Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Medical therapy for renal artery stenosis

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The management of renal artery stenosis remains controversial with randomized trials suggesting that revascularization is no better than medical therapy. Thus all patients with atheromatous renovascular disease should be treated with medical therapy. However optimal therapy has not been clearly defined by atheromatous renovascular disease trials; despite this, there are data to support the use of several pharmacologic agents among this group of patients. Such a regimen should include an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, a β-blocker, a statin and aspirin. Additional therapies will often be required and need to be individualized to a given patient based upon comorbid conditions.

Keywords: β-blocker • angiotensin-converting enzyme inhibitor • angiotensin-receptor blocker • renal artery stenosis • statins

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Renal artery stenosis may be due to fibromuscular dysplasia or most commonly atherosclerosis. Atherosclerotic renal artery stenosis, or atheromatous renovascular disease (ARVD), is a frequent manifestation of atherosclerosis and is commonly encountered in patients with other forms of atherosclerotic disease, such as coronary artery disease, peripheral arterial disease and stroke as detailed in Table 1 [1–7]. Despite its high prevalence, the management of atherosclerotic ARVD remains controversial. Several retrospective and cohort studies have demonstrated some benefits of stenting for ARVD [8–15]. However, a total of five randomized trials comparing revascularization to medical therapy for ARVD have not demonstrated revascularization to be beneficial [16–20]. The results of these randomized trials are summarized in Table 2. As the role for revascularization in ARVD is still being defined, it is important to understand how to provide patients with optimal medical management.

When determining the medical management strategy for patients with ARVD it is important to keep the goals of therapy in mind. ARVD is linked to both hypertension and renal insufficiency, so medical therapies should be aimed at lowering blood pressure and preserving renal function. Specifically renal insufficiency may be what prompts an investigation for ARVD. Additionally, ARVD is also related to the progression of baseline renal insufficiency once it has been diagnosed. In addition to hypertension and renal insufficiency, ARVD is associated with increased cardiovascular morbidity and mortality [21–24]. This association between ARVD and worse cardiovascular outcomes has been known for decades. In 1968, Wollenweber reported that the 5-year mortality among ARVD patients was 33%, compared with 8% among patients without ARVD [22]. In a study of patients undergoing renal angiography at the time of cardiac catheterization Conlon reported a mortality rate of 35% among patients with ARVD, compared with 14% in those without ARVD [21]. In an analysis of patients age 67 or older, ARVD was associated with significantly higher rates of coronary artery disease (303.9 vs 73.5 events per 1000 patient years), peripheral arterial disease (258.6 vs 52.2 events per 1000 patient years), congestive heart failure (194.5 vs 56.3 events per 1000 patient years), cerebrovascular

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Table 1. Prevalence of renal artery stenosis among patients with other forms of atherosclerosis.

Condition (no. of patients [n])	ARVD prevalence (%)
Stroke (3)	10
Carotid artery disease (7)	19
Coronary artery disease (1)	22
Myocardial infarction (2)	12
Abdominal aortic aneurysm (5)	20
Iliac and lower extremity occlusive disease (4)	40

ARVD: Atheromatous renovascular disease.

events (175.5 vs 52.9 events per 1000 patient years) and death (166.3 vs 63.3 events per 1000 patient years) [25]. Thus, the goal of medical therapy in ARVD should be to reduce these high event rates.

Pathophysiologic effects of renal artery stenosis

Atheromatous renovascular disease leads to activation of the renin–angiotensin–aldosterone system via neuroendocrine activation of juxtaglomerular cells, which results in the release of renin. Renin cleaves angiotensinogen producing angiotensin I, which is then converted to angiotensin II by a variety of pathways, most notably angiotensin-converting enzyme (ACE). Angiotensin II has multiple adverse effects on the cardiovascular system [26]. Specific effects of angiotensin II include endothelial dysfunction, endothelial cell apoptosis, oxidation of low-density lipoprotein, vasoconstriction, aldosterone release, antidiuretic hormone release and metalloproteinase production [27–30]. Angiotensin II can also result in left ventricular hypertrophy and increased plasma norepinephrine levels [31]. All of these effects of angiotensin II combine to increase adverse cardiovascular events.

