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Update on intervention versus medical therapy for atherosclerotic renal artery stenosis

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Abstract

Atherosclerotic renal artery stenosis is known to be one of the most common causes of secondary hypertension, and early nonrandomized studies suggested that renal artery stenting (RASt) improved outcomes. The vascular community embraced this less invasive treatment alternative to surgery, and RASt increased in popularity during the late 1990s. However, recent randomized studies have failed to show a benefit regarding blood pressure or renal function when RASt was compared with best medical therapy, creating significant concerns about procedural efficacy. In the wake of these randomized trial results, hypertension and renal disease experts along with vascular interventional specialists now struggle with how to best manage atherosclerotic renal artery stenosis. This review objectively analyzes the current literature and highlights each trial's design weaknesses and strengths. We have provided our recommendations for contemporary treatment guidelines based on our interpretation of the available empirical data.

Renal artery stenosis (RAS) is a recognized cause of secondary hypertension, renal dysfunction, and flash pulmonary edema (Pickering syndrome).[1] Atherosclerotic renal artery stenosis (ARAS) is the most common cause of RAS, accounting for more than 90% of cases[2]; about 16% of those patients currently undergo revascularization in the United States.[3] Other nonatherosclerotic causes include vasculitis, dissection, and fibromuscular dysplasia. Nonatherosclerotic RAS treatment paradigms vary from angioplasty for

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fibromuscular dysplasia to anti-inflammatory treatments for vasculitis and thus are beyond the scope of this review.

ARAS is associated with advanced systemic atherosclerosis and is present in 38%, 33%, and 39% of patients with abdominal aortic aneurysms, aortoiliac occlusive disease, and peripheral vascular disease, respectively.[4] Autopsy data suggest that the prevalence of ARAS increases with age, diabetes, peripheral arterial disease, coronary artery disease, hypertension, and dyslipidemia.[2] It is estimated that 15% of hypertensive patients will have evidence of ARAS, with one fifth of them having >60% RAS by angiography.[5] The prevalence among patients with coronary artery disease is estimated to be 5.4% to 38.8%,[6-8] although the incidence is slightly higher in women >60 years old who have ≥coronary artery disease involving two or more vessels.[9] Epidemiologic data suggest that ARAS appears to be a relatively common clinical finding and is present in 6.8% of patients older than 65 years.[2] In patients with peripheral artery disease, incidental RAS (diameter reduction >50%) predicts long-term mortality (65% vs 43%).[4]

The goals of therapy in patients with ARAS are to control blood pressure, to reduce fluid shifts that may cause sudden pulmonary congestion, and to improve or stabilize renal function. There have been significant advances in contemporary pharmaceutical antihypertensive discovery, including angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin receptor blockers, and beta blockers; thus, blood pressure control has become less of a challenge. In addition, the evolution of statin and antiplatelet therapy may have improved medical outcomes, further narrowing the risk/benefit window.

When intervention was indicated, surgical revascularization was the “gold standard,“ with many acceptable techniques, including endarterectomy and aortorenal, splenorenal, or hepatorenal bypasses. However, during the last two decades, renal artery stenting (RASt) has become an attractive alternative to surgery because of the less invasive approach and low morbidity.[10,11] The initial enthusiasm for RASt was augmented by a refinement in technology and a decrease in the complication rates. This led to an exponential increase in patients undergoing RASt in the late 1990s, with 7500 patients undergoing RASt in 1996 compared with 18,500 in 2000.[12] However, recent conflicting data from multiple trials have added significant uncertainty as to whether RASt provides a clear-cut benefit over best medical therapy.[13-16] This invited review outlines current available data from retrospective, prospective, and randomized trials in an attempt to define the selected population that would gain the most benefit from renal revascularization. We believe that the best outcome can be achieved by selecting the appropriate patient with clear indications in a center with an experienced team.

ARTICLE SELECTION AND REVIEW METRICS

To perform a thorough literature search for trials addressing medical therapy or percutaneous intervention for ARAS, we selected trials with enough patients to have statistical validity and that followed contemporary outcome guidelines. Various studies were chosen on the basis of their design, including patient number and treatment arms. Studies were included that were recent (at least in the past decade), had a sample size of 50 or more,

reported actual outcome measures such as hypertension or renal function, defined the type of treatment or intervention, or were recent prospective clinical trials. Baseline characteristics for each study population were collected when reported. Clinical outcomes included renal function, blood pressure response (systolic [SBP], diastolic [DBP], or both), number of antihypertensive medications, mortality, restenosis, and target vessel revascularization (TVR). Because of nonuniform presentation of data, we reported results as a statistically significant change from baseline ($P < .05$) or not ($P > .05$), according to the publication conclusions and data presented. In some cases, no statistical value was given for a clinical outcome, but it was reported as stabilized, improved, or worsened.

Study outcomes were captured during mean/median follow-up or at study end point as reported by the authors. Indications and exclusions varied by study and in some cases were not reported. In general, patients had to have either renal dysfunction or hypertension and imaging findings of ABAS to be included in the trials. Exclusion criteria generally included anatovious intervention, renal size on ultrasound, and severe renal dysfunction based on study definition. Renal improvement was recorded when a statistically significant change in renal function was reported. Some studies reported renal stabilization and were recorded as such. If no statistically significant change in renal function or stabilization was reported, then neither was recorded. Thus, no change was coded as 0, whereas 1 and 2 were used for improvement and stabilization, respectively. All other variables were coded as 0 (not occurring) or 1 (occurred or existence). A quasi–meta-analysis method was used to combine, collate, and compare all of the data elements that were extracted from the selected studies. The studies included in our overall analysis are detailed in Table I.

