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Endovascular Versus Medical Therapy for Atherosclerotic Renovascular Disease

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Abstract

The diagnosis of renal artery stenosis (RAS) has become increasingly common in part due to greater awareness of ischemic renal disease and increased use of diagnostic techniques. Over 90 % of RAS cases are caused by atherosclerotic renovascular disease (ARVD). Patients with ARVD are at high risk for fatal and nonfatal cardiovascular and renal events. The mortality rate in patients with ARVD is high, especially with other cardiovascular or renal comorbidities. Recent clinical studies have provided substantial evidence concerning medical therapy and endovascular

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Compliance with Ethics Guidelines

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Conflict of Interest Mark Shipeng Yu, David A. Folt, Christopher A. Drummond, Steven T. Haller, Emily L. Cooper, Pamela Brewster, Kaleigh L. Evans, and Christopher J. Cooper declare that they have no conflict of interest.

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interventional therapeutic approaches for ARVD. Despite previous randomized clinical trials, the optimal therapy for ARVD remained uncertain until the results of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial were released recently. CORAL demonstrated that optimal medical therapy was equally effective to endovascular therapy in the treatment of ARVD. Clinicians can now practice with more evidence-based medicine to treat ARVD and potentially decrease mortality in patients with ARVD using optimal medical therapy.

Keywords

Renal artery stenosis; Atherosclerotic renovascular disease; Ischemic nephropathy; Chronic kidney disease; Stent; Angioplasty; Medicaltherapy; Interventional therapy

Introduction

The diagnosis of renal artery stenosis (RAS) has become increasingly common. This is in part due to the increased awareness of ischemic renal disease among clinicians as well as the increasing use of noninvasive diagnostic imaging techniques such as magnetic resonance angiography, computed tomography (CT) angiography, and duplex sonography [1•, 2•]. Over 90 % of RAS cases are caused by atherosclerotic renovascular disease (ARVD). ARVD was found in about 7 % of the general population older than 65 years of age when a liberal duplex velocity threshold of 1.8 m/s was used during community screening [3, 4]. The prevalence of ARVD in patients with comorbidities is even higher [5], reaching 20 % in patients with hypertension and diabetes, 25.3 % in patients with peripheral vascular disease, and 54.1 % in patients with congestive heart failure. In aggregate, these studies suggest that ARVD is common in the elderly. In this review, endovascular interventional therapy and optimal medical therapy for ARVD will be reviewed using evidence from recent clinical studies.

RAS Is Associated with High Rates of Adverse Cardiovascular and Renal Events

Appropriate management of ARVD is important because people with ARVD are at high risk for fatal and nonfatal cardiovascular and renal events. Johansson and colleagues found that the risk ratio (vs. age-matched controls) was 3.3 for overall mortality and 5.7 for cardiovascular mortality in a cohort of patients with RAS lesions exceeding 50 % [6]. In a Medicare analysis, Kalra and coworkers found the annual mortality rate in patients with ARVD to be 16.3 %, which was three times higher than that observed in patients without ARVD [7]. In this regard, Dorros and colleagues identified a strong relationship between chronic kidney disease and mortality in patients undergoing stent revascularization [8]. Similarly, Kennedy et al. reported a high rate of fatal and nonfatal events that was strongly related to the severity of chronic kidney disease in those who were treated with stent revascularization [9].

Patients with ARVD are 6 to 28 times more likely to die of a cardiovascular event than to develop end-stage renal disease (ESRD) [1•, 10]. The number of individuals who progress

to ESRD is historically difficult to measure accurately; however, failure to detect RAS is likely in patients diagnosed with ESRD and underlying causality may be attributed to hypertensive nephrosclerosis. In a review of patients starting renal replacement therapy, Fatica et al. found that the prevalence of renovascular disease ranged from 1.4 to 2.1 % [11]. Scoble et al. prospectively performed renal arteriography in all new patients with ESRD during an 18-month period and determined RAS to be the cause of ESRD in 6 % of the cohort and in 14 % of the subset older than 50 [12]. Appel and coworkers suggest that renovascular disease accounts for 11 % of all patients with ESRD older than 50 years of age and 20 % of ESRD cases among whites older than 50 [13]. Additionally, Guo et al. found that ARVD patients on dialysis have an annual mortality rate of 36 % [14]. These data indicate that ARVD leads to ESRD more often than generally appreciated by clinicians and that it is associated with a heightened risk of mortality in those with and without ESRD.

