. https://doi.org/10.1016/j.kint.2021.04.029
107. Courand P-Y, Dinic M, Lorthioir A *et al.* Resistant hypertension and atherosclerotic renal artery stenosis: effects of angioplasty on ambulatory blood pressure. A retrospective uncontrolled single-center study. *Hypertension* 2019;**74**:1516–23. https://doi.org/10.1161/HYPERTENSIONAHA.119.13393
108. MacDowall P, Kalra P, O'Donoghue D *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998;**352**:13–6. https://doi.org/10.1016/S0140-6736(97)11060-1
109. Ritchie J, Green D, Chrysochou T *et al.* Effect of renal artery revascularization upon cardiac structure and function in atherosclerotic renal artery stenosis: cardiac magnetic resonance sub-study of the ASTRAL trial. *Nephrol Dial Transplant* 2017;**32**:1006–13.
110. Green D, Vassallo D, Handley K *et al.* Cardiac structure and function after revascularization versus medical therapy for renal artery stenosis: the ASTRAL heart echocardiographic sub-study. *BMC Nephrol* 2019;**20**:220. https://doi.org/10.1186/s12882-019-1406-y
111. Chrysochou C, Schmitt M, Siddals K *et al.* Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. *Nephrol Dial Transplant* 2013;**28**:479–83. https://doi.org/10.1093/ndt/gfr745
112. Bloch MJ, Trost DW, Pickering TG *et al.* Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *Am J Hypertens* 1999;**12**:1–7. https://doi.org/10.1016/S0895-7061(98)00201-5
113. Green D, Ritchie JP, Chrysochou C *et al.* Revascularisation of renal artery stenosis as a therapy for heart failure: an observational cohort study. *Lancet* 2015;**385**(Suppl 1):S11. https://doi.org/10.1016/S0140-6736(15)60326-9
114. Green D, Ritchie JP, Chrysochou C *et al.* Revascularization of atherosclerotic renal artery stenosis for chronic heart failure versus acute pulmonary oedema. *Nephrology* 2018;**23**:411–7. https://doi.org/10.1111/nep.13038
115. Heidenreich PA, Bozkurt B, Aguilar D *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–80. https://doi.org/10.1016/j.jacc.2021.12.011
116. McDonagh TA, Metra M, Adamo M *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment

of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131.

