Atherosclerotic Renovascular Disease: A KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference

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The diagnosis and management of atherosclerotic renovascular disease (ARVD) is complex and controversial. Despite evidence from the ASTRAL (2009) and CORAL (2013) randomized controlled trials showing that percutaneous renal artery revascularization did not improve major outcomes compared with best medical therapy alone over 3-5 years, several areas of uncertainty remain. Medical therapy, including statin and antihypertensive medications, has evolved in recent years, and the use of renin-angiotensin-aldosterone system blockers is now considered the primary means to treat hypertension in the setting of ARVD. However, the criteria to identify kidneys with renal artery stenosis that have potentially salvageable function are evolving. There are also data suggesting that certain high-risk populations with specific clinical manifestations may benefit from revascularization. Here, we provide an overview of the epidemiology, diagnosis, and treatment of ARVD based on consensus recommendations from a panel of physician experts who attended the recent KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference on central and peripheral arterial diseases in chronic kidney disease. Most focus is provided for contentious issues, and we also outline aspects of investigation and management of ARVD that require further research.

Introduction

In February 2020, KDIGO (Kidney Disease: Improving Global Outcomes) convened a Controversies Conference on central and peripheral arterial diseases in chronic kidney disease (CKD) in Dublin, Ireland. The objectives were to examine the current state of knowledge about cerebrovascular diseases, central aortic disease, renovascular disease, and peripheral artery disease in persons with CKD and to determine what needs to be done in these areas to improve patient care and outcomes. An executive summary of the conference proceedings has been published elsewhere.1 The conference included a total of 10 international experts who specifically focused on the topic of atherosclerotic renovascular disease (ARVD), including nephrologists, cardiologists, interventional radiologists, and vascular surgeons. Here, those experts and the conference leadership provide a more detailed expert consensus summary of the epidemiology, pathophysiology, investigation, and management of ARVD, as well as research recommendations for future consideration.

Epidemiology

Prevalence in Comorbid Conditions

The comorbidity most strongly associated with ARVD is heart failure (HF). De Silva et al identified that 54% of patients with systolic HF who underwent magnetic resonance (MR) imaging screening had evidence of renal artery stenosis (RAS).2 In the subgroup of patients with HF who had CKD, this increased to 68%.

ARVD is also independently associated with peripheral artery disease, coronary artery disease, and hypertension.1 4-5 Radiologic ARVD (defined as ≥50% stenosis) has also been shown to be present in 22%-45% of patients with suspected peripheral artery disease1 and 14%-30% of patients evaluated for coronary artery disease. ARVD is evident in 14.1% of all patients with hypertension and in 20% of patients with hypertension and diabetes.6 Given this strong association, the European Society of Cardiology7 and American College of Cardiology/American Heart Association8 recommend screening for renovascular disease in patients with hypertension with a more severe phenotype, including those with treatment resistance or accelerated hypertension or those presenting with HF.

CKD and Dialysis Populations

Even though the association of CKD with ARVD is well described7 and is often termed ischemic nephropathy,1 10,11 the incidence and prevalence of ARVD in patients with kidney failure treated by dialysis is poorly characterized. In patients >50 years of age with advanced CKD, the prevalence of ARVD varies between 5% and 22%.12-17 ARVD appears to have a similar prevalence among patients with incident kidney failure. Based on data from the US Renal Data System, 9.2% of patients had a diagnosis of ARVD in the 2-year period before dialysis initiation, and the incidence has increased (11.2%) in recent years.18 Other estimates of the prevalence of RAS in dialysis patients range from 11% to 22%.12,15,16,19 The degree to which ARVD plays a causal role in progressive CKD in these populations is uncertain.
Outcomes

The morbidity and mortality rates associated with ARVD are high, with the risk of death markedly exceeding the risk of progression to dialysis (44% vs 16% over a median of 4 years). In patients not receiving dialysis therapy, ARVD is associated with a 1.5 times higher mortality rate than other causes of CKD. In dialysis patients, the mortality rate with ARVD is more than 3 times higher than with other primary renal diagnoses. The high burden of cardiovascular comorbidity in patients with ARVD is likely to be a major contributor to these outcomes; over a 4-year follow-up period, 33% of patients with ARVD experienced a major cardiovascular event. Patients who present with acute pulmonary edema have a further increased risk of adverse outcomes compared with lower-risk ARVD phenotypes (i.e., those without flash pulmonary edema, refractory hypertension, or rapid loss of kidney function), with hazard ratios for death and cardiovascular events of 2.2 and 3.1, respectively.