Medical Therapy for Atherosclerotic Renovascular Disease

The ultimate goal of ARVD treatment is the reduction of mortality (mainly cardiovascular and renal mortality) and morbidity (adverse cardiovascular and renal events) and prevention of complications. Medical therapy is the cornerstone of care for patients with ARVD. There is, unfortunately, little comparative data between different regimens of medical therapy. Clearly, anti-atherosclerotic therapies are indicated, such as lipid-lowering, antiplatelet, hypoglycemic, and antihypertensive medications. Lifestyle modification is also important such as smoking cessation, exercise, and weight reduction. Smoking is not only a cardiovascular risk factor but also a risk factor for chronic kidney disease (CKD) and increases the risk of nephropathy progression [15]. All patients with cardiovascular disease or cardiovascular disease equivalents are high-risk patients for adverse cardiovascular events. Importantly, with optimal medical treatment of ARVD, the mortality rate may be decreased, at least in the setting of cohorts selected for participation in clinical trials, as shown by the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial (average annual mortality rate of 8 %) [16] and the more recent CORAL trial (average annual mortality rate of 4 %) [1•].

Blood Pressure Control

Optimal blood pressure (BP) in the setting of ARVD is not known, as there is insufficient evidence to set a specific target for patients with this condition. Since ARVD is considered a coronary artery disease equivalent [17•], imparting a high risk of cardiovascular disease and related mortality, it is reasonable to keep well-controlled blood pressure in these patients [18•]. The BP goal according to the 2014 guidelines for hypertensive patients with CKD with or without diabetes is less than 140/90 mmHg [19•]. However, the most recent CORAL trial established a goal of 140/80 in patients without diabetes or CKD and 130/80 mmHg in those with these comorbidities, which was consistent with clinical care guidelines at the time when the study was conducted. Some have hypothesized that patients with severe RAS might require higher blood pressures to maintain adequate blood flow across a stenosis; however, very low rates of progression to ESRD in medically managed patients in CORAL and other studies with medically managed study groups have been argued against pursuing such a strategy. Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor

blocker (ARB), calcium channel blockers, and beta-blockers are all reasonable options for hypertension therapy in ARVD, with the caveats detailed for ACEI/ARB treatment below [18•, 20].

ACEI/ARB in Treatment of ARVD

Functionally significant RAS leads to the activation of the renin–angiotensin–aldosterone axis. Interruption of angiotensin-dependent efferent arteriolar vasoconstriction may cause reductions in glomerular pressure and result in hemodynamically mediated acute renal failure [21]. Decreases in renal blood flow in animal models of RAS can be blunted by angiotensin receptor blockers, suggesting that angiotensin II plays a role in renal ischemia [22]. However, it has been suggested that ACEI and ARBs may accentuate renal atrophy that occurs in the two-kidney–one-clip model used experimentally to achieve the effects of RAS, independent of the effects of lowering systemic blood pressure [23, 24]. Recently, large observational studies by Hackam et al., Chrysochou et al., and Losito et al. [25, 26•, 27] have shown the potential benefits of ACEI/ARB in reducing mortality and morbidity in patients with ARVD. Hackam et al. followed a population-based cohort comprising 3570 patients with ARVD for 2.0 years (SD 2.1) in Canada [25]. In this study, treatment with ACEI/ARB was associated with lower cardiovascular event rates (10 vs. 13 %) and need for dialysis (1.5 vs. 2.5 %) at the expense of an increased risk of acute kidney injury hospitalizations (1.2 vs. 0.6 %). Acute renal failure was significantly more common in patients with diabetes and chronic kidney failure or on loop diuretics [25].

In another prospective observational study of ARVD subjects conducted by Chrysochou and colleagues, the mortality rate was significantly lower [hazard ratio (HR) 0.61; 95 % confidence interval (CI) 0.40–0.91; $p=0.02$] with ACEI/ARB treatment [26•]. In this study, 92 % of patients (357 of 378) tolerated ACEI/ARB, including 78.3 % (54/69) of patients with bilateral renal artery stenosis, which was greater than 60 % or entailed total occlusion, and 4 cases with RAS in a solitary kidney. For patients who were intolerant to ACEI/ARB before or after enrollment and underwent percutaneous renal revascularization, all but one became tolerant to ACEI/ARB, with the only failure due to an allergic rash. In 71 of these 74 patients who were intolerant to ACEI/ARB, the intolerance was documented to be deterioration of renal function. In this study, there was only one case with irreversible elevation of creatinine associated with ACEI/ARB use. A review of 12 randomized controlled trials of ACEI/ARB use concluded that increases in creatinine >30 % should be the cutoff for discontinuation of treatment; however, this was not specific to patients with ARVD [28]. In most cases, increases in serum creatinine usually return to baseline levels upon cessation of ACEI/ARB use in patients with ARVD [26•, 29].