Many studies attempted to identify which patients are most likely to experience a change in their blood pressure after intervention. Although hypertension was rarely cured (no medication required to keep blood pressure <140/90 mm Hg), improvement from baseline was noted in the majority of studies, and fewer antihypertensive medications were generally required. Various stenting-only studies noted that patients with the greatest blood pressure benefit were those having the highest preintervention blood pressure.[17-20] Some studies also found that stenting enhanced blood pressure control with fewer required antihypertensive medications.[17,21-28] Bilateral stenting seemed to confer a minor advantage in blood pressure outcome in some studies[27,29-32] but not in others.[17,18,20,22,24,33] A poor blood pressure response was predicted by male sex,[18,23] poor renal function,[18,24] degree of stenosis,[24] and left ventricular hypertrophy.[24] The number of baseline antihypertensive medications was found to be a predictor of improved blood pressure control in one study[19] but the opposite in another.[24] In some studies, normal renal parenchymal thickness was found to be a good predictor of blood pressure response.[31,32]

Three recent clinical trials (Cardiovascular Outcome in Renal Atherosclerotic Lesions [CORAL],[14] Angioplasty and Stenting for Renal Artery Lesions [ASTRAL],[15] and Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function [STAR][13]) reported an improved blood pressure outcome in both the stenting and medical therapy arms of their trials. CORAL noted that the stenting arm had a small but statistically significant lower SBP compared with the medical arm. The Stenting of Renal Artery Stenosis in Coronary Artery Disease (RAS-CAD)[16] reported improved blood

pressure control with medical therapy but did not find a statistically significant improvement with percutaneous intervention. All four of these clinical trials employed statins, antiplatelet agents, and optimal blood pressure medications for use in their groups.

On the other hand, Pizzolo et al[30] found improvement in blood pressure in the percutaneous intervention group but not after medical management. Two older studies comparing percutaneous transluminal angioplasty (PTA) with medical therapy found no difference. However, PTA did allow blood pressure control with fewer antihypertensive drugs, although portions of the medical group crossed over to the angioplasty group during the study.[34,35] van de Ven et al[36] reported superior rates of primary patency and lower restenosis for stenting but no difference in clinical outcomes. One study demonstrated a significant improvement in blood pressure control for patients with bilateral RAS randomized to RASt.[29] Studies indicating blood pressure improvement are summarized in Table II.

An interesting prospective review by Kalra et al[3] has shown an improvement in renal function in the intervention group compared with medical treatment, particularly in the latter stages of chronic kidney disease (stage 4-5), with survival advantage by reducing risk of death by 45% in all patients combined (relative risk, 0.55; $P = .013$).

Attempts to identify patients who are most likely to benefit in renal function after intervention have been extensively studied. Various study results suggest that patients with baseline[17,26,37,38] or more severe[24,31,39] renal dysfunction are more likely to have improved or stabilized renal function after stenting. Others reported that patients with poor baseline renal function were less likely to improve after stenting[31] or had associated increased mortality.[22,40-42] Other studies have noted that patients with a recent decline in glomerular filtration rate (GFR) derive the greatest benefit.[25,37,42-44] Bilateral stenting was found to improve or to stabilize renal function in some studies[32,37] but not in others.[16,21,29,38,43-45] Bilateral disease was noted to adversely affect survival,[22,40] whereas baseline stenosis[32] and good left ventricular function[39] were found to be predictors for improved renal function. Bates et al[42] demonstrated that comorbid conditions, including pulmonary and cardiac conditions, were independently associated with mortality. Multiple trials noted protective effects of distal protection devices during RASt.[37,46,47] None of the recent clinical trials (CORAL, ASTRAL, STAR, RAS-CAD) showed improvement in renal function with RASt. The ASTRAL trial reported higher creatinine values at 5 years for both the stenting and medical therapy groups, although higher in the stenting group, but no change or difference was reported. RAS-CAD reported no significant change in GFR for either group at 1 year. Likewise, STAR did not report change or difference between groups, but the medical arm had more of a mean increase in creatinine at the 2-year primary end point. CORAL reported no statistically significant difference in renal function outcomes between the two arms. Pizzolo et al[30] found stabilization or improvement in renal function in their percutaneous group (42 of 63 stenting, 21 of 63 angioplasty alone) but did not observe a change for medical management. Studies indicating renal function improvement or stabilization (RFIS) are summarized in Table III; studies indicating blood pressure improvement and RFIS are summarized in Table IV. There is an association of improved prognosis for renal vascular disease with statins,[48] and although angiotensin-converting enzyme inhibitors may improve survival in renal vascular disease,[49] their benefit is balanced by acute toxicity risk.[50]