Pathophysiology

ARVD causes a reduction of blood flow and perfusion pressure to the kidney which initiates a series of changes, including compensatory mechanisms and adverse parenchymal injury. It has long been recognized that renal artery pressure reduction activates the release of renin, thereby increasing the production of angiotensin and aldosterone. Modest changes in renal arterial diameter have minimal hemodynamic effects, and activation of these systems occurs only when translesional gradients across RAS develop with 70%-80% luminal obstruction. These hormonal systems aimed at restoring renal perfusion have widespread effects, including increasing sympathetic nerve activity, arterial remodeling and vasoconstriction, sodium retention, and activation of inflammatory pathways. The increase in arterial pressure is dependent on these functional changes and can be reversed by restoring renal perfusion pressure, at least initially. At some point, renovascular hypertension is no longer reversed simply by resolving the stenotic lesion.

An important corollary related to the gradient between systemic and renal pressures is that effective antihypertensive drug therapy that lowers systemic pressures magnifies the reduction in blood flow to the poststenotic kidney. As blood pressure goals remain the same independent of high-grade ARVD, many kidneys are subjected to substantially reduced blood flow for prolonged periods of time. The kidneys are filtering organs, and they normally receive more blood and oxygen delivery than needed for metabolic demands. Within the kidney, the cortex is abundantly perfused, whereas the deeper medullary regions have less blood flow via postglomerular arterioles and greater oxygen consumption related to metabolic work, including solute transport. Despite this gradient leading to relative medullary hypoxia, the kidney can withstand substantial reductions (30%-40%) of blood flow without exacerbation of tissue hypoxia. Part of this “adaptation” is due to reduced filtration and the consequent reduced oxygen consumption. However, as blood flow is further reduced in the setting of high-grade RAS, the limits of compensation are exceeded. Experimental and clinical investigations indicate that overt cortical hypoxia develops. This is associated with rarefaction of renal microvessels, mitochondrial dysfunction, and activation of tissue inflammatory pathways, including oxidative stress, as reflected in renal vein biomarkers and cellular infiltration in kidney tissue (Fig 1). These processes are amplified by dyslipidemia, diabetes, smoking, and other atherosclerotic disease risk factors. With time, inflammation induces fibrosis and nephron loss, and, consequently, deteriorating kidney function can no longer recover despite the restoration of renal blood flow.

Investigation of ARVD

Clinical Presentations

Patients with ARVD may present in a variety of ways. Many are identified by the incidental findings of ARVD during arterial imaging studies. The most common clinical presentations are (i) refractory hypertension despite multiple blood pressure–lowering agents and (ii) CKD. Although the prevalence of ARVD among patients with mild hypertension is <1%, in patients with severe and/or refractory hypertension its prevalence ranges between 10% and 40%. Other clinical presentations of ARVD include loss of glomerular filtration rate (GFR) during renin-angiotensin-aldosterone system (RAAS) blockade (defined as a >50% increase in serum creatinine level ≤1 week after initiating an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker); unexplained rapid decline in kidney function (acute kidney injury [AKI]); acute pulmonary edema and/or acute decompensations of HF, particularly in patients with hypertension and CKD; and renal asymmetry >1.5 cm.

When and Why To Investigate

Given the range of presentations and the significant co-morbid risk burden of patients with ARVD, the decision to investigate requires an individualized approach, balancing the benefit of establishing an ARVD diagnosis versus the potential risk from contrast media and/or intervention. High-risk clinical phenotypes (e.g., HF or AKI) that may benefit from revascularization warrant investigation. Other indications to evaluate for ARVD include a desire to provide safe RAAS blockade, such as for antiproteinuric effects, treatment for HF, or to reduce global vascular risk in patients with coronary artery disease.

Historically, screening patients for ARVD has been performed by assessing renal symmetry or atrophy on ultrasound. However, awareness of comorbidities that are associated with a very high prevalence of ARVD is likely to
be more informative. For example, ARVD has been diagnosed in 54% of patients with HF in the setting of abnormal kidney function (ie, estimated GFR < 60 mL/min/1.73 m²) and in 48% of patients referred for coronary artery bypass grafts. In contrast, other findings such as normal echocardiography can indicate that ARVD is very unlikely, considering that < 5% of patients with ARVD have normal echocardiographic findings. Because of the high prevalence of HF in patients with ARVD, patients who present with acute pulmonary edema with hypertension and/or evidence of generalized atheroma should undergo a workup for ARVD.