In summary, ACEI/ARB treatment in observational studies is associated with a significant mortality and morbidity benefit in patients with ARVD; however, it is also associated with a slightly elevated risk of acute renal failure. The usage of ACEI/ARB should be considered for all patients with ARVD [26•], although monitoring of renal function and electrolytes should be undertaken when these drugs are started. Patients with diabetes and chronic kidney failure or on loop diuretics need to be closely monitored for kidney function due to the elevated risk of acute renal failure.

Statins

In patients with ARVD, treatment with 3-hydroxy-3-methyl-glutaryl-coenzyme (HMG-CoA) reductase inhibitors may particularly improve clinical outcomes by reducing mortality and morbidity. Statins are the mainstay of treatment for all atherosclerotic vascular disease [30•, 31]. According to 2014 guidelines on cholesterol management, four major groups were identified as benefiting from statin therapy, in whom the atherosclerotic cardiovascular disease (ASCVD) risk reduction clearly outweighs the risk of adverse events: (1) clinical ASCVD, (2) LDL-C 190 mg/dL, (3) diabetes ages 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD, and (4) LDL-C 70 to 189 mg/dL ages 40 to 75 years and estimated 10-year ASCVD risk $\geq 7.5\%$ [32•]. Peripheral arterial disease presumed to be of atherosclerotic origin, together with several other disorders, qualifies as clinical ASCVD. ARVD is considered a coronary artery disease equivalent, and these patients are at high risk for cardiovascular events [17••]. Aggressive lipid management should be pursued according to the current 2014 guidelines [32•].

Statins are the cornerstone of treatment for reducing cardiovascular events and mortality in patients with CKD not requiring dialysis [31, 33]. While the data for this are largely observational, they are consistent with randomized trials of statins for other atherosclerotic disorders. What has been observed in the patients with ARVD is improved survival and lessened lesion progression [34–38]. It has also been suggested that statins may reduce the occurrence of restenosis after stent revascularization [36]. Statins may reduce cardiovascular events in kidney transplant recipients [39]. The statin has not been proven to be beneficial in patients on dialysis, as shown by the studies of the German Diabetes and Dialysis Study (4D) [40] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [41].

Antiplatelet Therapy

Few data on the utility of platelet-inhibiting therapies in patients with ARVD exist. In high-risk patients with coronary artery disease equivalent, the benefit of aspirin in reducing risk of myocardial infarction is believed to outweigh uncommon bleeding complications. Because ARVD is associated with generalized atherosclerosis and considered as coronary artery disease equivalent, antiplatelet therapy is integral to managing ARVD [17••, 42]. Patrono and colleagues illustrated that aspirin reduced serious vascular event rates by 22 per 1000 high-risk patients, including those with peripheral arterial disease, stable angina, and atrial fibrillation [43]. Interestingly, Kanjwal et al. revealed that, in a prospective study of embolic protection, a surprisingly high rate of platelet-rich thrombi were recovered during renal artery stenting [44]. In a follow-up study, Cooper et al. observed that a platelet glycoprotein IIb/IIIa inhibitor, abciximab, was associated with better renal function 1 month after the procedure [45]. Antiplatelet therapy is important in optimal medical therapy of ARVD and is used for all patients with ARVD.

Diabetes Management

Atherosclerosis is accelerated in both types 1 and 2 diabetes [46]. Some controversy exists over the effects of blood glucose control in diabetics overall. The Action in Diabetes and

Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) randomized clinical trial showed that strict glucose control (hemoglobin A1C 6.5 %) reduced nephropathy by 21 %, although it had no effect on all-cause or cardiovascular mortality and macrovascular events (myocardial infarction and stroke) [47]. It was believed by some investigators that the hypoglycemia and weight gain associated with strict glucose control may neutralize the benefits of strict glucose control [48•]. In another trial, Gaede et al. found that intensive intervention and behavioral modification in type 2 diabetes and persistent microalbuminuria resulted in a sustained all-cause and cardiovascular mortality benefit [49]. Recent findings from the 10-year follow-up of UK Prospective Diabetes Study (UKPDS) trial showed that intensively treated groups had a significant reduction in cardiovascular events with prolonged follow-up [50]. Diabetic patients with peripheral arterial disease should have a glucose level controlled with their glycosylated hemoglobin to 7.0 % [51•], and we recommend the same target for most patients with ARVD. However, a more liberalized goal for HbA1C target may be appropriate [52] for elderly patients (e.g., age>60 years old) with longstanding established diabetes (e.g., duration 8–11 years) and either known CVD or multiple risk factors or patients with risk of hypoglycemia. The liberal goal for this subgroup of patients largely results from the findings of three recent clinical trials, i.e., the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [53], ADVANCE [54], and the Veterans Affairs Diabetes Trial (VADT) [55]. In the three trials, it was found that the intensive glycemic control (HbA1C <6.5 to 6.9) did not show significant benefit over standard glycemic control (HbA1C 7.0 to 8.5) in elderly patients (e.g., age>60 years old) with long-standing established diabetes (e.g., duration 8–11 years) and either known CVD or multiple risk factors or patients with risk of hypoglycemia. In the ACCORD trial [53], the intensive glycemic control group showed more mortality.