ENDOVASCULAR THERAPY FOR ARAS AND PROGRESSION OF THE DISEASE

It is important to understand how stenting may affect the progression of renal disease. A retrospective analysis[51] was conducted of 104 patients who had endovascular therapy for ARAS (PTA in 25 patients and RASt in 79 patients) during a 13-year period at one institution. On postintervention day 1, all patients showed a statistically significant decrease in the mean SBP (all patients, $P = .002$; stent-PTA group, $P = .023$; PTA group, $P = .022$). Also, a significant decrease in the mean SBP persisted at 1 and 2 years after intervention (all patients, $P = .009$ and $P = .007$, respectively; stent-PTA group, $P = .039$ and $P = .015$, respectively). In patients with a RASt between 2001 and 2007, there was no significant reduction of prescribed antihypertensive drugs ($P = .023$ and $P = .046$, respectively). The mean creatinine concentrations decreased during the first and second postintervention years; however, increases were noted with year 3. It was noted that patients with baseline elevated serum creatinine levels had an increase in mean serum creatinine levels starting in year 5. The authors concluded that endovascular therapy for ARAS delays worsening of renal function and stabilized blood pressure and the number of prescribed antihypertensive drugs. This confirms multiple other studies that showed renal improvement in patients with baseline renal dysfunction. Furthermore, it offers an extended timeline that shows that the patient may achieve a benefit for at least several years after stenting.

The minimal luminal diameter of the renal artery, irrespective of the degree of stenosis, may be independently associated with estimated GFR and resistant hypertension. In more than 700 patients, Zanoli et al[33] demonstrated a positive significant association between the reference diameter and GFR in patients without luminal narrowing. Reference diameter <5.2 mm was associated with an increased risk of resistant hypertension (odds ratio, 2.63; 95% confidence interval, 1.02-6.77; $P < .05$). The authors reported that the intralesion, minimal luminal area was more important than the percentage of stenosis and that the smaller the reference vessel, the less the percentage of stenosis was needed to see hemodynamic significance. This study indicated that even small lesions within small arteries can be of clinical value and may warrant diagnostic intervention as well.

Our team[37] evaluated the impact of RASt on renal function in a single-center retrospective review of 194 patients. Abnormal baseline creatinine concentration was defined as ≥%1.5 mg/dL, and follow-up creatinine concentration was improved, unchanged, or worsened if it decreased by >20%, stayed within 20%, or increased >20%, respectively. This study concluded that renal function improvement was achieved in two thirds of patients, with stabilization in the overall decline. Interestingly, bilateral RASt predicted normal follow-up creatinine concentration, and baseline creatinine concentration ≥%2.1 mg/dL was a predictor for long-term improvement. Therefore, this study suggested that RASt has a beneficial effect in stabilizing renal function, and bilateral RASt augments this effect.

Also, in a retrospective analysis, we studied predictors of mortality after RASt in 748 patients with ARAS.[42] In-hospital, 30-day, and 6-month mortality rates were 0.5%, 2.0%, and 6.3%, respectively. Overall patient survival at 1, 5, and 10 years was 91.2%, 66.6%, and 40.9%, respectively. Patients with chronic obstructive pulmonary disease and congestive

heart failure undergoing RASt revascularization were shown to have a poor long-term prognosis. Baseline azotemia was the strongest independent predictor of all-cause mortality, with a mortality of >70% noted in patients with creatinine concentration >2.5 mg/dL.

In a similar retrospective, single-center, single-operator RASt analysis of more than 700 patients,[52] we reported on the durability of RASt and predictors of restenosis, and only 10% of stented arteries required TVR during long-term follow-up (mean, 45.8 ± 26.5 months). Arteries with a final stent diameter of 5.0 mm were twice as likely to require TVR. In addition, patients with a solitary kidney were more likely to need TVR, but this may have been due to selection bias.

Preservation of renal function and size after RASt was assessed in 33 patients[53] with chronic renal insufficiency (defined by a creatinine concentration >1.5 mg · dL^{-1}) and global renovascular obstruction (bilateral RAS or unilateral stenosis in the presence of a solitary or single functional kidney). In this small series, RASt was deployed in 61 vessels, and follow-up was completed in 25 patients (mean, 20 ± 11 months). Before RASt, all patients exhibited a negative reciprocal creatinine slope, indicating progressive renal insufficiency; however, after stent deployment, slopes were positive in 18 and negative in seven patients. Thus, the mean slope increased from 0.0079 to 0.0043 dL · mg^{-1} · mo^{-1} ($P < .001$). Kidney size was preserved in 41 patients on the basis of ultrasound examination. Thus, this study concluded that RASt improved or stabilized renal function and preserved kidney size in patients with chronic renal insufficiency and global obstructive RAS.

