Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL)

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ABSTRACT

Many patients with occlusive atherosclerotic renovascular disease (ARVD) may be managed effectively with medical therapy for several years without endovascular stenting, as demonstrated by randomized, prospective trials including the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial and the Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) and ASTRAL. These trials share the limitation of excluding subsets of patients with high-risk clinical presentations, including episodic pulmonary edema and rapidly progressing renal failure and hypertension. Although hemodynamically significant, ARVD can reduce renal blood flow and glomerular filtration rate; adaptive mechanisms preserve both cortical and medullary oxygenation over a wide range of vascular occlusion. Progression of ARVD to severe vascular compromise eventually produces cortical hypoxia, however, associated with active inflammatory cytokine release and cellular infiltration of the renal parenchyma. In such cases ARVD produces a loss of glomerular filtration rate that no longer is reversible simply by restoring vessel patency with technically successful renal revascularization. Each of these trials reported adverse renal functional outcomes ranging between 16 and 22% over periods of 2–5 years of follow-up. Blood pressure control and medication adjustment may become more difficult with declining renal function and may prevent the use of angiotensin receptor blocker and angiotensin-converting enzyme inhibitors. The objective of this review is to evaluate the current management of ARVD for clinical nephrologists in the context of recent randomized clinical trials and experimental research.

Keywords: renal artery stenosis, atherosclerosis, angioplasty, stent, renovascular hypertension
INTRODUCTION

Occlusive renovascular disease (RVD) remains a major causal factor for secondary hypertension and renal ischemic disease. It mainly reflects atherosclerotic disease (90% of US cases) and is increasingly a disorder of the aging population, with a prevalence rate of ~7% (defined as vascular occlusion >60% by duplex ultrasound) in community-based studies of individuals over 65 years of age [1]. RVD is recognized to generate multiple clinical syndromes ranging from incidental, asymptomatic disease to malignant phase hypertension, ‘Flash’ pulmonary edema and development of irreversible kidney parenchymal injury designated ‘ischemic nephropathy’ [2, 3]. For many years, it seemed self-evident that identifying high-grade RVD — and restoring blood flow to the kidney(s) by either surgical or endovascular procedures — should be undertaken whenever possible to control or ‘cure’ hypertension and to avoid serious adverse events [4]. That paradigm has been challenged in recent years by two major developments: (i) more effective medical therapy and (ii) failure of several prospective randomized clinical trials (RCTs) to establish substantial clinical benefits regarding either blood pressure (BP) control, renal function or, in the case of the US Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, risk for adverse cardiovascular (CV) outcomes [5, 6].

While RCT data argue that many patients with RVD can be managed with current medical therapy, decades of clinical experience indicate that important subsets not included in RCTs suffer preventable morbidity and mortality when critical vascular lesions are overlooked [2, 7]. Because the clinical syndromes associated with RVD are consequences of impaired circulation to the kidney, restoring blood flow by means of either surgical or endovascular revascularization has intuitive ‘face validity’. Recent experimental and clinical investigation provide important additional insights into the pathogenesis of target-organ injury related to RVD and suggest that this disorder undergoes a transition from a primarily hemodynamic disorder reducing kidney perfusion toward an inflammatory and fibrotic process within the kidney that ultimately cannot fully be reversed by restoring blood flow alone. In this review, we examine how clinicians managing patients with atherosclerotic RVD may incorporate the results of RCTs and developing mechanistic understanding of RVD into meaningful treatment strategies.

PREVALENCE AND CLINICAL SYNDROMES WITH ATHEROSCLEROTIC RENOVASCULAR DISEASE

Risk factors for atherosclerotic renovascular disease (ARVD) include age, symptomatic atherosclerotic CV disease, elevated cholesterol levels, hypertension and smoking history [8]. In a systematic review of patients with clinically suspected renovascular hypertension who underwent angiography, renal artery stenosis was identified in 14.1% [9]. Atherosclerotic CV disease is a systemic disorder with focal manifestations affecting multiple sites, such as the renal, carotid artery, lower extremity peripheral arterial beds and coronary arteries. In a study of 1734 patients (with an average age of 71 years) referred for coronary angiography, 72% had coronary artery disease (CAD) and of these, the prevalence rates of carotid artery stenosis, ARVD (>60% stenosis) and lower extremity peripheral artery disease were 7, 9 and 16%, respectively [10]. Allowing a lesser degree of stenosis (e.g. 50%) makes the association even higher, reaching 16–19% [11, 12]. Patients with heart failure due to CAD and hypertension can also have a high prevalence of RVD. Heart failure was present in approximately one-third of 163 consecutive patients with renal dysfunction (serum creatinine >2 mg/dL) who were referred for percutaneous transluminal renal angioplasty (PTRA) due to ARVD [13]. In addition, 54% of outpatient heart failure patients followed in the UK had ARVD >50% [14].