### Diagnostic Imaging

There are a variety of imaging modalities available for the diagnosis of ARVD, each with different strengths and limitations (Fig 2; Table 1). Duplex ultrasound is frequently used for screening because it is inexpensive and noninvasive and provides flow data such as peak systolic velocity (PSV) and renal-to-aorta PSV ratio, as well as assessment of intrinsic kidney disease through the renal resistive index. A renal-to-aorta PSV ratio of ≥3.5 strongly correlates with > 60% stenosis on catheter angiography. Baseline resistive index < 0.7-0.8 in the ipsilateral kidney before revascularization has been found to correlate with a higher likelihood of improved blood pressure control. Unlike duplex ultrasound, multi-detector computed tomographic angiography also reliably detects accessory renal arteries that are important when considering the potential value of revascularization. Contrast medium–induced nephropathy risks are low (~ 5%), even with GFR < 30 mL/min/1.73 m². The sensitivity and specificity are higher for gadolinium-enhanced MR angiography. Historically, the risk of nephrogenic systemic fibrosis limited the use of certain gadolinium agents in cases of GFR < 30 mL/min/1.73 m², but newer group II gadolinium agents have shown excellent safety profiles when used in patients with CKD. More recent protocols using high field strength (3-T) magnets and blood-pool contrast agents may enable higher resolution and accuracy. For example, blood oxygen level–dependent (BOLD) MR imaging has the potential to identify kidneys in which revascularization can reverse abnormal function by detecting preserved tissue oxygenation levels.

### Standard Medical Therapy

Medical management of ARVD is fundamentally targeted to reducing coexisting global cardiovascular risk and protecting kidney viability. Intensive management of arterial hypertension is the single most important and modifiable cardiovascular risk factor, with the latest American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommending a target blood pressure < 130/80 mm Hg and KDIGO recommending systolic blood pressure < 120 mm Hg. Initial
antihypertensive therapy often includes multiple drugs, but RAAS blockers are preferred. Before the introduction of angiotensin-converting enzyme inhibitors and, later, angiotensin receptor blockers, renovascular hypertension often manifested as intractable or malignant-phase hypertension. Because reduced renal perfusion pressure triggers activation of the RAAS, these agents are physiologically rational agents to treat renovascular hypertension and have made the disorder more manageable. Hence, RAAS blockade is recommended in the setting of ARVD.

RAAS blockade has a potential disadvantage, however. Glomerular filtration depends on the action of angiotensin II under some conditions, specifically those with marginal renal perfusion pressure and/or sodium depletion. As a result, many clinicians are wary of observing a decrease in GFR (manifest as increasing serum creatinine level) in patients with ARVD and/or CKD. A marked increase in creatinine level can serve as a marker of impending “critical” RAS with marginal flow and filtration dependent on angiotensin II. Removal of the stenosis with successful revascularization has been associated with removal of angiotensin dependence and stable kidney function despite reintroduction of RAAS blockade. Importantly, numerous registries and a few prospective trials in which RAAS blockade was universally applied indicate that RAAS blockade is well tolerated in most individuals with unilateral and/or bilateral ARVD. It should be emphasized that the presence of a high-grade RAS renders the kidney susceptible to further reductions in blood flow and loss of function with any form of systemic antihypertensive drug therapy. In any case, drug therapy in patients deemed at higher risk requires careful supervision and prompt investigation of the cause of unexplained loss of GFR with imaging studies to evaluate for ARVD.

Other medications are also important in the management of ARVD. Lipid-lowering drugs are strongly recommended to achieve cholesterol targets appropriate to the level of cardiovascular risk; by definition, ARVD represents a clinical manifestation of atherosclerotic disease and should be considered to pose very high risk. Antiplatelet therapy with at least a low dose of aspirin is also considered as standard care for secondary prevention of cardiovascular events. Additional measures to manage

![Figure 2. Examples of atherosclerotic renovascular disease imaged using multidetector computed tomographic angiography (CTA; A), magnetic resonance angiography (MRA; B), and catheter angiography using carbon dioxide (C) or iodinated contrast medium.](image)