Data on the efficacy of embolic protection devices (EPDs) in ARAS are currently limited, and there are no protection systems specifically designed for renal use. In a systematic review, [54] the authors concluded that EPDs may be beneficial in some patients, but there was inadequate empirical data to clearly define the risk/benefit. In a small four-arm randomized study of 100 patients, it was noted that the use of adjuvant IIb/IIIa glycoprotein inhibitors and EPDs may have a synergistic benefit.[55]

As discussed earlier, various investigators have found renal revascularization to be beneficial. Studies in favor of renal revascularization[3,50,53] indicate that its benefit is augmented in patients with rapid deterioration of their renal functions with acute worsening of estimated GFR and associated with RAS affecting both renal arteries or a single functioning kidney. [56]

On the other hand, some other studies showed no benefit of renal revascularization vs medical therapy. A systematic review has indicated that there is no benefit of renal revascularization over medical therapy.[57] Another meta-analysis study showed no benefit between the two arms.[54] Some studies have shown that the only benefit is blood pressure control, not renal function.[55,58,59]

STRENGTHS AND WEAKNESSES OF THE MOST-QUOTED CLINICAL TRIALS

The ASTRAL trial[15] enrolled 806 patients in 57 centers during a 7-year period. ASTRAL investigators concluded that renal revascularization carries considerable risk, but no clinical benefit, compared with medical therapy in patients with ARAS. Limitations to the study design include selection bias because the primary indication was to “enroll patients in whom you were uncertain stenting would be beneficial.” Only two patients were randomized in each center per year, most likely contributing to the lower technical success (79%) and a higher incidence of procedure-related complications (8%) compared with most other studies. Also, the selection of patients with RAS was based entirely on renal duplex ultrasound results, without confirming the degree of stenosis during subtraction angiography or reporting the renal resistive index, resulting in significant type I error risk. The latter weakness explains why the baseline percentage stenosis was often <50%, and this could have caused a negative impact on renal revascularization because patients who benefited the most were those with severe bilateral renal ostial lesions or a single severe lesion in one functioning kidney. For no clear reason, 17% of the patients in the revascularization group did not receive intervention after invasive angiography. Less than 20% of the patients were still observed at the 5-year end point. Furthermore, creatinine concentration was a rough measurement of the GFR. Therefore, ASTRAL has no conclusive evidence to change or to guide current practice.

The STAR was a randomized study that included 140 patients with RAS (>50% by duplex ultrasound) without any objective assessment of the severity of the lesions.[13] In the stent group, only 72% received RASt; the rest were excluded because their lesions were <50% on angiography. Only 16% in the stent group and 22% in the medical therapy group reached the primary end point, with no difference in blood pressure control or overall mortality between the two arms. Therefore, the authors concluded that there is no perceived benefit for stenting. However, the editors noted that the study was underpowered as the rate of events in the control group was lower than expected. A significant portion of the population had <70% stenosis, and hemodynamic significance was not assessed. Blood pressure was required to be treated to less than 140/90 mm Hg on entry, which likely excluded patients with truly resistant hypertension who may be more likely to benefit from stenting for renovascular hypertension. These weaknesses and study limitations made it difficult for STAR to influence clinical practice in the area of RASt for ARAS.

The HERCULES trial[18] was a prospective multicenter trial of RASt in patients with uncontrolled hypertension and ARAS that evaluated the safety and effectiveness of the RX Herculink Elite Renal Stent System (Abbott Vascular, Santa Clara, Calif). There were a total of 202 patients (241 total lesions; 78 bilateral lesions). The primary end point was 9-month binary restenosis determined by duplex ultrasound or angiography. Secondary end points included changes in blood pressure, antihypertensive medications, and renal function between baseline and 9 months. The restenosis rate was 10.5% at 9 months. Freedom from major adverse events was 94.8%. At 9 months, tire mean SBP significantly decreased ($P < .0001$) after stenting with no change in medications. The authors concluded that the

HERCULES trial demonstrated a clinically and statistically significant reduction in SBP in patients with uncontrolled hypertension along with a low in-stent restenosis rate (10.5% at 9 months) and low complication rate (1.5% at 30 days). This study highlights that when appropriate patients are selected for RASt, impressive reductions in blood pressure may be anticipated; however, the magnitude of absolute reduction in SBP was related to baseline SBP.

The CORAL trial is the most recent update in the world of renal artery angioplasty and stenting.[60] This was a National Institutes of Health-funded open-label randomized controlled trial that compared medical therapy alone with medical therapy and RASt in patients with ARAS. The primary end points were mortality, renal function, and the occurrence of adverse cardiovascular and renal events defined as “a composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, or hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy.” They found no difference between stenting and medical therapy for these end points in this cohort of 931 patients. The secondary end point was blood pressure improvement, and there was an almost parallel reduction in systolic hypertension in the control arm compared with stenting, with a statistically significant 2.3 mm Hg lower SBP in the stent arm. The severity of stenosis (>80%) did not seem to affect the outcome, but the study was not designed to answer that question. There were numerous weaknesses involved with the trial, including enrollment problems that nearly ended in a declaration of futility. However, the indications for enrollment were loosened, and patients with controlled blood pressure were included. The average baseline SBP was lower than in any of the well-controlled nonrandomized trials. Furthermore, the study period was increased from 2 to 3 years to allow a lower number of patients to reach predictive statistical significance. There was a significant potential heterogeneity of technique, which even in the presence of roll-in analysis could have affected outcomes. However, it could be argued that RAS technique has a limited opportunity for wide variation, and any existing heterogeneity in those large experiences combined with the use of comparison groups receiving structured and described medical management regimens provides much greater generalizability than any single-center or single-operator experience.