The prevalence of ARVD is also high in patients with unexplained chronic kidney disease (CKD). In a prospective study of 133 patients above the age of 50 years with a history of hypertension and /or chronic renal failure unrelated to any other cause, ARVD was diagnosed by ultrasound and/or renal scintigraphy in 20 and 25% of patients >60 and 70 years of age, respectively [15].

Landmark studies of Goldblatt and Loesch [16, 17] in the 1930s established that sustained decrease of renal perfusion pressures can raise systemic arterial BP. Studies of experimental RVD remain a cornerstone for the study of the interactions between the kidney and regulation of arterial pressures and the role of the renin–angiotensin system [18]. Clinical syndromes including accelerated and/or malignant phase hypertension can develop in such cases [7, 19, 20]. Reduction of arterial pressure after restoring renal perfusion could reverse this syndrome, which prompted the clinical search for RVD as a cause of reversible, secondary hypertension. The BP response to renal revascularization is inconsistent, however, as we and others have reviewed [21, 22]. A number of small trials targeting hypertension identify only partial reduction of BP and clinically meaningful reductions only in a subset of patients [23–25]. The major results of these studies are summarized in Table 1.

In the 1980s, RVD was recognized to have important additional manifestations (Figure 1). First, it became clear that ‘critical’ levels of reduced renal blood flow eventually led to loss of kidney function. The potential importance of this observation was underscored by occasional dramatic recovery of renal function after successful renal revascularization, sometimes leading to reversal of dialysis-dependent renal failure [26]. Secondly, a syndrome of rapidly developing circulatory congestion, usually associated with severe hypertension and bilateral renal artery stenosis, became identified as ‘flash pulmonary edema’. Physiologic studies in humans identified a role for left ventricular pump failure produced, in part, by severe hypertension as a precipitating factor [19, 20]. This has been designated as ‘The Pickering Syndrome’. Clinical reports indicate that circulatory congestion (i.e. congestive heart failure) in patients with ARVD carries a significant risk of death, and revascularization in this population results in improved heart failure control and a reduction in hospitalizations
for pulmonary edema [13, 19]. Recent registry data indicate a distinct mortality benefit from renal revascularization in such patients when compared with those managed without revascularization [2].

**Table 1. Prospective randomized clinical trials with PTRA without stenting versus medical therapy for hypertension associated with ARVD**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients (N)</th>
<th>Unilateral or bilateral ARVD</th>
<th>Inclusion criteria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRAS (1998)</td>
<td>Medical Tx: 30, PTRA: 25</td>
<td>Hypertension on two drugs with unilateral or bilateral disease</td>
<td>DBP ≥95 mmHg, ARVD &gt;50%</td>
<td>No BP difference in unilateral ARVD</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>But lower BP in bilateral ARVD</td>
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<td></td>
<td></td>
<td></td>
<td>No difference in renal outcomes or event-free survival</td>
</tr>
<tr>
<td>EMMA (1998)</td>
<td>Medical Tx: 26, PTRA: 23</td>
<td>Hypertension with unilateral disease only</td>
<td>ARVD &gt;60% with positive lateralization test or &gt;75% without</td>
<td>No difference in BP or CrCl, but fewer antihypertensive drug requirements in the PTRA group</td>
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<tr>
<td>DRASTIC (2000)</td>
<td>Medical Tx: 50, PTRA: 56</td>
<td>Hypertension on two drugs with unilateral or bilateral disease</td>
<td>DBP &gt;95 mmHg or creatinine rise with ACEI, ARVD &gt;50%</td>
<td>Renal outcomes not addressed</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Fewer antihypertensive drug requirements in the PTRA group</td>
</tr>
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SNRAS, Scottish and Newcastle Renal Artery Stenosis Collaborative Group; EMMA, Essai Multicentrique Medicaments versus Angioplastie; DRASTIC, Dutch Renal Artery Stenosis Intervention Cooperative; DBP indicates diastolic BP; Tx, therapy; N, number of patients.