In addition to cardiovascular effects, angiotensin II also leads to direct tubulointerstitial injury [32]. This worsens the development of chronic renal insufficiency, which is linked to worse outcomes. Among patients with ARVD treated with stenting, Dorros found that impaired baseline renal function increased long-term mortality. Specifically 4-year mortality increased from 15% in patients with normal renal function, to 22% in patients with mild renal insufficiency and 51% in patients with severely impaired renal function [12]. A similar trend was demonstrated by Kennedy even when the rates of coronary artery disease and other comordities were the same at baseline [33].

Given the potential impact of renin–angiotensin–aldosterone system activation on the cardiovascular system, medical therapy that inhibits this pathway is a biologically attractive option. Therapies targeting lipids may also be beneficial for these patients, as such therapies may mitigate the progression of atherosclerosis caused by the oxidative effects of angiotensin II on lipids. Additionally due to the neuroactivation of the sympathetic nervous system, β-blockers may have a special role in managing patients with ARVD. Each of these therapies will be discussed in detail in the following sections.

Renin–angiotensin–aldosterone system as a therapeutic target

■ ACE inhibitors

There are several therapeutic classes of drugs that target the renin–angiotensin–aldosterone system. Among these are ACE inhibitors, which have a demonstrated mortality benefit among patients with congestive heart failure, as well as among patients with established coronary artery disease [34,35]. Traditionally ACE inhibitors have been either avoided or used with great caution in patients with ARVD due to concerns about worsening

Table 2. Randomized trials of revascularization versus medical therapy in renal artery stenosis.

Study	No. of subjects (n)	Strategy compared	Follow-up (months)	Primary outcome	p-value	Ref.
EMMA	49	PTA vs medicine	6	24-h ambulatory BP	NS	[16]
Scottish and Newcastle Renal Artery Stenosis collaborative group	55	PTA vs medicine	3–54	Change in SBP (bilateral disease; 34 vs 8 mmHg PTA better)	0.018	[17]
				Change in SBP (unilateral disease)	NS	
				Change in serum creatinine	NS	
DRASTIC	106	PTA vs medicine	12	Change in SBP and DBP	NS	[18]
STAR	140	Stenting vs medicine	24	≥20% decrease in estimated creatinine clearance	NS	[19]
ASTRAL	806	PTA ± stenting vs medicine	60	Change in renal function (trend favors revascularization)	0.06	[20]

BP: Blood pressure; DBP: Diastolic BP; NS: Not significant; PTA: Percutaneous transluminal angioplasty; SBP: Systolic BP.

renal function after the initiation of therapy. Despite this caution data are emerging that ACE inhibition may offer significant advantages among patients with ARVD.

The primary concern with ACE inhibitor use in ARVD is the potential for inducing acute renal failure. While this is a concern that merits careful laboratory monitoring following the initiation of therapy, it should not preclude the use of ACE inhibitors among patients with ARVD. Overall the incidence of acute renal failure following the introduction of an ACE inhibitor among patients with ARVD is less than 10% [36,37]. More commonly, what is seen is a rise in serum creatinine that is typically reversible with drug cessation [37]. While acute renal failure has been defined variably in different studies, there are data suggesting that a rise of up to 30% in serum creatinine may be seen within the first 2 months of initiating therapy and that despite this rise, there is long-term preservation of renal function [38]. Moreover, acute renal failure following the initiation of an ACE inhibitor can occur without the presence of ARVD. This decrease in renal function occurs when the glomerular filtration rate is dependent on angiotensin II-mediated vasoconstriction of efferent arterioles. This may occur in low output heart failure, as well as longstanding hypertension, in addition to ARVD [39].

Among patients with ARVD, ACE inhibitors have been shown to be more effective at blood pressure lowering than other strategies. Franklin and Smith compared enalapril and hydrochlorothiazide to a regimen of timolol, hydralazine and hydrochlorothiazide in patients with documented ARVD [40]. They demonstrated that enalapril-based therapy resulted in better control of both systolic and diastolic blood pressure than the standard three drug regimen with a low rate of increase in serum creatinine. Experimental evidence also suggests that ACE inhibitors may be better at controlling blood pressure than calcium channel blockers in the setting of ARVD [41].