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex ultrasound</td>
<td>91%-100%</td>
<td>82%-91%</td>
<td>Inexpensive, noninvasive, provides waveform and velocity data, provides data about kidney viability (resistive index)</td>
<td>Operator-dependent, limited by high BMI, limited availability in some countries</td>
</tr>
<tr>
<td>Multidetector CTA</td>
<td>64%-96%</td>
<td>90%-92%</td>
<td>Rapid multiplanar acquisition, allows detection of accessory renal arteries</td>
<td>Low/moderate levels of radiation, requires iodinated contrast</td>
</tr>
<tr>
<td>MRA</td>
<td>94%-97%</td>
<td>85%-93%</td>
<td>No radiation or iodinated contrast required</td>
<td>Long acquisition times (~1 h), may overestimate degree of stenosis</td>
</tr>
<tr>
<td>Catheter angiography</td>
<td>100%</td>
<td>100%</td>
<td>Gold standard of renal artery evaluation, enables measurement of pre- and postintervention gradients, can evaluate and treat in same setting</td>
<td>Invasive procedure, only 2D planar images acquired, ideally requires iodinated contrast (CO₂ can be substituted with lesser resolution)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; 2D, 2-dimensional.
ARVD risk include tobacco cessation and glycemic control. Application of guideline-directed medical treatment was fundamental to the success of "optimized" medical therapy in the CORAL trial.

**Revascularization in ARVD**

Beginning in the 1960s, surgical revascularization of the kidney became standard therapy for selected patients with identified renovascular hypertension. Numerous series of such patients reported improvement (and occasionally "cure") in hypertension. With the expansion of endovascular revascularization procedures in the 1980s, percutaneous angioplasty with stent implantation was later widely applied to ARVD, allowing treatment of individuals deemed to be at high surgical risk. Endovascular interventions were developed in parallel with major advances in antihypertensive drug therapy (including RAAS blockade) and medical therapies to treat atherosclerotic disease. As interventional procedures have some risks and are not always effective in older individuals with ARVD, several attempts to characterize their appropriateness have been undertaken.

**Data From Randomized Controlled Trials**

A number of small randomized controlled trials (RCTs) evaluated the clinical effectiveness of revascularization for hypertension associated with ARVD. Three early RCTs comparing renal artery angioplasty versus medical therapy showed no consistent benefit in blood pressure control with angioplasty. However, these studies were small (N = 49-135 participants) and had high rates (27%-44%) of crossover from medical therapy to intervention. A decade later, 3 RCTs (STAR, ASTRAL, and CORAL) directly compared renal artery stent placement with medical therapy versus medical treatment alone for the prevention of kidney disease progression in patients with ARVD (Table 2).

In analyses of the overall changes for the particular populations enrolled in these trials, renal revascularization did not consistently lower blood pressure, restore kidney function, or prevent cardiovascular outcomes more effectively than optimal medical therapy alone over a follow-up of 3-5 years. For those reasons, the standard of care for initial management of ARVD migrated away from revascularization toward primary medical therapy with the aim of achieving goal blood pressures and stable kidney function.

Despite the RCT findings, there remains substantial controversy about whether selected patients should still be considered for revascularization. Fundamentally, the kidneys require arterial blood flow to function, so, presumably, there is a threshold beyond which the viability of the kidney can be lost. Under some conditions, restoring patency and blood flow may lead to renal recovery. There are exceptional patients with nearly occluded renal arteries who, upon the opening of the vessel, have an immediate beneficial effect with a substantial decrease in blood pressure and/or a significant improvement in kidney function. There also continue to be reports from hypertension centers of clinically important blood pressure reductions after stent placement in treatment-resistant hypertension, as confirmed by ambulatory blood pressure monitoring. There is also a possibility that revascularization in patients with CKD and bilateral RAS (or single RAS with a solitary kidney) may delay the worsening of kidney function. However, these cases are in the minority and were not well represented in the aforementioned clinical trials. Based on the available evidence, revascularization for ARVD is categorized as having a class of recommendation of IIb (weak) and a level of evidence of C-EO (consensus of expert opinion) in the 2017 American Heart Association/American College of Cardiology hypertension guidelines.

**High-Risk Clinical Presentations**

Despite the absence of consistent benefits from renal revascularization in any of the previous RCTs, there have been countless reports in the literature of individual cases, case series, and particular patient phenotypes that improve after renal artery revascularization. Large ARVD registries and cohort studies have suggested that patients with higher-risk clinical presentations such as AKI, acute and chronic HF, and rapidly declining kidney function, especially if accompanied by severe hypertension, are more likely to show a positive clinical outcome (Table 2). Unfortunately, few patients with these presentations were included in RCTs. Congestive HF was an exclusion for participation in the CORAL trial. Many such patients therefore received renal artery stent placement without being entered into the trials.