*Two patients underwent revascularization with stent.

**FIGURE 1:** Spectrum of RVD manifestations: advances in imaging demonstrate some degree of RVD in many clinical conditions, much of which may be of minor importance. The clinical expression of RVD ranges from raising arterial pressure to ‘high-risk’ manifestations including flash pulmonary edema and progressive kidney injury (see text).

Despite a rapid increase in renal artery interventional procedures in the 1990s for treatment of ARVD, the real efficacy in decreasing systemic arterial pressure was not clear. Previous uncontrolled and unblinded assessments of angioplasty reported larger BP reductions (an average of 20 mmHg) than those observed in subsequent prospective RCTs [27, 28]. Initial trials comparing medical therapy with or without PTRA (mostly without stents) failed to show significant differences in systolic BP (SBP) between treatment groups when patients with unilateral and bilateral disease were combined (Table 1) [23–25]. Subgroup analyses of patients with bilateral disease [Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRAS) trial] indeed showed a larger drop in SBP in the PTRA group at the latest follow-up (in the range of 3–54 months) [24]. Patients in the Essai Multicentrique Medicaments versus Angioplastie (EMMA) and Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) studies who underwent angioplasty required fewer antihypertensive drugs at the end of follow-up, when compared with those managed with medical therapy alone [23, 25]. These trials generally were analyzed by ‘intention-to-treat’ methodology. One potential explanation for the modest antihypertensive effect of balloon angioplasty in these studies may relate to the substantial number of crossovers to balloon angioplasty (27–44%), occurring after randomization in the medical therapy group because of refractory hypertension or signs of progressive occlusive RVD [23, 25]. SNRAS and DRASTIC did not
identify any average difference in renal function, nor any difference in event-free survival over short periods of follow-up. A meta-analysis of these studies concluded that the effect of revascularization of renal artery produces a slight improvement in BP [29, 30].

ARVD AND RENAL FUNCTION AND CV OUTCOMES

Improved technical success with lesions that were previously difficult to treat, such as renal aorto-ostial lesions and restenotic lesions after angioplasty, became more feasible after introduction of stenting technology [31]. Promising initial results in single-armed stent studies led to further application of these procedures [32, 33]. As a consequence, the use of PTRA with stenting for ARVD expanded rapidly, particularly among interventional cardiologists in the USA between 1996 and 2000, and further up to 2005 [4]. The frequency of these procedures varied widely among different regions of the USA, reflecting broad differences among physicians, some in favor of medical therapy over revascularization or vice versa, with little consensus in how to treat ARVD [4]. The Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial and the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial were undertaken to examine the efficacy of renal revascularization in delaying the progression of renal dysfunction attributed to ARVD. The CORAL trial further sought to examine whether overall ‘CV outcomes’ would be improved by renal revascularization. Unfortunately, these trials were replete with potential confounders, which will be discussed further below.

CORAL TRIAL

The CORAL trial was designed to test whether renal artery stenting, when added to optimal medical therapy including blockade of the renin-angiotensin system, improves CV outcomes in individuals with atherosclerotic renal artery stenosis. It is the largest RCT in ARVD to date (listing 113 centers) with a total of 947 participants randomly assigned to stenting plus medical therapy (467 patients) or medical therapy alone (480 patients). Patients, at baseline, had an average estimated glomerular filtration rate (eGFR) of 58 mL/min/1.73 m². Funded by the National Heart, Lung, and Blood Institute in the USA, this trial sought to standardize evaluation of vascular stenosis by means of translesional gradient measurement and ‘core laboratory’ review. It required experienced interventionalists and hypertension specialists, and implemented protocol-driven BP and lipid control. After a mean of 43 months of follow-up, no difference was identified in the primary composite end point (death from CV or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency or the need for renal-replacement therapy) between the stent group and medical therapy-only group [35.1 and 35.8%, respectively; hazard ratio (HR), 0.94; 95% confidence interval (CI), 0.76–1.17; P = 0.58]. The SBP averaged 150 mmHg at baseline in both groups and decreased over time, associated with an increase in the number of antihypertensive drugs. Final SBP was slightly lower in the revascularization arm (−2.3 mmHg; 95% CI, −4.4 to −0.2 mmHg; P = 0.03). This difference persisted throughout the follow-up period but did not translate in improvement of clinical outcomes during this interval. Complications per vessel treated were 5.2% in the stent group. No patient in either group required dialysis within 30 days of randomization.