The RAS-CAD study was a clinical trial designed to examine the effect of RASt and medical therapy vs medical therapy alone on the progression of left ventricular hypertrophy in patients with coronary artery disease and RAS.[16] Exclusion criteria included RAS >80%, as the authors acknowledged the probable protective effect of RASt for severe stenosis. In 83 patients at 1 year, there was a statistically significant drop in SBP and DBP in the medical therapy arm and a nonstatistically significant drop in SBP and DBP in the stenting with medical therapy arm. Neither study group had a statistically significant change in renal function at 1 year, although the GFR was stable in both groups. Both arms had a statistically significant reduction in left ventricular mass index (LVMI), but there was no difference between the groups. The authors concluded that there was no significant clinical benefit of renal revascularization on LVMI in patients with RAS of 50% to 80% with coronary artery disease. The main limitations of this study included the exclusion of patients with >80% RAS and an 80% power of the study to detect a $P < .05$ difference between the two groups

for LVMI change based on patient enrollment. Furthermore, the study was designed to assess the impact of RAS treatment on cardiac structure and function, not clinical end points.

SUMMARY OF CLINICAL DATA

From these studies, we created a summary table to demonstrate the various study treatment groups based on the type of intervention, such as PTA, stent, medical treatment, or any combination of the three, along with the subsequent outcomes (Table I). In addition, the summary table and later analysis gave equal weight to all study arms regardless of being retrospective, prospective, or randomized. However, as we mentioned in our review, many of the prospective and randomized studies also suffered from enrollment and execution bias. If a study contained more than one treatment arm, it is represented as multiple rows, so there is one row for each type of treatment. In summary, there were 47 treatment arms, and the overall average age of participants at enrollment was 67 ± 4.3 years. There were slightly more men (55% ± 10%), with an average baseline stenosis of 74.2% ± 8.6%. On average, 25% ± 15.5% of patients had bilateral RAS (regardless of treatment), 29% ± 11.9% of patients had diabetes, and 48.8% ± 11.4% of patients had peripheral vascular disease (although several studies did not report peripheral vascular disease or diabetes mellitus).

For the clinical outcome of blood pressure after intervention, 37 of the 46 study treatment groups (78.7%) reported improvement in blood pressure during the follow-up period. We found a significantly lower percentage of diabetics in the study treatment groups that reported improvement (27.5% ± 16.1% vs 41.7% ± 2.6%; $P = .022$). We found no difference in the type of study, retrospective (60%) vs prospective clinical trials (83.8%; $P = .186$), for reporting blood pressure improvement. In addition, there was a trend toward shorter average follow-up (in months) for the treatment groups that showed improvement (20.2 ± 11.2 months) than for those without improvement (27.7 ± 12.9 months; $P = .075$). When analyzing renal artery angioplasty/stenting for improvement in hypertension, we found improvement in 31 (83.8%) of the 37 treatment arms. The treatment arms reporting hypertension improvement contained a lower percentage of patients with diabetes (28.1% ± 11.8% vs 42.9% ± 1.0%; $P = .041$). Likewise, they were more likely to record baseline SBP (96.8% vs 50%; $P = .010$) and DBP (93.5% vs 50%; $P = .022$). In addition, the blood pressure improvement study arms were more likely to report mortality (83.9% vs 33.3%; $P = .022$) and restenosis (74.2% vs 33.3%; $P = .073$; Table III). It appears that the treatment arms that report hypertension improvement were more likely to measure and to report these other types of end points as well.

For the clinical outcome of renal function after intervention, we found that 10 (21.3%) of the 47 study treatment groups showed a statistically significant RFIS from baseline after intervention, and all but one also reported an improvement in blood pressure control. In general, the majority of studies did not report a significant change in renal function, but in some studies it was noted to worsen, although not significantly. Two studies did report a statistically significant worsening of renal function in either creatinine concentration or GFR for the overall population.[21,40] Some studies reported stabilization of renal function, but this definition varied across groups. We found a significantly higher rate of bilateral stenosis at

enrollment (37.1% ± 18.5%) for the study groups with RFIS compared with those without (21.2% ± 12.3%; *P* = .003). The RFIS study arms also reported a trend toward a larger percentage of diabetics (34.6% ± 7.3% vs 27.3% ± 12.6%; *P* = .109). Baseline GFR was significantly lower in the RFIS group (39.7% ± 16.9% vs 57.1% ± 10.1%; *P* = .012), and baseline stenosis was not significantly higher (78.2% ± 8.4% vs 73.2% ± 8.5%; *P* = .149). Retrospective studies reported more cases of RFIS (60% vs 10.8%; *P* = .003) than clinical trials did; and all (10 of 10) were stent treatment arms, one of which was PTA plus stent, and nine of 10 of these arms also had blood pressure improvement. The RFIS treatment arms were less likely to exclude patients on the basis of renal function (ie, elevated creatinine concentration or low GFR; 10% vs 62.2%; *P* = .004). Interestingly, most of the focus on RFIS occurred between 2000 and 2008 (83%; 10 of 12), with more recent studies including CORAL, ASTRAL, RAS-CAD, and STAR not reporting these outcomes for either medical therapy or stenting.

When we compared the medical therapy–only with the stent-only arms, we found that stent-only arms were significantly more likely to report RFIS (34.6% vs 0%; *P* = .039) and trended toward better blood pressure control (88.5% vs 60%; *P* = .076). However, some studies did not necessarily report their results in a manner in which we could determine the outcome.

WHO IS THE APPROPRIATE PATIENT FOR REVASCULARIZATION?