Revascularization and Endovascular Therapy

Surgery

There is a long history of surgical revascularization for patients with RAS. Novick et al. [56] reported on a modest number of subjects and demonstrated an improvement in approximately two thirds of patients during a short follow-up period. The utility of this observation, like many surgical series, is modest; since there was no concurrent control group, randomization was not performed, and the number of individuals was limited. In consequence, it is often difficult to determine the absolute or relative advantage of this approach and to what degree patient selection accounts for the outcomes of these studies. Dean et al. have reported some of the best surgical results indicating that patients with bilateral occlusive disease and moderate azotemia or a serum creatinine above 3.0 mg/dL had the greatest apparent benefit from surgical revascularization [57]. Overall, however, a significant association between the degree of stenosis and the benefit of revascularization has yet to be established.

The risk of vascular surgery in elderly patients with widespread atherosclerosis is a major concern. Safian and Textor report that the major complication rate is 8 to 11 % and that the mortality rate is 2 to 8 % [58]. The attendant risks have been highlighted in a recent review of a large and contemporary US hospital discharge database by Modrall et al., demonstrating

10 % in-hospital mortality [59]. In a follow-up study by Modrall and colleagues, which sought to determine the effects of hospital volume on outcome, only a marginal effect was seen: High-risk patients did no better or worse at high-volume centers, whereas low-risk patients apparently benefited from treatment in a high-volume center [60]. Overall, these data suggest that elderly patients with cardiovascular comorbidities should be considered as a group at high risk for mortality during surgical revascularization. Even when revascularization is deemed appropriate in some cases, angioplasty and stenting are preferred over surgery.

Angioplasty

Percutaneous transluminal renal angioplasty (PTRA) is a less invasive approach compared to surgical revascularization. The use of PTRA has largely been relegated to treatment of fibromuscular dysplasia and supplanted by stenting for the treatment of atherosclerotic renal stenosis. There is only one head-to-head comparison of angioplasty and surgical revascularization. In 1993, Weibull et al. [61] demonstrated a relative equivalence between PTRA and surgical revascularization for the primary outcomes of primary renal artery patency, kidney function, and blood pressure control, after both approaches were directly compared in a cohort of 58 patients with unilateral RAS. Improved or stable renal function was seen in 83 % after PTRA and 72 % after surgery [61].

Much of the literature concentrating on renal angioplasty intervention is targeted primarily at the treatment of hypertension. Typical rates of major complications have been reported to be between 3 and 15 % [62, 63] and may include bleeding at the puncture site, pseudoaneurysm of the femoral artery, rupture or thrombosis of the renal artery, dissection of the renal artery or access artery, cholesterol emboli syndrome, and contrast nephropathy.

In 2000, van Jaarsveld et al. [64] published the results of the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study, the largest randomized controlled trial to address the use of renal artery angioplasty without stenting. In this study, 106 patients with hypertension who had ARVD were randomly assigned to undergo renal angioplasty ($n=56$) or medical therapy ($n=50$). RAS was defined as at least 50 % stenosis of the renal artery, and patients with a solitary kidney were excluded. Twenty-one percent of the subjects had less than 70 % stenosis, and only 23 % had bilateral RAS. Nine percent of the medical group progressed to occlusion. Creatinine clearance was better in the PTRA group at 3 months (70 vs. 59 ml/min; $p=0.03$), but the same at 12 months (70 vs. 62 ml/min; $p=0.11$), and no significant difference was seen in blood pressure control between the two groups at either time point. The liberal use of rescue revascularization (crossover) may have reduced the significance of any treatment advantage in the intention-to-treat analysis. A meta-analysis of the randomized trials of renal angioplasty demonstrated that balloon angioplasty has a modest effect on blood pressure but has no effect on renal function [65]. Thus, balloon angioplasty is not as effective as the stent treatment strategy.

Stenting

Endovascularly deployed stents appear to provide a better rate of restenosis-free long-term patency than angioplasty alone [66] while remaining to be less invasive and more appealing

than surgery. This is especially true for ostial stenoses, which constitute the majority of atherosclerotic stenoses. Stenting achieves higher initial technical success rates, improved immediate patency, and lower restenosis rates in comparison to balloon angioplasty alone [66]. Technical problems with stent placement include malpositioning, main renal artery rupture, distal arterial wire perforation, dissection, or branch vessel occlusion. Stents that are coated with antiproliferative medications (such as sirolimus, everolimus, or paclitaxel) have shown success in reducing restenosis rates in coronary arteries [67–69]. However, there has been only one study of a drug-coated renal artery stent, the sirolimus-eluting Genesis stent, which failed to meet its pre-specified performance metrics, after which work on this platform was abandoned [70]. There are limited data suggesting that drug-eluting coronary stents may have some utility for the treatment of in-stent restenosis, but the data remain to be mixed [71, 72].