Limitations of CORAL: as the authors’ acknowledge, recruitment for CORAL was difficult and took longer than anticipated. Most participating centers enrolled fewer than 10 subjects over the 4–5-year period [6]. Several elements of recruitment and intervention protocols changed over time. The original intention was to include patients with severe renal artery stenosis and a SBP of 155 mmHg or higher while receiving two or more antihypertensive medications. Severe renal artery stenosis was defined by an angiographic diameter stenosis of 80 to <100% in isolation of 60–80% stenosis with a translesional systolic pressure gradient of at least 20 mmHg. Subsequently, the SBP threshold was removed. Eventually, patients with ARVD and eGFR of <60 mL/min/1.73 m² of body surface area by the modified modification of diet in renal disease formula could be enrolled with or without hypertension. Requirements for angiography, measurement of translesional gradients and embolic protection were relaxed, allowing patients to be enrolled by means of duplex ultrasonography, magnetic resonance angiography or computed tomographic angiography. At the end, the average degree of stenosis was 67% (quantified by the angiographic core laboratory) and was lower than estimates by the investigators on site, ~73%. It is likely that many of these lesions were below the threshold of 75 and 80% occlusion usually required to cause a rise in BP and a reduction in renal function in experimental studies [34]. Furthermore, 25% of the patients had reached BP goal before entry.

Specific groups, including those with congestive heart failure within 30 days, were excluded. Based upon estimates of >20 000 renal stenting procedures annually (Medicare claims data from 2000), it is clear that screening and enrollment for CORAL encompassed only a small fraction of treatment candidates, for which no contemporaneous US registry comparison is available. Registry data from >800 patients followed in the UK for atherosclerotic RVD are included in the report from Ritchie et al. [2]. Five-year mortality and CV event rates in these registry patients were far higher than those observed in CORAL, suggesting that enrolled CORAL subjects represented a group with only moderate atherosclerotic disease burden. The 5-year event rate was considerably lower even than ASTRAL, which specifically excluded those subjects that clinicians thought would definitely benefit from renal revascularization [6, 35].

The authors concluded that renal revascularization, at best, provides better BP control, but that restoration of blood flow does not change major outcomes, such as death, CV and renal events. However, these studies have limited generalizability since they included a great portion of patients with stable and lower risk disease and excluded a high-risk population for whom optimal medical therapy alone may not be effective.
**ASTRAL TRIAL**

The ASTRAL trial was a multicenter, randomized, unblinded clinical trial with a total of 806 patients enrolled (1:1) based mainly in the UK. Patients with uncontrolled hypertension (SBP = 155 mmHg) as well as unexplained renal failure with significant ARVD (>60%) identified by renal artery imaging (computed tomography, magnetic resonance or renal ultrasonography) was considered. The stated enrollment criterion—and potentially the greatest pitfall—for this study derived from the fact that the primary physician had to be uncertain of whether or not revascularization would provide a worthwhile clinical benefit. Therefore, all those patients who would definitely benefit from renal revascularization were excluded. Criteria for who would definitely benefit were not identified, nor were the numbers of patients with ARVD treated during the period of the study specified. Moreover, of all patients included, 40% had low-grade ARVD (between 50 and 70%) at the time of the angiography. A subset of these patients randomized to stenting was not treated (68 patients –17%) partly due to the lack of identifiable stenosis (33 patients –8%) or other reasons, such as refusal or withdrawal of consent, and therefore did not receive revascularization.

By the end of the 5-year study period, the SBP decreased to the same degree in both study groups. Renal and CV end points and patient survival were similar among the groups. Importantly, progression to a renal end point developed in 16–20% of both treatment arms, without measurable difference from revascularization. Most participants in this trial had unilateral ARVD (80%). A significant fraction of patients in ASTRAL had preserved renal function at baseline [creatinine <1.7 mg/dL (40% in each both groups)]. The ASTRAL trial also had a number of adverse procedure-related complications, including two deaths in the group randomized to stents, resulting in an overall complication rate of 17% [35]. The authors concluded that when compared with medical therapy, revascularization carries a substantial risk, without adding benefit with respect to renal function, BP control, CV events or mortality.