Individualized patient selection is essential to make a case for revascularization in high-risk phenotypes, which we recommend should be based on 3 important considerations:

1. The presence of a high-grade RAS lesion (>75% or with radiologic evidence suggesting compromised blood flow).
2. State of the kidney beyond RAS: Is there evidence of renal parenchymal viability (Table 3)?
3. The clinical presentation of the patient attributable to ARVD (Box 1).

There are clear precedents for these recommendations. It would be difficult to deny renovascular stent placement in a patient who presents with anuric nonobstructive AKI when there is evidence of high-grade RAS, or in a patient with similar renovascular anatomy and acute pulmonary edema who has no evidence of myocardial ischemia. Newer imaging techniques such as BOLD MR imaging have also provided additional insights that may be of benefit in patient selection. As kidney volume atrophies as a result of irreparable ischemic damage, including fibrosis, the GFR of that kidney generally decreases in parallel. There is some evidence that kidneys with a higher ratio of renal parenchymal volume to GFR...
Table 2. Controlled Studies of Renal Revascularization or Medical Therapy for Atherosclerotic Renovascular Disease

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>F/U, mo</th>
<th>Treatment</th>
<th>Primary Endpoint</th>
<th>Key Clinical Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webster et al (1993)</td>
<td>58</td>
<td>Nondiabetic, ≤70 y, untreated BP ≥160/100 mm Hg, significant unilateral RAS, Scr &lt;300 μmol/L</td>
<td>24</td>
<td>29 PTRA vs 29 surgery</td>
<td>Technical success, primary and secondary patency, and changes in BP and kidney function from baseline</td>
<td>DBP &lt;90 mm Hg: secondary results; PTRA, 5/29 (17%); surgery, 5/29 (17%); Secondary improved/ stable kidney function: PTRA, 83% (72% (P = 0.53); Complications: PTRA, 5/29 (17%); surgery, 9/29 (31%; P = 0.17); Primary patency rate at 24 mo: PTRA, 75%; surgery, 96%</td>
<td>Given tight inclusion criteria and highly selected population, unclear if clinical benefit seen with both interventions can be extrapolated to general ARVD population</td>
</tr>
<tr>
<td>Plouin et al (1998)</td>
<td>49</td>
<td>&lt;75 y, DBP &gt;95 mm Hg, Cr ≥50 mL/min, significant unilateral RAS</td>
<td>6</td>
<td>23 PTRA vs 26 medical Rx</td>
<td>BP at 6 mo and change vs baseline</td>
<td>No statistical difference in mean ambulatory BP at 6 mo and average reduction in BP between groups; Complications: PTRA, 6/23 (26%); medical Rx, 2/25 (8%)</td>
<td>PTRA reduced antihypertensive medication use at 6 mo, but was associated with higher risk of complications</td>
</tr>
<tr>
<td>Webster et al (1998)</td>
<td>55</td>
<td>&lt;75 y, DBP ≤95 mm Hg, ≥50% unilateral /bilateral stenosis, Scr &lt;500 μmol/L</td>
<td>3-54</td>
<td>25 PTRA vs 30 medical Rx</td>
<td>BP at 6 mo and change from baseline</td>
<td>Statistically significant drop in BP (P &lt; 0.05) detected only in patients with bilateral disease randomized to PTRA; No significant differences in kidney function or survival between groups</td>
<td>BP decreased significantly after 4-wk run-in period with standardized antihypertensives</td>
</tr>
<tr>
<td>van de Ven et al (1999)</td>
<td>85</td>
<td>≥50% ostial ARVD, BP &gt;160/96 mm Hg, positive captopril renography or increase in Scr of ≥20% with ACEI</td>
<td>6</td>
<td>42 PTRA vs 43 PTRAS</td>
<td>Primary success rate and patency rate at 6 mo</td>
<td>Primary success rate: PTRA, 24/42 (57%); PTRAS, 37/42 (88%); Restenosis at 6 mo: PTRA, 11/23 (48%); PTRAS, 5/35 (14%); Complications: PTRA, 18/42 (43%); PTRAS, 21/42 (50%); DBP &lt;90 mm Hg: PTRA, 2/41 (5%); PTRAS, 6/40 (15%); Improved kidney function: PTRA, 4/41 (10%); PTRAS, 5/40 (13%);</td>
<td>PTRA is technically more successful than PTRA whereas 12 patients who underwent PTRA required secondary PTRA due to failed primary PTRA; this argued for primary PTRAS for ostial atherosclerotic RAS</td>
</tr>
<tr>
<td>van Jaarsveld et al (2000)</td>
<td>106</td>
<td>&lt;75 y, Scr ≤200 μmol/L, DBP ≥95 mm Hg, &gt;50% unilateral or bilateral RAS</td>
<td>12</td>
<td>56 PTRA vs 50 medical Rx</td>
<td>BP at 3 and 12 mo after randomization</td>
<td>No significant between-group differences at 12 mo in kidney function and BP control</td>
<td>PTRA may only be of benefit in controlling BP in patients with bilateral renal artery disease</td>
</tr>
<tr>
<td>Bax et al (2009)</td>
<td>140</td>
<td>Unilateral/bilateral ostial ARAS ≥50%, CrL &lt;80 mL/min, controlled BP &lt;140/90 mm Hg for 1 mo</td>
<td>24</td>
<td>≥20% decrease in eCLcr vs baseline</td>
<td>&gt;20% decrease in eCLcr vs baseline: medical Rx, 16/76 (22%); intervention, 10/62 (16%); Death: medical Rx, 6/74 (8%); intervention, 5/62 (8%)</td>
<td>Significant no. of PTRAS-related complications: 2/62 (3%) periprocedural mortality; 1 late death secondary to infected hematoma; 1 kidney failure needing dialysis</td>
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(Continued)
Table 2 (Cont’d). Controlled Studies of Renal Revascularization or Medical Therapy for Atherosclerotic Renovascular Disease

