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REVIEW

Comparative Effectiveness of Management Strategies for Renal Artery Stenosis

An Updated Systematic Review

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Background: Atherosclerotic renal artery stenosis (ARAS) is associated with high blood pressure (BP), decreased kidney function, renal replacement therapy (RRT), and death.

Purpose: To compare benefits and harms of percutaneous transluminal renal angioplasty with stent placement (PTRAS) versus medical therapy alone in adults with ARAS.

Data Sources: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials from 1993 to 16 March 2016; gray literature; and prior systematic reviews.

Study Selection: Randomized, controlled trials (RCTs); nonrandomized, comparative studies (NRCSs); single-group studies; and selected case reports that reported all-cause and cardiovascular mortality, RRT, kidney function, BP, and adverse events.

Data Extraction: Six researchers extracted data on design, interventions, outcomes, and study quality into a Web-based database.

Data Synthesis: Eighty-three studies met eligibility criteria. In 5 of 7 RCTs, PTRAS and medical therapy led to similar BP control in patients with ARAS, and no RCTs showed statistically significant differences in kidney function, mortality, RRT, cardiovascular events, or pulmonary edema. Eight NRCSs had more variable results, finding mostly no significant differences in mortality, RRT, or cardiovascular events but heterogeneous effects on kidney function and BP. Procedure-related adverse events were rare, and medication-related adverse events were not reported. Two RCTs found no patient characteristics that were associated with outcomes with either PTRAS or medical therapy. Single-group studies found various but inconsistent factors that predict outcomes. Case reports provided examples of clinical improvement after PTRAS in patients with acute decompensation.

Limitation: Limited clinical applicability and power in RCTs, and possible publication bias and lack of adjusted analyses in NRCSs.

Conclusion: The strength of evidence regarding the relative benefits and harms of PTRAS versus medical therapy alone for patients with ARAS is low. Studies have generally focused on patients with less severe ARAS.

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As the population continues to age, the prevalence of atherosclerotic renal artery stenosis (ARAS) is increasing. Prevalence is particularly high among persons with risk factors for cardiovascular disease (CVD), with estimates ranging from 10.5% among patients undergoing coronary angiography to 54% among those with congestive heart failure (1). Among persons aged 66 years or older, 6.8% have been found to have ARAS (2). Hemodynamically significant ARAS, defined as at least 50% to 70% stenosis, is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (3, 4). Options for ARAS treatment are medical therapy—including aggressive blood pressure (BP) control, statins, and antiplatelets—or renal artery revascularization with continued medical therapy. Percutaneous transluminal renal angioplasty with stent placement (PTRAS) is the current standard for revascularization (5). Use of PTRAS has decreased from its peak in 2006 but remains common at 6.7 procedures per 100 000 adults (6).

A 2007 systematic review of management strategies for ARAS concluded that the evidence did not support one treatment approach over another, and no defined set of clinical or intervention characteristics was convincingly associated with CVD, BP control, and kidney function (7, 8). Since then, 2 large trials—CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) (9) and ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) (10)—have been published, each calling into question the clinical value of invasive intervention for ARAS. Given the inconclusive prior review and new evidence, it is timely to reevaluate the comparative benefits and harms of strategies for management of patients with ARAS and to identify factors that may predict which patients are most likely to benefit from each intervention.

METHODS

This review was based on a systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ). It followed a standard AHRQ protocol with input from a panel of nephrologists, invasive cardiologists, radiologists, and vascular surgeons. The protocol was published at www.effectivehealthcare.ahrq.gov on 20 January 2015.

See also:

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Data Sources

We searched MEDLINE and EMBASE from January 2007 through 16 March 2016 and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews through the fourth quarter of 2015. Eligible studies published between 1993 and 2007 from our previous systematic reviews (7, 8) were also included. We supplemented the search with studies in the U.S. Food and Drug Administration database, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform; recent systematic reviews; and proceedings of national renal, vascular surgery, and urology conferences from 2012 through 2014. We solicited additional citations from our expert panel and from manufacturers. The electronic search strategy combined terms for renal artery stenosis, renal hypertension, and renal vascular disease and was limited to adult humans, relevant research designs, and the English language (**Supplement Table 1**, available at www.annals.org).

Study Selection

Six researchers screened citations in duplicate. We included studies of adults treated for ARAS that reported long-term (≥6 months) outcomes or adverse events. The outcomes of interest were all-cause mortality; kidney function (renal replacement therapy [RRT] and categorical and continuous changes in glomerular filtration rate [GFR], creatinine clearance, or serum creatinine level); BP control (hypertension and categorical and continuous changes in BP); CVD, including congestive heart failure; and adverse events, including medication-related and procedural complications. We included randomized, controlled trials (RCTs) and nonrandomized, comparative studies (NRCSs) comparing PTRAS versus any medical therapy with at least 10 participants per group. Noncomparative (single-group) studies were eligible only if they reported adverse events or outcome predictors and had at least 30 participants (PTRAS studies) or at least 10 participants (medication-only studies). We also included the 20 most recent (through 2014) case reports of patients with acute ARAS decompensation because of a concern that these patients would not have been included in other studies. Studies of open surgical revascularization and other noncomparative studies are reported elsewhere (11). We excluded studies that evaluated ARAS treatment in patients with kidney transplantation, renal cell or other carcinoma, concurrent aortic or aortoiliac aneurysm repair, or prior revascularization and studies in which more than 20% of the study population had non-ARAS disease.