**STAR TRIAL**

In 2009, results of the STAR trial became available. This was a small randomized trial (n = 140 patients) involving 10 centers (9 in the Netherlands and 1 in France), in which patients were randomly assigned to undergo renal artery stent placement combined with medical treatment or medical treatment only. Eligibility criteria included reduced renal function [creatinine clearance (CrCl) <80 mL/min per 1.73 m²], ostial ARVD detected by various imaging studies and stable BP. This last criterion is relevant, since patients needed to have controlled BP for 1 month prior to inclusion. Not surprisingly, at the end of 2-year follow-up, the groups did not differ in BP control. Also, there was no difference in CV morbidity and mortality and no difference in progression of renal failure over 2 years—defined as a 20% or greater decrease in estimated CrCl—compared with baseline in those treated with stenting plus medication compared with those treated with medication only. An important aspect of this study relates to the fact that from 64 patients allocated to stent therapy, a substantial number (30%) did not undergo revascularization because at the time of the angiogram the ARVD lesion was found to be <50% in 18 patients and 2 were lost in follow-up. This study was underpowered due to the low rate in reaching the primary end point (>20% CrCl decline), which occurred in only 16 patients (22%) in the medication group and 10 (16%) in the stented group (including 2 who did not receive a stent) over 2 years. The study showed a small trend in favor of the revascularization group [HR, 0.73 (95% CI, 0.33–1.61)], but significance was not reached due to the wide CI. The authors of the STAR trial concluded that since a considerable number of stent-related complications occurred, including two procedure-related deaths, one death secondary to an infected hematoma and one case of deterioration of renal function resulting in dialysis, that renal stenting for ARVD may cause more harm than benefit in a community setting [36].

**HIGH-RISK PRESENTATIONS OF ARVD**

Where do these trials leave clinicians managing high-risk ARVD patients? Major differences between observational data sets and the RCT results suggest that the recent trials may not be directly applicable to patients with the highest risk presentation of ARVD. Ritchie et al. [2] reported a single-center prospective registry cohort study, with 467 patients with ARVD ≥50%, who were characterized according to clinical presentation. The groups identified as high risk had historical features endorsed by previous published guidelines (recurrent flash pulmonary edema, rapidly declining kidney function and refractory hypertension) [37]. They were compared with a low-risk population (none of those phenotypes) for the following end points: death, CV events and end-stage renal disease (ESRD). After a follow-up of 3.8 (range 1.8–5.8) years, 55% of the high-risk cohort died, 33% had a CV event and 18% reached ESRD. The decision as to whether to undergo renal revascularization (27%) was at the discretion of the managing clinician. Medically treated patients with flash pulmonary edema had an increased HR for death and CV events but not for ESRD. No increased risk for any end point was observed in patients with rapidly declining kidney function or refractory hypertension. However, those patients with the combination of both refractory hypertension and rapid loss of kidney function, medical treatment alone had increased risks for CV events and ESRD when compared with stenting. Revascularization was associated with reduced risk of death, but not CV events or ESRD, in patients with flash pulmonary edema. Major complication rate was of 4.8% in the revascularization group. A separate report combining data from treated cohorts from the UK (treated conservatively with medical therapy primarily) and Germany (treated ‘pro-actively’) indicated that recovery of some degree of kidney function in CKD Stages 4–5 was more likely with revascularization than in medically treated subjects, and perhaps more importantly, that stented
patients had a major mortality benefit in this series [38]. A published report from HERCULES, another prospective, multicenter single arm trial of 202 patients with ARVD undergoing intervention for uncontrolled hypertension (on average pre-procedural stenosis of 81%, 3.4 antihypertensive medications) found that the absolute reduction in SBP after 9 months was related to the severity of the baseline hypertension before the intervention. Of the subjects with pre-procedure SBP >180 mmHg, those experiencing a reduction in SBP fell by a mean of 48 mmHg at 9 months, while those patients whose baseline SBP was between 140 and 160 mmHg had a 23 mmHg reduction in SBP at 9 months [39]. This trial demonstrated excellent procedure-related safety, with a 30-day composite safety end point rate of 1.5%.