117. Thatipelli M, Misra S, Johnson CM *et al.* Renal artery stent placement for restoration of renal function in hemodialysis recipients with renal artery stenosis. *J Vasc Interv Radiol* 2008;**19**:1563–8. https://doi.org/10.1016/j.jvir.2008.08.016
118. de Bhailis Á, Al-Chalabi S, Hagemann R *et al.* Managing acute presentations of atheromatous renal artery stenosis. *BMC Nephrol* 2022;**23**:210. https://doi.org/10.1186/s12882-022-02813-8
119. Ramos F, Kotliar C, Alvarez D *et al.* Renal function and outcome of PTRA and stenting for atherosclerotic renal artery stenosis. *Kidney Int* 2003;**63**:276–82. https://doi.org/10.1046/j.1523-1755.2003.00734.x
120. Takahashi W, Morita T, Tanaka K *et al.* Determinant role of renal artery stenting in recovery from acute worsening of atherosclerotic renal failure. *J Cardiol Cases* 2021;**24**:49–51. https://doi.org/10.1016/j.jccase.2020.12.011
121. Kuznetsov E, Schifferdecker B, Jaber BL *et al.* Recovery of acute renal failure following bilateral renal artery angioplasty and stenting. *Clin Nephrol* 2007;**68**:32–7. https://doi.org/10.5414/CNP68032
122. Kanamori H, Toma M, Fukatsu A. Improvement of renal function after opening occluded atherosclerotic renal arteries. *J Invasive Cardiol* 2009;**21**:E171–4.
123. Modrall JG, Zhu H, Prasad T *et al.* Retrieval of renal function after renal artery stenting improves event-free survival in a sub-group analysis of the cardiovascular outcomes in renal atherosclerotic lesions trial. *J Vasc Surg* 2023;**77**:1685–92.e2. https://doi.org/10.1016/j.jvs.2022.12.067
124. Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? *Annu Rev Med* 2001;**52**:421–42. https://doi.org/10.1146/annurev.med.52.1.421
125. Rouer M, Godier S, Monnot A *et al.* Long-term outcomes after transplant renal artery stenosis surgery. *Ann Vasc Surg* 2019;**54**:261–8. https://doi.org/10.1016/j.avsg.2018.05.066
126. Nicholson ML, Yong C, Trotter PB *et al.* Risk factors for transplant renal artery stenosis after live donor transplantation. *Br J Surg* 2019;**106**:199–205. https://doi.org/10.1002/bjs.10997
127. Patel U, Kumar S, Johnson OW *et al.* Long-term graft and patient survival after percutaneous angioplasty or arterial stent placement for transplant renal artery stenosis: a 21-year matched cohort study. *Radiology* 2019;**290**:555–63. https://doi.org/10.1148/radiol.2018181320
128. Halimi JM, Al-Najjar A, Buchler M *et al.* Transplant renal artery stenosis: potential role of ischemia/reperfusion injury and long-term outcome following angioplasty. *J Urol* 1999;**161**:28–32. https://doi.org/10.1016/S0022-5347(01)62051-2
129. Marini M, Fernandez-Rivera C, Cao I *et al.* Treatment of transplant renal artery stenosis by percutaneous transluminal angioplasty and/or stenting: study in 63 patients in a single institution. *Transplant Proc* 2011;**43**:2205–7. https://doi.org/10.1016/j.transproceed.2011.06.049
130. Wongpraparut N, Chaipruckmalakarn T, Tongdee T *et al.* Long-term outcome of percutaneous transluminal renal angioplasty (PTRA) versus PTRA with stenting (PTRAS) in transplant renal artery stenosis. *BMC Cardiovasc Disord* 2021;**21**:212. https://doi.org/10.1186/s12872-021-02015-4
131. Mousa AY, Broce M, Campbell J *et al.* Clopidogrel use before renal artery angioplasty with/without stent placement resulted in tertiary procedure risk reduction. *J Vasc Surg* 2012;**56**:416–23. https://doi.org/10.1016/j.jvs.2012.01.027
132. Ivanovic V, McKusick MA, Johnson CM *et al.* Renal artery stent placement: complications at a single tertiary care center. *J Vasc Interv Radiol* 2003;**14**:217–25. https://doi.org/10.1097/01.RVI.0000058324.82956.2a
133. Hiramoto J, Hansen KJ, Pan XM *et al.* Atheroemboli during renal artery angioplasty: an ex vivo study. *J Vasc Surg* 2005;**41**:1026–30. https://doi.org/10.1016/j.jvs.2005.02.042
134. Misra S, Gomes MT, Mathew V *et al.* Embolic protection devices in patients with renal artery stenosis with chronic renal insufficiency: a clinical study. *J Vasc Interv Radiol* 2008;**19**:1639–45. https://doi.org/10.1016/j.jvir.2008.08.002
135. Thatipelli MR, Misra S, Sanikommu SR *et al.* Embolic protection device use in renal artery stent placement. *J Vasc Interv Radiol* 2009;**20**:580–6. https://doi.org/10.1016/j.jvir.2009.01.025
136. Holden A, Hill A. Renal angioplasty and stenting with distal protection of the main renal artery in ischemic nephropathy: early experience. *J Vasc Surg* 2003;**38**:962–8. https://doi.org/10.1016/S0741-5214(03)00606-2
137. Holden A, Hill A, Jaff MR *et al.* Renal artery stent revascularization with embolic protection in patients with ischemic nephropathy. *Kidney Int* 2006;**70**:948–55. https://doi.org/10.1038/sj.ki.5001671
138. Henry M, Henry I, Klonaris C *et al.* Renal angioplasty and stenting under protection: the way for the future? *Catheter Cardiovasc Interv* 2003;**60**:299–312. https://doi.org/10.1002/ccd.10669
139. Cooper CJ, Haller ST, Colyer W *et al.* Embolic protection and platelet inhibition during renal artery stenting. *Circulation* 2008;**117**:2752–60. https://doi.org/10.1161/CIRCULATIONAHA.107.730259
140. Marenzi G, Assanelli E, Marana I *et al.* N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006;**354**:2773–82. https://doi.org/10.1056/NEJMoa054209
141. Solomon R. Hydration: intravenous and oral: approaches, principals, and differing regimens: is it what goes in or what comes out that is important? *Interv Cardiol Clin* 2020;**9**:385–93.
142. Soomro QH, Anand ST, Weisbord SD *et al.* The relationship between rate and volume of intravenous fluid administration and kidney outcomes after angiography. *Clin J Amer Soc Nephrol* 2022;**17**:1446–56. https://doi.org/10.2215/CJN.02160222
143. Abela R, Ivanova S, Lidder S *et al.* An analysis comparing open surgical and endovascular treatment of atherosclerotic renal artery stenosis. *Eur J Vasc Endovasc Surg* 2009;**38**:666–75. https://doi.org/10.1016/j.ejvs.2009.08.002
144. Kopani K, Liao S, Shaffer K. The coral reef aorta: diagnosis and treatment following CT. *Radiol Case Rep* 2009;**4**:209. https://doi.org/10.2484/rcr.v4i1.209
145. Steuer J, Bergqvist D, Björck M. Surgical renovascular reconstruction for renal artery stenosis and aneurysm: long-term durability and survival. *Eur J Vasc Endovasc Surg* 2019;**57**:562–8. https://doi.org/10.1016/j.ejvs.2018.09.014
146. Iwashima Y, Ishimitsu T. How should we define appropriate patients for percutaneous transluminal renal angioplasty treatment? *Hypertens Res* 2020;**43**:1015–27. https://doi.org/10.1038/s41440-020-0496-z

147. Boateng FK, Greco BA. Renal artery stenosis: prevalence of, risk factors for, and management of in-stent stenosis. *Am J Kidney Dis* 2013;**61**:147–60. https://doi.org/10.1053/j.ajkd.2012.07.025

148. Lederman RJ, Mendelsohn FO, Santos R *et al.* Primary renal artery stenting: characteristics and outcomes after 363 procedures. *Am Heart J* 2001;**142**:314–23. https://doi.org/10.1067/mhj.2001.116958

Received: March 4, 2023; Editorial decision: May 15, 2023