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<tbody>
<tr>
<td>Wheatley et al (2009)⁷¹</td>
<td>806</td>
<td>Unilateral/bilateral “substantial” ARAS, uncertainty regarding benefit from revascularization</td>
<td>33.6⁴</td>
<td>403 medical Rx vs 403 medical Rx + PTRAS (95%) or PTRA (intervention group)</td>
<td>Change in kidney function (measured by mean slope of reciprocal of Scr) vs baseline</td>
<td>BP control: no statistically significant difference in SBP; DBP lower in medically treated group ($P = 0.06$)</td>
<td>Revascularization associated with SAEs in 23/403 (6.7%) patients, including 2 deaths and 3 amputations; revascularization conferred no advantage vs optimal medical Rx</td>
</tr>
<tr>
<td>Marcantoni et al (2012)⁵⁴</td>
<td>84</td>
<td>Unilateral/bilateral RAS &gt;50%-≤80%; IHD and elective coronary angiography</td>
<td>12</td>
<td>41 medical Rx vs 43 medical Rx + PTRAS (intervention group)</td>
<td>Change in echocardiographic LVMI vs baseline</td>
<td>Controlled vs improved BP control: medical Rx, 81%; intervention, 75%</td>
<td>LVMI, a surrogate CV endpoint, decreased by equivalent amounts in both groups</td>
</tr>
<tr>
<td>Cooper et al (2014)⁶³</td>
<td>947</td>
<td>Unilateral or bilateral ARAS ≥80%</td>
<td>43⁵</td>
<td>480 medical Rx vs 467 medical Rx + PTRAS (95%) or PTRA (intervention group)</td>
<td>Composite endpoint of death from CV or renal causes, MI, stroke, hospitalization from CHF, progressive renal impairment or need for KRT</td>
<td>Composite primary endpoint: medical Rx, 169/472 (36.8%); intervention, 161/459 (35.1%); $P = 0.58$</td>
<td>Revascularization conferred no benefit vs optimal medical treatment in terms of clinical outcomes</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; ARAS, atherosclerotic renal artery stenosis; ARVD, atherosclerotic renovascular disease; BP, blood pressure; CHF, congestive heart failure; CrCl (or CrClₑₑ, estimated creatinine clearance; CV, cardiovascular; DBP, diastolic blood pressure; HD, ischemic heart disease; KRT, kidney replacement therapy; LVMI, left ventricular mass index; MI, myocardial infarction; PTRA, percutaneous transluminal renal angioplasty; PTRAS, percutaneous transluminal renal angioplasty and stenting; RAS, renal artery stenosis; SBP, systolic blood pressure; Scr, serum creatinine; SAE, serious adverse event.