Multiple single-center cohort studies on renal artery stenting have been published. In 2000, Leertouwer et al. published a meta-analysis of 14 studies of stenting in 678 patients as compared with 10 studies of PTRAs in 644 patients [73]. They found that the restenosis rate at 6 to 29 months was 17 % after stenting and 26 % after PTRAs. After stenting, renal function improved in 30 %, stabilized in 38 %, and worsened in 32 %; the improvement rate was greater after PTRAs (38 %, $p=0.001$). Multiple observational studies have documented an early decline in blood pressure after stenting and a decrease in the number of required medicines to treat hypertension [74].

These early studies did show the benefit of the transition from an invasive surgical approach to angioplasty and then to stenting with regard to patency and restenosis concerns, but these early studies failed to provide solid evidence about mortality and morbidity benefits of these interventional approaches. Critiques mostly focused on the studies not being randomized controlled trials, having low power, and achieving poor patient enrollment, among others.

Stenting in Specific Populations

Several studies suggest that stenting may improve kidney function in patients with stenoses affecting all of the kidney parenchyma. A study by Watson et al. focused on patients with progressive, but not severe, chronic renal insufficiency and with global high-grade stenosis [75]. Renal artery stenting was performed in 33 patients who displayed a serum creatinine more than 1.5 mg/dl (mean, 2.1 mg/dl) and found an improvement in the rate of loss of GFR. Another study found favorable responses to revascularization for patients with ARVD and rapidly declining kidney function [76]. Although the findings of these studies support the idea of using stenting to treat ischemic nephropathy, the lack of medically managed control groups and randomization to limit confounding limits the validity of these conclusions.

In a single-center observational study, in patients with ARVD presenting with flash pulmonary edema, as compared to medical therapy, revascularization reduced mortality (HR 0.4; 95 % CI 0.2–0.9; $p=0.01$) but did not affect cardiovascular event or ESRD rates [77•]. It seems that in high-risk subgroups of patients with ARVD presenting with flash pulmonary

edema or rapidly declining kidney function, revascularization may be favored over medical therapy alone.

There have been efforts in developing predictors that can identify subgroups of patients who will benefit from revascularization. High ratios of renal parenchymal volume (assessed by MRI) to single-kidney GFR were reported to be an indicator of improvement in GFR after revascularization in a study of 50 patients [78]. High blood oxygen level-dependent (BOLD) MRI signal to single-kidney isotopic GFR has been shown to be a predictor for improvement of renal function after revascularization in one clinical study of 28 patients [79]. Pre-intervention brain natriuretic peptide (BNP) levels of >80 pg/ml were reported to be predictive of a response to revascularization in a study of 27 patients [80]. On the other hand, a renal resistance index of more than 80 by duplex Doppler ultrasound was reported to be an indicator of unresponsiveness to revascularization [62]. These measures seem to be promising predictors of revascularization success, but more data are needed for confirmation before general utilization can be recommended.

Randomized Controlled Trials

More recently, three randomized trials have been completed that directly compared medical therapy alone against medical therapy with stenting, namely the trial of 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), ASTRAL, and CORAL trials [16, 16, 81]. The STAR trial [81] was a randomized trial that tested whether stenting could reduce by 50 % the proportion of patients that experienced a 20 % decline in GFR. Unfortunately, 28 % of the patients who were enrolled in the stent arm had no significant renal artery stenosis and were not treated. Not surprisingly, with a substantial false positive rate during enrollment, in addition to being underpowered, the study authors concluded that “confidence bounds are compatible with both efficacy and harm, so the finding is inconclusive.”

The ASTRAL trial [16], published in late 2009, enrolled 806 patients. The study demonstrated a trend toward an improvement in the primary end point of slope of reciprocal creatinine (-0.0713×10^{-3} vs. -0.13×10^{-3} $\mu\text{mol/l/year}$, $p=0.06$). However, this difference was neither statistically nor clinically significant, as were the findings of the secondary analyses. From these recent studies, we would conclude that if stenting has an effect on the progression of ischemic nephropathy, it is likely modest in size. Some have criticized the ASTRAL result for an apparently higher than expected rate of complications and lower than expected success rate; however, it is unclear whether the ASTRAL result better reflects the *realities of stenting* when compared to single-center publications or whether technical issues were more extensive in this study.