In addition to improved blood pressure lowering, ACE inhibitors appear to provide survival benefit among patients with ARVD. Losito and colleagues evaluated 190 patients with ARVD treated with revascularization (136 patients) and medical therapy (54 patients), with an average follow up of 4.5 years [42]. A similar proportion of patients were treated with ACE inhibitors in the revascularization and medical therapy groups. ACE inhibition was associated with improved survival in both groups, and the effect was greater among those treated medically. Hackam and colleagues also evaluated the effect of ACE inhibitors on outcomes among patients with ARVD and demonstrated a mortality benefit, as well as a decreased rate of hospitalization for heart failure [43]. Thus given this survival advantage, ACE inhibitors should be considered as one of the components of 'optimal medical therapy' for patients with ARVD.

Angiotensin-receptor blockers

Angiotensin-receptor blockers (ARBs) represent another pharmacologic class of drugs that target the renin–angiotensin–aldosterone system. As the name implies, these agents directly block the action of angiotensin II at the receptor sites. Although introduced more recently than ACE inhibitors, ARBs improve clinical outcomes, in particular cardiovascular outcomes, among multiple subsets of patients, including those with congestive heart failure and established coronary artery disease [44–47]. In a study by Hackam, ARBs were found to reduce mortality, as well as hospitalization for heart failure, just as ACE inhibitors did [43]. Interestingly ARBs had a lower hazard ratio (0.50) than ACE inhibitors (0.74) for the primary composite end point of death, myocardial infarction or stroke [43]. Further data regarding ARBs on survival and other cardiovascular outcomes will come from the ongoing CORAL trial, which has completed enrollment and continues in follow-up [48]. In CORAL, treatment with the ARB candesartan is considered first-line, with ACE inhibitor therapy used as a substitute among candesartan-intolerant patients.

In addition to a survival benefit, ARBs may help stabilize the degree of stenosis among patients with ARVD. Cianci demonstrated this in an observational study in which 53 patients with ARVD were treated with revascularization and 40 patients were treated with medical therapy only [49]. At 12 months of follow up, among the medically treated patients the percent stenosis remained stable in 78% of patients treated with an ARB, compared with 57% treated with an ACE inhibitor and 54% treated with a calcium channel blocker ($p < 0.05$). While provocative, the idea that ARBs may prevent atherosclerosis progression needs to be further evaluated; however, due to the blunting of the atherosclerotic effects of angiotensin II described above it is biologically plausible.

As with ACE inhibitors, there is some risk in precipitating acute renal failure when initiating therapy with an ARB [50]. Thus careful laboratory monitoring should take place following the initiation of an ARB; however, they should not be withheld for ARVD patients, as they appear to offer many benefits. Indeed just as with ACE inhibitors, ARBs have been shown to have renal protective effects [51–53].

ACE inhibitor or ARB

To date there is a greater accumulation of evidence supporting the use of ACE inhibitors for ARVD than there is for ARBs, although there are limited data that suggest ARBs may perform slightly better. Due to the lack of direct comparative data, the choice of which agent to use is up to the clinician. A number of factors may impact this choice such as side effects, as ARBs may be somewhat better tolerated than ACE inhibitors. Cost

may also be a choice as many generic ACE inhibitors are available for approximately US$5/month, whereas most ARBs remained branded agents and are more expensive. While the choice of ACE inhibitor or ARB may remain unsettled, based on current data the use of one of these agents should be used routinely in patients with ARVD.

Other agents that target the renin–angiotensin–aldosterone system

In addition to ACE inhibitors and ARBs, the renin–angiotensin–aldosterone system may be targeted upstream by direct renin inhibitors or downstream by aldosterone antagonists. Direct renin inhibition is a relatively new therapeutic modality and aliskerin is the first agent in this class approved for use in the USA [54]. To date there are no data on the use of direct renin inhibitors in ARVD; however, there may be potential benefit with this approach and studies evaluating this approach should be pursued. Direct aldosterone inhibition has been proven beneficial in multiple clinical settings and help prevent progression of renal disease in general [55]. To date there are no data evaluating aldosterone blockade in ARVD, but it is another concept that deserves investigation. Until further data are available the routine use of either of these strategies for patients with ARVD cannot be recommended.