Despite evident clinical and survival benefits related to 'flash pulmonary edema' and some cases of rapidly progressive renal failure, overall CV mortality in the registry data from Ritchie et al. remained high. These features further emphasize the likelihood that many patients enrolled in the prospective trials including CORAL and ASTRAL carried lower atherosclerotic disease and risk burden than those reported in the 'high-risk' reports. These reports suggest that identifying 'high-risk' clinical characteristics can be used to predict benefit from revascularization, and depending upon medical therapy alone may not be the best decision for these patients.

**CONTEMPORARY MANAGEMENT OF ARVD**

**Medical therapy**

A major goal underlying the CORAL trial was to determine whether revascularization provided added benefit to pharmacologic blockade of the renin–angiotensin system regarding the risk of developing CV events. All patients were provided with an angiotensin receptor blocker (candesartan). No additional benefits from renal artery stenting were identified over the course of this trial for the patients enrolled [6, 35, 36]. We interpret these data and the results of all the prospective RCTs to support the current trend toward intensive medical therapy as the initial step. For the majority of patients with ARVD, highly effective antihypertensive drug regimens that include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) can achieve satisfactory BP levels, particularly in the setting of unilateral ARVD or minor bilateral disease. Complications such as hyperkalemia or worsening renal failure remain uncommon, consistent with the relatively stable kidney function in those trials. However, in patients with more advanced vascular compromise ACE/ARB therapy may cause progressive worsening of renal function. Work previously published by Onuigbo recommends withdrawal of ACE or ARB therapy in patients who do not have another explanation for their kidney dysfunction [40]. Moreover, the addition of available antihypertensive classes such as calcium channel blockers, β-blockers and diuretics facilitates BP control. Results from all of the prospective trials confirm that antihypertensive drug therapy after ARVD revascularization will be continued since cure for atherosclerotic renovascular hypertension is distinctly uncommon.

By definition, ARVD represents a clinical manifestation of atherosclerotic disease, and is often associated with hyperlipidemia and smoking. Therefore, the use of statins, antiplatelet therapy and lifestyle modifications such as smoking cessation, diet and exercise are paramount to reduce these risks.

Taken together, medical management of patients with ARVD is directed primarily to controlling BP and maintaining adequate kidney function as portrayed in Figure 2.

**WHEN SHOULD REVASCULARIZATION BE CONSIDERED?**

Do the results of the prospective trials indicate that renal revascularization with stenting should no longer be performed? It seems clear that many patients with moderate renovascular occlusive disease can achieve adequate BP control with stable renal function for several years. Hence, the initial concept of generally favoring pre-emptive renal revascularization in such patients cannot be supported based on current trial data. However, we interpret these results to underscore the fundamental obligation of the managing clinician to identify subsets of patients who fail medical therapy and/or progress to develop high-risk clinical phenotypes. Results published by authors of both ASTRAL and CORAL indicate major improvements in both rapidly progressive renal dysfunction and episodic pulmonary edema in high-risk patients who fail effective medical therapy. It is now likely that such patients will be identified later in the course of their disease after failure of initial medical management.

Current American Heart Association (AHA) guidelines provide a rather broad range of indications for ARVD and underscore the need of revascularization in high-risk clinical presentation such as in patients with recurrent episodes of heart failure or sudden unexplained pulmonary edema (Class I) [37]. Revascularization is deemed reasonable for BP control in the presence of accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney and hypertension with intolerance to medication (Class IIA). For preservation of renal function, the guidelines consider revascularization reasonable in the presence of progressive CKD with bilateral RVD or RVD of a solitary functioning kidney (Class IIA) and state that it may be considered in the setting of chronic renal insufficiency with unilateral ARVD (Class IIb). We have summarized a practical approach to the patient with renovascular hypertension and declining GFR in Figure 2.

In general, a degree of luminal stenosis of at least 75% is required to result in a drop in pressure across the lesion significant enough to result in a reduction of perfusion pressure and renal blood flow [41]. Accurately, identifying patients with truly hemodynamically significant stenosis can be challenging nonetheless. In clinical studies, detectable hypoxia of the cortex by blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) is not observed regularly until peak Doppler flow systolic velocities exceed 385 cm/s [42]. The best functional approach would be to confirm the presence of high-grade ARVD and evaluate the clinical phenotype. Some
non-invasive studies can be useful to define who would not benefit from a revascularization procedure: those with kidney sizes <7 cm in longest diameter, small parenchymal volume and cortical thickness or renal restive indices in segmental arteries >0.80. Patients with ARVD that seem to benefit the most are those with a short duration (6–12 months) of BP elevation and renal function deterioration prior to diagnosis. These principles conflict with the practice of a ‘wait-and-see’ approach until BP or renal function is no longer controllable. One should closely evaluate the stability of renal function and/or organ viability in the presence of progressive occlusion of the renal artery.