The most recent CORAL trial [16], published in 2014, was designed to compare optimal medical therapy alone to stenting with optimal medical therapy, with a primary end point of the occurrence of major cardiovascular or renal events. This was defined as a composite of death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for permanent renal

replacement therapy. In CORAL, 947 patients with ARVD and either hypertension or chronic kidney disease were randomized into two groups: optimal medical therapy (ARB, atorvastatin, and an antiplatelet agent, with or without thiazide or amlodipine) or optimal medical therapy with stenting. There was no significant difference in the occurrence of the primary composite end point or any of its individual components between the stent group and medical therapy-only group and no difference in all-cause mortality. Systolic blood pressure was modestly lower in the stent group than in the medical therapy-only group (-2.3 mmHg; 95 % CI -4.4 to -0.2 mmHg; $p=0.03$), and the difference persisted throughout the follow-up period.

The CORAL study showed that, when added to a background of high-quality medical therapy, contemporary renal artery stenting provides no incremental benefit for patients with ARVD. From this result, it is clear that optimal medical therapy without stenting is the preferred management strategy for the majority of people with ARVD.

Conclusion

Atherosclerotic renovascular disease is a common problem in older adults that is associated with high rates of adverse cardiovascular and renal events and high mortality. With the result from CORAL, a randomized controlled trial with solid design and execution, it is now clear that the majority of such patients with ARVD are best served with medical therapy alone. The optimal therapy for ARVD according to the evidence available includes lipid-lowering treatment, antiplatelet medication, ACEI/ARB, blood pressure control, diabetes management, and lifestyle modification. With good implementation of optimal medical therapy, mortality and morbidity can be decreased.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

- 1•• Cooper CJ, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014; 370(1):13–22. This is the primary report from the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), a prospective randomized clinical trial. This trial compared patients receiving optimal medical therapy alone versus optimal medical therapy with stenting and concluded that stenting therapy does not provide more benefit than medical therapy alone. [PubMed: 24245566]
- 2• Evans KL, et al. Use of renin-angiotensin inhibitors in people with renal artery stenosis. *Clin J Am Soc Nephrol*. 2014; 9(7):1199–206. This article reported the current ACEI/ARB usage in patients with atherosclerotic renal artery stenosis from the CORAL trial. Although ACEI/ARB usage has

been shown to be beneficial in reducing mortality and morbidity in patients with ARVD, clinicians do not always prescribe ACEI/ARBs to these patients. [PubMed: 24903387]

3. Hansen KJ, et al. Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg.* 2002; 36(3):443–51. [PubMed: 12218965]
4. Kalra PA, et al. Atherosclerotic renovascular disease in the United States. *Kidney Int.* 2010; 77(1): 37–43. [PubMed: 19865075]
5. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens.* 2009; 27(7):1333–40. [PubMed: 19365285]
6. Johansson M, et al. Increased cardiovascular mortality in hypertensive patients with renal artery stenosis. Relation to sympathetic activation, renal function and treatment regimens. *J Hypertens.* 1999; 17(12 Pt 1):1743–50. [PubMed: 10658941]
7. Kalra PA, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. *Kidney Int.* 2005; 68(1):293–301. [PubMed: 15954920]
8. Dorros G, et al. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. *Circulation.* 1998; 98(7):642–7. [PubMed: 9715856]
9. Kennedy DJ, et al. Renal insufficiency as a predictor of adverse events and mortality after renal artery stent placement. *Am J Kidney Dis.* 2003; 42(5):926–35. [PubMed: 14582036]
10. Alderson HV, Ritchie JP, Kalra PA. Revascularization as a treatment to improve renal function. *Int J Nephrol Renov Dis.* 2014; 7:89–99.
11. Fatica RA, Port FK, Young EW. Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. *Am J Kidney Dis.* 2001; 37(6):1184–90. [PubMed: 11382687]
12. Scoble JE, et al. Atherosclerotic renovascular disease causing renal impairment—a case for treatment. *Clin Nephrol.* 1989; 31(3):119–22. [PubMed: 2523265]
13. Appel RG, et al. Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int.* 1995; 48(1):171–6. [PubMed: 7564074]
14. Guo H, et al. Atherosclerotic renovascular disease in older US patients starting dialysis, 1996 to 2001. *Circulation.* 2007; 115(1):50–8. [PubMed: 17179020]
15. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence? *Clin J Am Soc Nephrol.* 2008; 3(1):226–36. [PubMed: 18003763]
16. Wheatley K, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med.* 2009; 361(20):1953–62. [PubMed: 19907042]
- 17•. Balafa O, Kalaitzidis R, Siamopoulos KC. Optimal medical management in patients with renovascular hypertension. *Am J Cardiovasc Drugs.* 2013; 13(2):71–8. A review of optimal medical management of ARVD with citation of current literature. [PubMed: 23494905]
- 18•. Jennings CG, et al. Renal artery stenosis—when to screen, what to stent? *Curr Atheroscler Rep.* 2014; 16(6):416. A review article on the management of ARVD based on current literature. [PubMed: 24743868]
- 19•. James PA, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014; 311(5):507–20. New guidelines for the management of high blood pressure in adults. [PubMed: 24352797]
20. Rooke TW, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011; 124(18):2020–45. [PubMed: 21959305]
21. Hricik DE, et al. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. *N Engl J Med.* 1983; 308(7):373–6. [PubMed: 6337327]
22. Sigmon DH, Beierwaltes WH. Renal nitric oxide and angiotensin II interaction in renovascular hypertension. *Hypertension.* 1993; 22(2):237–42. [PubMed: 8340159]