Adapted from Vassallo and Kaira ⁷⁷ with permission from the copyright holder; original content ©2015 the authors and published by Oxford University Press on behalf of ERA-EDTA.

Results achieved following intervention in the event of restenosis.

Patency after first intervention.

Without antihypertensive medication.

Scr decreased by >20% from baseline.

Median.

than predicted may manifest improved function after stent placement,⁷⁴ as the increased ratio may imply salvageable renal parenchyma (this has been termed “hibernating kidney”). That said, only patients with low levels of proteinuria had favorable outcomes with revascularization in the CORAL trial.⁷⁵

RCTs in some of these select phenotypes could provide definitive evidence, and their development should be encouraged. RCTs would be particularly valuable in patients with chronic HF and those with a combination of deteriorating kidney function and severe hypertension. In the meantime, the results of real-world renal revascularization practice in these higher-risk phenotypes and beyond have yet to be fully elucidated. These findings suggest that revascularization practice in these higher-risk phenotypes and beyond is of value and should be aggregated, but carefully curated to minimize bias.

**Surgical Revascularization**

Nearly all RCT data evaluating the efficacy of revascularization for ARVD are derived from endovascular interventions. As a result, high-quality data evaluating outcomes after surgical revascularization are lacking. Surgical revascularization has been associated with long-term stable or improved kidney function in more than two thirds of patients, but the risk of perioperative mortality is
substantial. A 2009 meta-analysis of 47 articles comparing open surgical revascularization versus endovascular therapy for ARVD demonstrated a 34% higher rate of improvement in kidney function with surgery, but a 3.1% higher rate of perioperative mortality. As a result, surgical revascularization is generally reserved for patients who are not suitable for renal artery angioplasty or stent placement as a result of complex anatomy (eg, “coral reef” aorta), those with concurrent abdominal aortic aneurysms undergoing planned open repair, or some patients with recurrent stenosis after percutaneous interventions. Notably, concurrent treatment of RAS during endovascular aortic aneurysm repair is considered a high-risk procedure because of a high incidence of adverse kidney outcomes, including AKI, progressive kidney function decline, and stent occlusion.

Management of ARVD in Special Populations

Dialysis Patients

Kidney damage in patients who require long-term dialysis is most often irreversible, making revascularization of severe ARVD in such patients futile. However, occasional patients may have nonfunctioning but still viable (ie, “hibernated”) kidneys that may recover function after revascularization and/or regenerative therapies (Table 3). Some of these kidneys may be sustained and kept viable by collateral vessels. Recent studies have shown that the loss of GFR initially related to reduced blood flow ultimately transitions to progressive injury associated with oxidative stress, active inflammation, and interstitial fibrosis that becomes irreversible. As the reversibility of damage is time-dependent, there is a general consensus to avoid revascularization in patients who have been receiving dialysis for >3 months. Currently, dialysis patients with reversible kidney damage related to severe ARVD who may benefit from revascularization are often denied this possibility because of our inability to identify them and also because of the decrease in use of renal revascularization procedures following the results of the RCTs. The case for identifying dialysis-dependent AKI associated with RAS has been raised earlier.

Kidney Transplant Patients

The prevalence of transplant RAS ranges from 1% to 23% depending on the definition. Transplant RAS is associated with a decrease in 5-year allograft survival rate (79% vs 89% in transplant recipients without transplant RAS), supporting the use of renal artery revascularization in these patients. Endovascular treatment of transplant RAS is usually very effective and seldom requires stent placement. In a recently published single-center experience of 63 patients undergoing angioplasty for transplant RAS (86% balloon angioplasty, 14% stent placement), 1-year primary and secondary patency rates were 85% and 100%, respectively; allograft survival rates were 89% at 5 years and 85% at 10 years. Surgical revascularization is currently limited to transplant RAS not amenable to angioplasty or after failure of endovascular treatment.
HF

ARVD is highly prevalent in HF, occurring in 34% of acute hospitalizations with systolic HF in patients aged >70 years92 and in 54% of cases of HF in outpatients with CKD.2 Some of the earliest case series describing response to revascularization in ARVD noted significant diuresis and improvement in echocardiographic parameters among patients with HF.93 Therefore, acute pulmonary edema in patients with ARVD likely represents acute decompensation of previously unknown HF. It is therefore recommended that, if a patient presents with acute pulmonary edema and ARVD is suspected or established, investigations to define the severity and etiology of HF should also be undertaken. Where both are present, “decompensation of HF” is the preferred term.