Patients with truly resistant hypertension should be given multiple medications, which in most cases should include the “CORAL cocktail” of candesartan, thiazide, and Caduet (amlodipine and atorvastatin) or the equivalent because these medications had a much higher than expected efficacy in the trial. The anatomic criteria should include hemodynamically significant stenosis and low-risk anatomy in patients with >75% of the overall renal mass (ie, would include pole to pole kidney length ≥%8 cm on ultrasound) with significant hypertension. All patients with documented pulmonary edema without valvular or ischemic substrate should be considered for renal stents. Institutions should revisit the current policy for renal stents, and it should be optimized to include an explanation of the CORAL trial[14] and the lack of “Level I” data for any indication.

In general, a patient will be referred for intervention for uncontrolled hypertension, deteriorating renal function, abrupt congestive heart failure, or a combination. With the maze of information available today but lack of clear guidance, we attempt to offer recommendations for deciding which patients are more likely to benefit from RASt.

The availability of medications today and recent studies showing their positive impact on ARAS lead us to believe that medication should be an adjunct to RASt. Therapy with statins, antiplatelet agents, and antihypertensive agents, as appropriate, should be offered to any patient with ARAS. Use of angiotensin-converting enzyme inhibitors should be carefully tailored to the individual, and renal function should be monitored.

A significant amount of evidence suggests that patients will derive clinical benefit in blood pressure control after RASt. This is largely seen in an appreciable decline in blood pressure

after intervention with the need for fewer antihypertensives. Whereas bilateral stenosis has not been definitively proved to be a predictor of blood pressure response, it should not deter the clinician from offering bilateral intervention. Patients with marked elevation in blood pressure have shown a good response to RASt as well and may be the best candidates for intervention.

Much evidence suggests that RASt will not be detrimental to renal function. Even if it does not improve renal function, it may stabilize renal function or delay renal replacement therapy. Patients with a rapid decline in renal function seem to derive benefit from RASt. Patients with baseline or worsened renal insufficiency may show improvement after RASt as well. However, the duration and stage of the renal disease may signal to the provider that renal function is no longer salvageable and that RASt would be fruitless.

LIMITATIONS

The current review is limited by the research approach, selected studies, and available data that have been presented in published reports. The inconsistent manner in which study results have been published has limited the ability to extract meaningful and useful data elements. There is tremendous heterogeneity of the presented data, with some data presented from prior trials of angioplasty for atherosclerotic disease. Such treatment practices are considered antiquated on the basis of prior trial data demonstrating the superiority of primary stent placement for this disease process. Although not exhaustive, an abundant amount of data have been extracted, compiled, and presented in a summary table that can be used for reference and to illustrate the most current published reports. A major limitation of the current review is that it centers on the studies that were selected for the construction of a summary table and then the later attempt to analyze the summary table. Although somewhat creative, a quasi– meta-analysis method to analyze the data in aggregate form or by study arm should be considered as lacking normal statistical robust methods for all comparisons. As such, the conclusions and recommendations of the current review should be viewed with caution. However, it offers more detail, comparisons, and summary information than a normal study-by-study critique and review.

Another limitation of the review is that the main focus is on blood pressure, renal function, and other surrogate outcomes that have consistently been reported in past literature. Blood pressure as a primary end point for a study is difficult to measure and to compare. Blood pressure is not a fixed and readily measurable end point, and superimposed drug therapy makes it difficult to measure. Likewise, the number of medications does not serve as a good proxy for intensity of therapy required. Also lacking was the fact that many of the studies selected for review did not contain other primary outcome variables, such as survival free from adverse renal and cardiac events. Our review attempt was a good faith effort to collate a large and variable quality of data from the literature and to help clarify what has actually been reported.

CONCLUSIONS

From all of these trials, we concluded that renal revascularization should not be performed in patients with marginal or unclear indications or in centers with limited experience. Atheroembolism during renal revascularization is a valid concern, which is currently underestimated and is largely affected by procedural and operator techniques. Once more sensitive markers of renal cell injury develop, procedural technique concerns can be adjudicated and EPDs may become an integral part of renal interventions. More refinement of the catheter and stent profile may allow transition to the radial artery as a portal access with the potential to decrease access site complications and atheroembolization with RASt.

It is imperative to carefully select patients for renal revascularization (excluding those with underlying nephropathy or primary parenchymal renal disease). We believe that RASt still plays an integral role in treating patients with RAS but should be offered only to patients with truly resistant hypertension (SBP > 150 mm Hg measured by strict guidelines, patient receiving more than three blood pressure medications including a diuretic if tolerated) and hemodynamically significant RAS based on angiography (>80% stenosis) or hemodynamic assessment (>24 mm Hg systolic gradient). Finally, RASt should be offered only in experienced centers with low mortality and morbidity.