23. Gobe GC, Axelsen RA, Searle JW. Cellular events in experimental unilateral ischemic renal atrophy and in regeneration after contra-lateral nephrectomy. *Lab Invest.* 1990; 63(6):770–9. [PubMed: 2255186]
24. Tokuyama H, et al. Differential regulation of elevated renal angiotensin II in chronic renal ischemia. *Hypertension.* 2002; 40(1):34–40. [PubMed: 12105135]
25. Hackam DG, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *Am Heart J.* 2008; 156(3):549–55. [PubMed: 18760140]
- 26•. Chrysochou C, et al. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. *Nephrol Dial Transplant.* 2012; 27(4):1403–9. This article provides evidence regarding the benefit of ACEI/ARB therapy in patients with renal artery stenosis. [PubMed: 21993376]
27. Losito A, et al. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. *Nephrol Dial Transplant.* 2005; 20(8):1604–9. [PubMed: 15870215]
28. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? *J Am Geriatr Soc.* 2002; 50(7):1297–300. [PubMed: 12133029]
29. van de Ven PJ, et al. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. *Kidney Int.* 1998; 53(4):986–93. [PubMed: 9551408]
- 30•. Anderson JL, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013; 61(14):1555–70. Current guideline on the management of peripheral artery disease. [PubMed: 23473760]
31. Navaneethan SD, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2009; 2:CD007784. [PubMed: 19370693]
- 32•. Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 129(25 Suppl 2):S1–45. Current guidelines on the management of blood cholesterol. [PubMed: 24222016]
33. Palmer SC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2014; 5:CD007784. [PubMed: 24880031]
34. Bates MC, et al. Factors affecting long-term survival following renal artery stenting. *Catheter Cardiovasc Interv.* 2007; 69(7):1037–43. [PubMed: 17525962]
35. Cheung CM, et al. The effects of statins on the progression of atherosclerotic renovascular disease. *Nephron Clin Pract.* 2007; 107(2):c35–42. [PubMed: 17713349]
36. Corriere MA, et al. Restenosis after renal artery angioplasty and stenting: incidence and risk factors. *J Vasc Surg.* 2009; 50(4):813–9. [PubMed: 19595532]
37. Silva VS, et al. Pleiotropic effects of statins may improve outcomes in atherosclerotic renovascular disease. *Am J Hypertens.* 2008; 21(10):1163–8. [PubMed: 18670414]
38. Sigmon DH, Beierwaltes WH. Degree of renal artery stenosis alters nitric oxide regulation of renal hemodynamics. *J Am Soc Nephrol.* 1994; 5(6):1369–77. [PubMed: 7894004]
39. Palmer SC, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev.* 2014; 1:CD005019. [PubMed: 24470059]
40. Wanner C, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med.* 2005; 353(3):238–48. [PubMed: 16034009]
41. Fellström BC, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med.* 2009; 360(14):1395–407. [PubMed: 19332456]
42. Vashist A, et al. Renal artery stenosis: a cardiovascular perspective. *Am Heart J.* 2002; 143(4):559–64. [PubMed: 11923791]
43. Patrono C, et al. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European Society of Cardiology. *Eur Heart J.* 2004; 25(2):166–81. [PubMed: 14720534]