β-blockade in renal artery stenosis

In addition to activation of the renin–angiotensin–aldosterone system, patients with ARVD have increased sympathetic activation [56–58]. Johansson found norepinephrine levels to be threefold greater among patients with ARVD as compared with healthy controls [56]. This suggests that β-blockade may be a useful strategy in managing patients with ARVD. Unfortunately the evidence evaluating this strategy is limited. Cianci demonstrated that β-blockers may also be beneficial. Specifically patients treated with an ARB and a β-blocker were more likely to have stabilization of the degree of stenosis than patients treated with an ARB and a calcium channel blocker or an ARB and an ACE inhibitor [49]. Interestingly patients treated with ARB monotherapy had more stabilization of stenosis than those treated with any combination therapy. While speculative, this may be due to the fact that patients requiring combination therapy to achieve blood pressure control are 'sicker' and therefore at a greater risk for progression of stenosis. Although this study is limited by small sample size, it does suggest an area to pursue further studies.

In a pilot study, Duranay and colleagues evaluated the effects of nebivolol in patients with ARVD who had undergone revascularization [59]. A total of 33 patients were randomized to either nebivolol or standard treatment following percutaneous renal artery revascularization, although only 24 of these patients were ultimately included in the analysis. The estimated glomerular filtration rate improved among patients treated with nebivolol whereas it was unchanged in the standard therapy group. Additionally the patients treated with nebivolol had a significant decrease in proteinuria, which was not seen in the standard treatment group, although the nebivolol group had a greater degree of proteinuria at baseline. While intriguing these data need to be confirmed in a larger study. Additionally, it is unclear if this may be a class effect of β-blockers or specific benefit of nebivolol. As most β-blockers are now generic agents, it is unlikely that the question regarding whether this is a unique benefit to nebivolol or a class effect will be answered.

Although the data are limited, it does seem that β-blockers may have a role to play in patients with ARVD. This role may also go beyond benefits specific to ARVD itself, as many of these patients have comorbid cardiovascular conditions such as coronary artery disease, prior myocardial infarction or congestive heart failure for which β-blockers are indicated [60].

Additional antihypertensive agents

In addition to interruption of the renin–angiotensin–aldosterone-system and β-blockade, patients with ARVD will often require additional agents to adequately control blood pressure. In these cases the additional therapies will often be targeted to specific patient needs based upon other comorbid conditions. Patients with congestive heart failure may benefit from the use of a diuretic, whereas patients with coronary artery disease and angina may benefit from the addition of a calcium channel blocker. While the choice of additional agents must be individualized, the goal should be to adequately control blood pressure.

Statin therapy

In addition to the drugs described above patients with ARVD may benefit from the cholesterol-lowering therapy and, in particular, statins. As with other forms of atherosclerosis, patients with ARVD have a target low-density lipoprotein cholesterol level of 70 mg/dl [61]. There are a number of benefits from lowering of low-density lipoprotein cholesterol with statins including improved survival, slowed progression of ARVD and stabilization of renal function.

Data from SOCRATES have been analyzed to identify factors affecting survival following stenting for ARVD [62]. The patients from SOCRATES were followed for up to 10 years. Among these patients lipid-lowering therapy, often with statins, was associated with a decreased mortality with a hazard ratio of 0.69. These data are limited by the fact that details about lipid levels and specific treatment regimens are not provided. Silva and colleagues have also reported a mortality benefit with

statin use in medically treated patients with ARVD [63]. Specifically the mortality among statin-treated patients was 6% compared with 36% among those not treated with a statin, despite very similar lipid profiles [63].

In addition to improving survival, statins may slow the progression of renal insufficiency seen in patients with ARVD. This is another parameter that Silva and colleagues assessed. Among patients treated with statins, 7% had a doubling of serum creatinine or the initiation of dialysis compared with 39% of patients who were not treated with a statin [63].