The procedures available for revascularization of ARVD include PTRA, stenting and surgery [43]. The latter usually entails bypass grafting of the stenosis and is usually reserved for those with complex anatomy such as early primary branching of the main renal artery, multiple small renal arteries or with highly diseased aortas or failed endovascular stents. It is also the choice if aortic surgery is performed near the renal arteries, e.g. aneurysm repair or bypass for severe aorto-iliac occlusive disease. Finally, surgical removal of a small atrophic kidney with near complete renal artery occlusion might be indicated for management resort of a so-called ‘pressor kidney’. The in-hospital mortality risk with aorto-renal bypass surgery can be as high as 7% in the USA, depending on the number and extent of comorbidities [44]. For most patients then, PTRA and stenting are the procedures of choice with high technical success and low complication rates. PTRA alone can be effective but is associated with higher restenosis rates. With stenting, the initial success rate is nearly 90% and restenosis rate is 15–20% at between 6 and 12 months [43, 45]. The overall complication rate is in the order of 5–17% and serious complications such as renal artery perforation, occlusion and embolization are encountered in 5% [6, 35, 36, 45].

Taken together, current practices for endovascular revascularization with stenting has a success rate comparable to surgical revascularization (close to 100%) with lower morbidity and mortality.

RENAL INJURY IN ARVD: THE ROLE OF THE NEPHROLOGIST

Among the troublesome observations from both CORAL and ASTRAL was the development of ‘renal end points’ in 16–22% of participants, regardless of specific treatment. These data reinforce the premise that some critically under-perfused kidneys lose GFR. Perhaps more importantly, restoring blood vessel patency with renal artery stenting does not commonly lead to recovery of function, an observation also well established in previous observational reports [32]. Recent studies in both experimental and human ARVD indicate that kidneys can ‘adapt’ to moderate reductions in blood flow without necessarily developing tissue hypoxia as measured by BOLD-MRI [46]. There are obvious limitations to these ‘adaptive’ changes, and more severe occlusive disease ultimately produces cortical hypoxia associated with microvascular rarefaction and inflammatory injury. Renal vein sampling from human
ARVD indicates large efflux of pro-inflammatory cytokines (TNF-α, interleukin-6 and neutrophil gelatinase-associated lipocalin) [47, 48]. Technically successful renal stenting can produce a rise in blood flow and reversal of tissue hypoxia, but at some point fails to affect these inflammatory cytokine signatures [49]. Clinical biopsy material from post-stenotic kidneys identifies widespread tissue activation of transforming growth factor and accumulation of tissue macrophages [50]. These observations indicate that although reductions in blood flow and tissue hypoxia may initiate vascular rarefaction and loss of GFR, activation of inflammatory pathways eventually becomes no longer dependent either upon hypoxia or reduced blood flow alone. As a result, renal revascularization only occasionally restores GFR, a recurrent finding in clinical experience and the RCTs outlined in Table 2. Improvement in GFR after revascularization is an important predictor of long-term survival in azotemic patients [51]. Current research is directed toward identifying pathways leading to irreversible kidney injury due to vascular occlusion. Recent experimental studies suggest that macrophage infiltration and polarity are major determinants of renal tubular recovery and regeneration after acute kidney injury (AKI) [52–54]. They also appear to play a pivotal role in the long-term transition from AKI to progressive CKD [55]. Administration of cell-based therapy (mesenchymal stromal/stem cells) known to modulate inflammation and macrophage polarization is capable of stimulating angiogenesis and recovery of function in a swine and murine models of ARVD [56]. Whether adjunctive therapy with cell-based measures, or perhaps modification of mitochondrial reactive oxygen species sometimes associated with reperfusion injury might improve long-term renal outcomes as seen in experimental models [57], merit further investigation.