44. Kanjwal K, et al. Complete versus partial distal embolic protection during renal artery stenting. *Catheter Cardiovasc Interv.* 2009; 73(6):725–30. [PubMed: 19198007]
45. Cooper CJ, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation.* 2008; 117(21):2752–60. [PubMed: 18490527]
46. Chait A, Bornfeldt KE. Diabetes and atherosclerosis: is there a role for hyperglycemia? *J Lipid Res.* 2009; 50(Suppl):S335–9. [PubMed: 19029122]
47. Heller SR. A summary of the ADVANCE trial. *Diabetes Care.* 2009; 32(Suppl 2):S357–61. [PubMed: 19875581]
- 48•. Giorgino F, Leonardini A, Laviola L. Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials. *Ann N Y Acad Sci.* 2013; 1281(1): 36–50. A summary of the current debate on glycemic control in type 2 diabetes and the potential benefit of strict glycemic control for some patients.
49. Gaede P, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med.* 2008; 358(6):580–91. [PubMed: 18256393]
50. Holman RR, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med.* 2008; 359(15):1565–76. [PubMed: 18784091]
- 51•. Poredos P, et al. Medical management of patients with peripheral arterial disease. *Int Angiol.* 2014 A summary of current medical management of peripheral arterial disease.
52. Skyler JS, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care.* 2009; 32(1):187–92. [PubMed: 19092168]
53. Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008; 358(24):2545–59. [PubMed: 18539917]
54. Patel A, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008; 358(24):2560–72. [PubMed: 18539916]
55. Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009; 360(2):129–39. [PubMed: 19092145]
56. Novick AC, et al. Trends in surgical revascularization for renal artery disease: ten year's experience. *JAMA.* 1987; 257(4):498–501. [PubMed: 3795433]
57. Dean RH, et al. Renovascular hypertension: anatomic and renal function changes during drug therapy. *Arch Surg.* 1981; 116(11):1408–15. [PubMed: 7305653]
58. Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med.* 2001; 344(6):431–42. [PubMed: 11172181]
59. Modrall JG, et al. Operative mortality for renal artery bypass in the United States: results from the national inpatient sample. *J Vasc Surg.* 2008; 48(2):317–22. [PubMed: 18472384]
60. Modrall JG, et al. Effect of hospital volume on in-hospital mortality for renal artery bypass. *Vasc Endovasc Surg.* 2009; 43(4):339–45.
61. Weibull H, et al. Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. *J Vasc Surg.* 1993; 18(5): 841–50. discussion 850–2. [PubMed: 8230572]
62. Radermacher J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med.* 2001; 344(6):410–7. [PubMed: 11172177]
63. Greco BA, Breyer JA. Atherosclerotic ischemic renal disease. *Am J Kidney Dis.* 1997; 29(2):167–87. [PubMed: 9016887]
64. van Jaarsveld BC, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med.* 2000; 342(14):1007–14. [PubMed: 10749962]
65. Nordmann AJ, et al. Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. *Am J Med.* 2003; 114(1):44–50. [PubMed: 12557864]

66. van de Ven PJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet*. 1999; 353(9149):282–6. [PubMed: 9929021]
67. Kastrati A, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005; 293(2):165–71. [PubMed: 15644543]
68. Sawhney N, et al. Treatment of left anterior descending coronary artery disease with sirolimus-eluting stents. *Circulation*. 2004; 110(4):374–9. [PubMed: 15249503]
69. Storger H, et al. Clinical experiences using everolimus-eluting stents in patients with coronary artery disease. *J Interv Cardiol*. 2004; 17(6):387–90. [PubMed: 15546290]
70. Zahringer M, et al. Sirolimus-eluting versus bare-metal low-profile stent for renal artery treatment (GREAT Trial): angiographic follow-up after 6 months and clinical outcome up to 2 years. *J Endovasc Ther*. 2007; 14(4):460–8. [PubMed: 17696619]
71. Kiernan TJ, et al. Treatment of renal artery in-stent restenosis with sirolimus-eluting stents. *Vasc Med*. 2010; 15(1):3–7. [PubMed: 19793778]
72. Zeller T, et al. Treatment of in-stent restenosis following stent-supported renal artery angioplasty. *Catheter Cardiovasc Interv*. 2007; 70(3):454–9. [PubMed: 17721946]
73. Leertouwer TC, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology*. 2000; 216(1):78–85. [PubMed: 10887230]
74. Burket MW, et al. Renal artery angioplasty and stent placement: predictors of a favorable outcome. *Am Heart J*. 2000; 139(1 Pt 1):64–71. [PubMed: 10618564]
75. Watson PS, et al. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. *Circulation*. 2000; 102(14):1671–7. [PubMed: 11015346]
76. Muray S, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis*. 2002; 39(1):60–6. [PubMed: 11774103]
- 77•. Ritchie J, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis*. 2014; 63(2):186–97. This article identifies a subgroup of high-risk patients with ARVD who may receive benefit from endovascular stenting therapy. [PubMed: 24074824]
78. Cheung CM, et al. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrol Dial Transplant*. 2010; 25(4):1133–40. [PubMed: 20028827]
- 79•. Chrysoschou C, et al. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrol Dial Transplant*. 2012; 27(3):1013–9. This article identifies patients with ARVD who may benefit from endovascular interventional therapy. [PubMed: 21856759]
80. Silva JA, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation*. 2005; 111(3):328–33. [PubMed: 15655135]
81. Bax L, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009; 150(12):840–8. W150-1. [PubMed: 19414832]