Medical therapy for ARVD encompasses many of the therapies established in HF, including RAAS blockade. Although some patients cannot tolerate RAAS blockers because of changes in kidney function, this problem is likely less common than generally perceived. Furthermore, there is emerging evidence that stopping RAAS blockade prematurely as a result of change in kidney function can worsen HF prognosis. Although not specific to ARVD, it is recommended that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers be continued until an increase in serum creatinine level of 30%-50% is noted or there is evidence of hemodynamic change or hyperkalemia.94,95 Other drugs established for use in HF, such as β-blockers and atherosclerotic secondary prevention with statins and aspirin, are also likely to be of benefit in ARVD (see Standard Medical Therapy).

The effectiveness of renal artery revascularization in patients with severe ARVD and HF remains unknown. HF was underrepresented in the large RCTs. Case reports show that improvement in cardiac structure and function can occur with renal artery revascularization in patients with high-grade stenosis,96 suggesting that this should be considered in patients presenting with acute pulmonary edema. The benefits of renal artery revascularization may extend to refractory chronic HF as well.61,72 Observational studies have shown a reduction in all-cause mortality73 and New York Heart Association Class31 after revascularization in patients with HF with no previous acute decompensation compared with medical therapy alone. Future investigations into the efficacy of renal artery revascularization for patients with HF and severe ARVD are warranted.

Fibromuscular Disease

Fibromuscular dysplasia (FMD) is a nonatherosclerotic condition that can affect any vascular bed, but most commonly affects the renal and carotid arteries. The prevalence of FMD affecting the renal arteries is estimated at 3%-4% in the general population based on living kidney donor data.97 The CORAL trial reported an FMD prevalence of 5.8% among patients with renovascular hypertension.98 Hypertension is the most common presenting symptom of FMD, and frequently occurs despite an absence of traditional atherosclerotic risk factors.

The mainstays of treatment for FMD are hypertension control99 and antiplatelet therapy.100 The outcomes of revascularization for renal FMD have been inconsistent. A 2010 meta-analysis showed that the rates of cure of hypertension (ie, normal blood pressure and no requirement for antihypertensive drugs) were 36% after angioplasty and 54% after open surgery.101 Younger patients and those who have received therapy with antihypertensive agents for a shorter period of time have a better chance of cure.101 Renal artery stent implantation is not indicated as a primary intervention in FMD because of concerns of stent kinking and fracture, and should be reserved to treat complications such as dissection or rupture.100 Open surgery is the treatment of choice in patients with complex lesions affecting the renal artery bifurcation or major branches, those with aneurysms, or those in whom angioplasty has failed.

Given the ability of FMD to affect any vascular bed, patients with confirmed FMD should undergo brain imaging with computed tomographic or MR angiography to assess for intracranial aneurysms, which are significantly more prevalent in FMD than in the general population.100

Recommendations for Future Trials

There are multiple research endeavors that would be helpful for understanding the pathogenesis, natural history, and outcomes of ARVD. Based on the most pertinent areas of uncertainty, we suggest that research should focus on the following issues.

- Achieve better understanding of parenchymal structure/gene expression in the pathogenetic pathway of ARVD.
- Ascertain the role of renal artery revascularization in heart failure.
- Access proteinuria and its relationship to outcomes.
- Examine long-term outcomes in ARVD.
- Facilitate identification of kidneys with potentially salvageable kidney function.
- Investigate novel treatments (eg, stem cells, VEGF, endothelin inhibitors) in ARVD.

Summary and KDIGO Consensus

ARVD is common and presents with heterogeneous phenotypes. The efficacy of renal artery revascularization versus medical therapy alone has not been proven in multiple RCTs, although there is evidence to suggest that specific high-risk populations may benefit. Despite the many unknowns in the natural history, diagnosis, and management of ARVD, the clinician evaluating a patient for possible renal revascularization should consider 3 important components in the composite clinical picture (Box 1).
Future research endeavors in this area are required to improve understanding of the time course of ischemia and renal parenchymal injury in ARVD, determine optimal techniques to confirm kidney viability before considering renal revascularization, and quantify the potential long-term benefits of renal artery revascularization in preventing renal atrophy.

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