What should the role of the nephrologist become as related to atherosclerotic RVD? To ignore progressive, critical loss of renal function beyond vascular occlusion seems unwarranted, despite the results of the RCTs summarized above. It seems likely that many patients with ARVD will escape early detection as a result of diminished enthusiasm for vascular intervention. For many patients this will be entirely appropriate, as suggested by CORAL and the other cohorts. The use of renal revascularization has fallen enormously in the UK after publication of ASTRAL [2]. We anticipate that more patients will surface to subspecialty attention as they develop evident progressive disease associated with advancing clinical manifestations including worsening CKD and/or pulmonary edema out of proportion to cardiac disease. In some cases, renal function may improve and/or stabilize after withdrawal of renin–angiotensin system blockade, which some argue should be an essential step in identifying critical ARVD [58]. The role of the nephrologist will be to identify this subgroup of patients at risk of developing ischemic nephropathy and other high-risk manifestations of ARVD at a time when they still may benefit

### Table 2. Randomized clinical trials: PTRA with stenting versus medical therapy alone for renal function and/or CV outcomes with ARVD

<table>
<thead>
<tr>
<th>Trials</th>
<th>N</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcomes</th>
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<tr>
<td>STAR (2009)</td>
<td>Med: 76</td>
<td>Patients with impaired renal function, ostial ARVD detected by various imaging studies and stable BP on statin and aspirin</td>
<td>ARVD &gt;50%</td>
<td>Kidney &lt;8 cm and, renal artery diameter &lt;4 mm, eCrCl &lt;15 mL/min per 1.73 m², DM with proteinuria (&gt;3 g/day), malignant hypertension</td>
<td>No difference in GFR decline (primary end point ≥20% change in clearance), but many did not undergo PTRA due to ARVD &lt;50% on angiography</td>
</tr>
<tr>
<td>ASTRAL (2009)</td>
<td>Med: 403</td>
<td>Patients with uncontrolled or refractory hypertension or unexplained renal dysfunction with unilateral or bilateral ARVD on statin and aspirin</td>
<td>CrCl &lt;80 mL/min/1.73 m²</td>
<td>Controlled BP 1 month before inclusion</td>
<td>Serious complication in the PTRA group</td>
</tr>
<tr>
<td>CORAL (2014)</td>
<td>Med: 480</td>
<td>Hypertension on two or more antihypertensives or CKD Stage ≥3 with ARVD with unilateral or bilateral disease on statin</td>
<td>SBP &gt;155 mmHg, at least two drugs</td>
<td>High likelihood of PTRA in &lt;6 months</td>
<td>No difference in BP, renal function, mortality, CV events (primary end point: 20% reduction in the mean slope of the reciprocal of the serum creatinine level)</td>
</tr>
<tr>
<td>PTRA: 64</td>
<td></td>
<td></td>
<td></td>
<td>Without ARVD, previous ARVD-PTRA FMD</td>
<td>Substantial risk in the PTRA group</td>
</tr>
<tr>
<td>PTRA: 403</td>
<td></td>
<td></td>
<td></td>
<td>Creatinine &gt;4.0 mg/dL, kidney length &lt;7 cm and use of &gt;1 stent FMD</td>
<td>No difference in death from CV or renal causes. Modest improvement in SBP in the stented group</td>
</tr>
<tr>
<td>PTRA: 467</td>
<td></td>
<td></td>
<td></td>
<td>ARVD &gt;60% Subsequent changes included that the SBP &gt;155 mmHg for defining systolic hypertension was no longer specified as long as the patient had CKD Stage 3</td>
<td>Total 26 complications (5.5%)</td>
</tr>
</tbody>
</table>

SBP indicates, systolic BP; Tx, therapy; N, number of patients; CV, cardiovascular; FMD, fibromuscular dysplasia.
from revascularization with or without adjunctive maneuvers. Nonetheless, recognizing these patients and better defining the potential for clinical and renal recovery is a critical unmet need. It behooves the nephrology community to be especially alert to this condition after the publication of CORAL.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

ABSTRACT

Focal and segmental glomerulosclerosis (FSGS) is a common histopathological lesion that can represent a primary podocytopathy, or occur as an adaptive phenomenon consequent to nephron mass reduction, a scar from a healing vasculitic lesion, direct drug toxicity or viral infection among other secondary causes. Thus, the presence of an FSGS lesion in a renal biopsy does not confer a disease diagnosis, but rather represents the beginning of an exploratory process, hopefully leading ultimately to identification of a specific etiology and its

Focal segmental glomerulosclerosis: towards a better understanding for the practicing nephrologist

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