In addition to survival and renal function advantages, statin therapy may also slow the progression or even lead to the regression of ARVD [64,65]. Cheung and colleagues have demonstrated that patients taking statins were less likely to have progression of the degree of ARVD as documented on baseline and follow-up angiograms with an average of 28 months between the angiograms [64]. Specifically the relative risk of progression with statin treatment was 0.28, compared with no statin treatment. Furthermore, while angiographic regression of ARVD occurred in only 12% of vessels, regression was much more likely in patients treated with a statin. Specifically 83% of patients who demonstrated regression were treated with a statin.

While there are limited study data demonstrating the benefits of statin therapy in patients with ARVD, there are animal model data that help support the biologic plausibility of the effects of statins. Chade and colleagues have demonstrated that renal fibrosis is reduced with simvastatin in a pig model of renovascular disease [66]. Furthermore Zhu and colleagues have shown that simvastatin prevents coronary microvascular remodeling in renovascular hypertensive pigs [67]. These findings provide some scientific basis for the clinical observations described above.

Owing to their ability to decrease mortality, stabilize renal function and slow the progression of ARVD, statins should be considered a key component of 'optimal medical therapy' for patients with ARVD. Although specific data are not available, when selecting a statin for a patient with ARVD a high dose of a highly potent statin seems reasonable. Ultimately, the choice of statin may depend upon a number of factors such as cost, as well as patient tolerability, as patients will sometimes be able to tolerate one statin, but not another.

Additional therapies

Other therapies that may provide benefit to patients with ARVD include aspirin. Aspirin has proven beneficial for many manifestations of atherosclerotic disease and should be included in the treatment regimen for most patients with ARVD. Specifically aspirin has been shown to reduce adverse cardiovascular events among patients with peripheral manifestations of atherosclerosis [68]. Other antiplatelet agents, such as thienopyridines, have not been tested for benefit among patients with ARVD. Thus prolonged use of thienopyridine therapy in this patient population cannot be specifically endorsed. However, ARVD does not represent a contraindication to the use of these agents especially if there is another compelling indication such as acute coronary syndrome or a coronary artery stent placement.

In addition to the specific medical therapies that have already been addressed, patients with ARVD should be counseled to make lifestyle changes to treat the atherosclerotic process. This includes tobacco cessation among patients using it and in this regard there is a role for therapies such as nicotine replacement, varenicline and bupropion. Clinicians also need to ensure appropriate glycemic control among diabetic patients. Additionally, all patients should be counseled to make therapeutic lifestyle changes related to diet and exercise as outlined in the National Cholesterol Education Program Adult Treatment Panel III statement [61].

Future perspective

As ongoing ARVD trials such as CORAL are completed more data about the optimal medical regimen for ARVD will become available. It is likely that information will become available about the utility of direct renin inhibitors and possibly aldosterone antagonists as well. While clinical trials will provide some insight in how to best treat patients with ARVD, the overall population will remain heterogeneous with a variety of comorbid conditions. In this sense there will be a need to personalize a treatment strategy to each patient. One emerging technology which may ultimately help personalize the optimal medical regimen for a patient with ARVD is genetic profiling. Already genetic tests are available to evaluate how an individual will metabolize drugs such as thienopyridines. It is likely that this technology will continue to expand and may ultimately help make the choice between an ACE inhibitor or an ARB and it may even help physicians select the optimal drug in a class for an individual.

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Executive summary

- The management of atheromatous renovascular disease (ARVD) remains controversial with regard to the role of medical therapy versus revascularization.
- Due to activation of the renin–angiotensin–aldosterone system in patients with ARVD, use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker should be considered first-line treatment; however, renal function must be monitored after the initiation of therapy.
- ARVD is associated with increased sympathetic activation. Thus β-blockers may be of particular benefit.
- Statin therapy can improve multiple outcomes among patients with ARVD and should be considered for routine use, regardless of lipid levels.
- Aspirin should be included as part of the optimal medical regimen for ARVD.
- Other therapies may be needed and should be individualized for a given patient with ARVD based upon comorbid conditions.

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