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Table I

Summary table

Study ID	Study	Year	Type	Intervention	No. of patients	Follow-up, months	Average age	% Male	Average stenosis	Bilateral stenosis	%DM	% PVD	SCr	eGFR	SBP	DBP	Renal improve	BP improve	Exclusions			
																			FMD	Occlusion	Kidney	Renal function
1	Gill	2003	2	3	100	25	68	60		26	23	36					0	1	0	0	0	0
2	Rocha-Singh	2005	2	3	208	24	70	37	62	21	26	44	1.4		168	82	0	1	0	0	1	1
3	Jaff	2012	2	3	202	9	72	38	66	32	45		1.2	58	162	78	0	1	0	0	1	1
4	Rocha-Singh	2008	2	3	100	36	71	48	68	17	26		1.4	52	157	75	0	1	0	0	0	1
5	Laird	2010	2	3	188	36	69	42	61	0	23	42	1.2		160	77	0	1	0	0	1	1
6	Zeller	2004	2	3	340	34	66	66	81	25	37	68	1.5	59	144	79	1	1	0	0	0	0
7	Dorros	2002	2	3	1058	30	69	49		36			1.7		168	84	1	1	1	0	1	0
8	Bush	2001	1	3	73	20	68	45	85	16	16	67	2.2		166	85	0	1	0	0	0	0
9	Zeller	2003	2	3	215	12	67	63	79	23	41		1.5		145	79	1	1	0	0	0	1
10	Kennedy	2002	2	3	261	21	70	41	70	38	31		1.5	51	168	82	0	1	0	0	0	0
11	Lederman	2001	1	3	300	16	70	52	62	48	29		1.5		164	84	2	1	0	0	0	0
12	Kashyap	2007	2	3	125	19	71	59	73	28	44		2.2	33	151	79	2	1	1	0	0	0
13	Bersin	2013	2	3	100	9	72	44	57	14	43	56	1.3	61	150	74	0	1	0	1	1	1
14	Prajapati	2013	2	3	86	6	56	78	85	27	40		1.3	66	170	98	0	1	0	1	1	1
15	Dangas	2001	2	3	131	15	71	46	74	17	46	60	1.9		170	84	0	1	0	0	0	0
16	Henry	2003	2	3	56	23	66	57	85	14	23		1.3		169	104	0	1	0	0	0	0
17	Nolan	2005	1	3	82	12	63	50		40	22	45			171	84	2	1	0	0	0	0
18	Burket	2000	2	3	127	15	69	46	74				1.6		169	84	0	1	0	0	0	0
19	Valluri	2012	1	3	127	3	74	46	77	35			1.8				0	0	0	0	0	0
20	Bates	2006	1	3	748	46	71	45	89	17	42	41	1.8				0	0	1	0	0	0
21	Bates	2008	1	3	748	46	71	45	89	17	42	41	1.8				2	0	0	0	0	0
22	Corriere	2008	1	3	99	2	69	49	79	42	30		1.6	47	161	79	1	1	1	0	0	0
23	Rocha-Singh	2002	1	3	51	30	72	53	75	82	35		2.3	20	177	92	1	1	1	0	1	0
24	Sapoval	2009	2	3	251	12	70	59	85	11	33		1.7	54	171	89	0	1	1	1	0	0
25	ASTRAL	2009	2	3	403	34	70	63	76	26	31	41	1.8	40	149	76	0	1	0	0	0	0
26	ASTRAL	2009	2	1	403	34	71	63	75	26	29	40	1.9	40	152	76	0	1	0	0	0	0
27	CORAL	2014	2	5	467	43	69	51	67	22	32			58	150		0	1	1	1	1	1

Study ID	Study	Year	Type	Intervention	No. of patients	Follow-up, months	Average age	% Male	Average stenosis	Bilateral stenosis	%DM	% PVD	SCr	eGFR	SBP	DBP	Renal improve	BP improve	Exclusions			
																			FMD	Occlusion	Kidney	Renal function
28	CORAL	2014	2	1	480	43	69	49	67	18	34			57	150		0	1	1	1	1	1
29	RAS-CAD	2012	2	5	43	12	69	54	60	9	44	44		68	133	73	0	0	1	0	1	1
30	RAS-CAD	2012	2	1	41	12	69	66	58	5	32	33		60	131	74	0	1	1	0	1	1
31	STAR	2009	2	5	64	24	66	67	78	50	30	48	1.7	45	160	83	0	1	1	0	1	1
32	STAR	2009	2	1	76	24	67	59	77	46	31	51	1.6	46	163	82	0	1	1	0	1	1
33	Plouin	1998	2	2	23	6	59	78	72	0	26		1.1	73	162	98	0	1	0	0	0	0
34	Plouin	1998	2	1	26	6	60	69	74	0	15		1.2	73	158	96	0	1	0	0	0	0
35	van Jaarsveld	2000	2	4	56	12	59	66	76	23	5		1.2	67	179	104	0	1	1	1	1	1
36	van Jaarsveld	2000	2	1	50	12	61	56	72	22	6		1.3	60	180	103		1	1	1	1	1
37	van de Ven	1999	2	2	42	6	64	45	77	19	7		1.5		182	101	0	1	0	0	1	1
38	van de Ven	1999	2	4	42	6	65	64	76	24	7		1.7		189	104	0	1	0	0	1	1
39	Webster	1998	2	2	12	29	59	58					2.1		185	94	0	1	0	0	0	1
40	Webster	1998	2	2	13	29	62	54					1.6		179	99	0	0	0	0	0	1
41	Webster	1998	2	2	29	29	62	55					1.9		186	96	0	0	0	0	0	1
42	Webster	1998	2	1	16	29	63	56					1.7		179	93	0	0	0	0	0	1
43	Webster	1998	2	1	14	29	60	64					1.9		171	90	0	0	0	0	0	1
44	Webster	1998	2	1	51	29	65	39					1.6		176	103	0	0	0	0	0	1
45	Pizzolo	2004	1	4	63	28	66	63	87	30	30	51	1.5		168	95	2	1	1	0	0	0
46	Pizzolo	2004	1	1	37	28	70	73	79	27	38	72	1.4		159	91	0	0	1	0	0	0
47	Beutler	2001	2	3	63	23	66	63		33	6		1.9		180	100	0	1	0	0	1	1

BP improve, Blood pressure improvement; *DBP*, diastolic blood pressure; *%DM*, percentage diabetes; *eGFR*, estimated glomerular filtration rate; *FMD*, fibromuscular dysplasia; *%PVD*, percentage peripheral artery disease; *Renal improve*, renal improvement or stabilization; *SBP*, systolic blood pressure; *SCr*, serum creatinine.

Study type: 1, retrospective; 2, clinical trial or prospective.

Study intervention: 1, medical therapy (MT); 2, percutaneous transluminal angioplasty (PTA); 3, stent; 4, PTA + stent; 5, stent + MT.

Renal improvement: 0, no change or data unavailable; 1, improvement; 2, stabilization.

All other outcomes–blood pressure improvement, study exclusions, FMD, artery occlusion, kidney size, and renal function–were coded 0 for not occurring or unavailable and 1 for improvement or existence.

Table II

Blood pressure improvement

Study ID	*Study*	*Year*	*Type*	*Intervention*
1	Gill	2003	Retrospective	Stent
2	Rocha-Singh	2005	Retrospective	Stent
3	Jaff	2012	Retrospective	Stent
4	Rocha-Singh	2008	Retrospective	Stent
5	Laird	2010	Retrospective	Stent
6	Zeller	2004	Retrospective	Stent
7	Dorros	2002	Retrospective	Stent
8	Bush	2001	Clinical trial	Stent
9	Zeller	2003	Retrospective	Stent
10	Kennedy	2002	Retrospective	Stent
11	Lederman	2001	Clinical trial	Stent
12	Kashyap	2007	Retrospective	Stent
13	Bersin	2013	Retrospective	Stent
14	Prajapati	2013	Retrospective	Stent
15	Dangas	2001	Retrospective	Stent
16	Henry	2003	Retrospective	Stent
17	Nolan	2005	Clinical trial	Stent
18	Burket	2000	Retrospective	Stent
22	Corriere	2008	Clinical trial	Stent
23	Rocha-Singh	2002	Clinical trial	Stent
24	Sapoval	2009	Retrospective	Stent
25	ASTRAL	2009	Retrospective	Stent
26	ASTRAL	2009	Retrospective	MT
27	CORAL	2014	Retrospective	Stent + MT
28	CORAL	2014	Retrospective	MT
30	RAS-CAD	2012	Retrospective	MT
31	STAR	2009	Retrospective	Stent + MT
32	STAR	2009	Retrospective	MT
33	Plouin	1998	Retrospective	PTA
34	Plouin	1998	Retrospective	MT
35	van Jaarsveld	2000	Retrospective	PTA + stent
36	van Jaarsveld	2000	Retrospective	MT
37	van de Ven	1999	Retrospective	PTA
38	van de Ven	1999	Retrospective	PTA + stent
39	Webster	1998	Retrospective	PTA
45	Pizzolo	2004	Clinical trial	PTA + stent
47	Beutler	2001	Retrospective	stent

MT, Medical therapy; *PTA*, percutaneous transluminal angioplasty.

Table III

Renal function improvement or stabilization (RFIS)

Study ID	*Study*	*Year*	*Type*	*Intervention*	*Renal function result*
6	Zeller	2004	Retrospective	Stent	Improve
7	Dorros	2002	Retrospective	Stent	Improve
9	Zeller	2003	Retrospective	Stent	Improve
22	Corriere	2008	Clinical trial	Stent	Improve
23	Rocha-Singh	2002	Clinical trial	Stent	Improve
45	Pizzolo	2004	Clinical trial	PTA + stent	Stabilize
11	Lederman	2001	Clinical trial	Stent	Stabilize
12	Kashyap	2007	Retrospective	Stent	Stabilize
17	Nolan	2005	Clinical trial	Stent	Stabilize
21	Bates	2008	Clinical trial	Stent	Stabilize

PTA, Percutaneous transluminal angioplasty.

Table IV

Blood pressure improvement and renal function improvement or stabilization (RFIS)

Study ID	*Study*	*Year*	*Type*	*Intervention*	*Renal function result*
6	Zeller	2004	Retrospective	Stent	Improve
7	Dorros	2002	Retrospective	Stent	Improve
9	Zeller	2003	Retrospective	Stent	Improve
22	Corriere	2008	Clinical trial	Stent	Improve
23	Rocha-Singh	2002	Clinical trial	Stent	Improve
45	Pizzolo	2004	Clinical trial	PTA + stent	Stabilize
11	Lederman	2001	Clinical trial	Stent	Stabilize
12	Kashyap	2007	Retrospective	Stent	Stabilize
17	Nolan	2005	Clinical trial	Stent	Stabilize

PTA, Percutaneous transluminal angioplasty.