Data Extraction and Assessment

Data from each study were extracted by 1 of 6 experienced methodologists and confirmed by at least 1 other. Extracted data included study, participant, and ARAS characteristics; interventions; outcomes; and study design. We applied the Cochrane risk-of-bias tool for RCTs (12) and selected questions from the Newcastle-Ottawa Scale (13) about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up. Two reviewers independently assessed risk of bias at the study level, with notation of specific outcomes at increased risk of bias (for example, due to high attrition). Two reviewers independently categorized the strength of evidence across studies as high, moderate, or low for each outcome category on the basis of the number of studies, study designs, study limitations (such as risk of bias), applicability, consistency of study results, precision of effect estimates, likelihood of reporting bias, other limitations, and summary findings across studies (14).

Data Synthesis

Meta-analysis was not conducted because of significant clinical heterogeneity. Between-group comparisons are summarized by effect size (expressed as either a hazard ratio [HR] or an odds ratio) and were synthesized qualitatively.

Role of the Funding Source

The funding agency (AHRQ) participated in protocol development and reviewed the full report. The research team independently conducted the review.

RESULTS

The literature search retrieved 1560 citations, of which 189 were evaluated as full-text articles in addition to 54 studies from the 2006 and 2007 evidence reports and other systematic reviews and 74 case reports (**Appendix Figure 1**, available at www.annals.org). In total, 83 studies (33 of which were newly identified) were eligible, including 15 that compared PTRAS with medical therapy; 39 that provided data on adverse events; 28 outcome predictor, subgroup, or cotreatment analyses; and 20 case reports of acute decompensation.

Characteristics of Comparative Studies

Fifteen comparative studies with 4006 total patients compared PTRAS with medical therapy for ARAS. Of these, 7 were RCTs (9, 10, 15–21) and 8 were NRCSs (22–29).

The 7 RCTs analyzed a total of 2178 patients. The 2 largest RCTs (CORAL [9] and ASTRAL [10]) reported on 931 and 806 patients, respectively, and the remaining RCTs included a range of 52 to 140 patients (9, 10, 15–17, 19, 21). Enrolled patients had uncontrolled BP while receiving at least 2 medications and up to about stage 3 or 4 CKD (**Table 1**; **Supplement Table 2**, available at www.annals.org). The definitions of ARAS varied across studies (**Supplement Table 3**, available at www.annals.org). Only the CORAL trial measured stenosis severity with translesional pressure gradients (9). All trials excluded patients with acute decompensation. Three of the 7 RCTs had high risk of attrition bias, and 2 had unclear risk. Two RCTs have been reported only as conference abstracts (19, 21); both had incomplete study descriptions and high risk of selective outcome reporting, and 1 included only selected patients from a terminated trial (21) (**Supplement Table 4**, available at www.annals.org).

Eight NRCSs compared PTRAS with medical therapy among 1828 patients (22–29). All NRCSs included patients who had uncontrolled BP while receiving at least 2 medications and about stage 3 to 4 CKD. Four studies included patients with acute flash pulmonary edema or acute kidney injury (25, 26, 28, 29). The NRCSs were about evenly divided between high and low risk of selection bias (5 with high risk and 3 with low risk), attrition bias (incomplete outcome data; 3 with high risk and 5 with low risk), and selective reporting bias (3 with high risk, 4 with low risk, and 1 with unclear risk). In all NRCSs, the sample representativeness was rated as having low risk of bias. Reporting of medical therapy was often incomplete, and none of the NRCSs adequately adjusted for potential confounders.

Effects of Interventions on Outcomes

Mortality

We found low strength of evidence of no difference in mortality, but none of the studies was powered to detect differences between PTRAS and medical therapy. Four RCTs (9, 10, 15, 16) reported mortality data for 1 to 5 years of follow-up, and 5 NRCSs (22, 24, 26, 27, 29) reported mortality at 6 months or later (**Table 1**; **Supplement Table 5**, available at www.annals.org). Effect sizes ranged from 0.55 to 2.35, with no clear explanation for the heterogeneity (**Figure 1**). In the 4 RCTs, no statistically significant differences were found between PTRAS and medical therapy alone in all-cause mortality and cardiovascular mortality. Among the 5 NRCSs, only 1 found a statistically significantly reduced risk for death (45% with PTRAS vs. medical therapy) (26).

RRT

We found low strength of evidence of no difference in progression to ESRD, but studies were generally not powered to detect differences between PTRAS and medical therapy. Four RCTs of PTRAS versus medical therapy reported on RRT (9, 10, 15, 17), and 5 NRCSs reported data on progression to ESRD (22, 24, 27–29). No statistically significant differences in initiation of RRT were found in the RCTs, with rates of initiation varying from 0.7% at 2 years to 10% at 4 years (**Figure 2**; **Supplement Table 6**, available at www.annals.org). Among NRCSs, 1 explicitly reported that no patients started dialysis, and the remaining 4 reported no significant differences for patients progressing to ESRD.

Cardiovascular Events

We found low strength of evidence of no difference in rates of CVD events, but none of the studies was powered to detect differences between PTRAS and medical therapy, and reported CVD outcomes varied widely across studies (**Supplement Table 7**, available at www.annals.org). Four RCTs reported similar event rates between interventions for myocardial infarction; stroke; incident coronary artery, peripheral artery, or cerebrovascular disease; cardiovascular mortality; and cardiovascular event–free survival (9, 10, 15, 19). In 3 RCTs (9, 15, 16), episodes of pulmonary edema or congestive heart failure were uncommon (1% to 6%) and did not differ significantly between treatment groups. Three NRCSs each reported on different cardiovascular outcomes (22, 27, 29); stroke, angina, and abdominal aortic aneurysm rupture each occurred in no more than 1 patient per study.

Kidney Function

We found low strength of evidence that kidney function may be improved in patients who undergo PTRAS; however, this conclusion is based primarily on NRCSs that did not adjust for confounders. Kidney function was heterogeneously reported in 6 RCTs (9, 10, 15–17, 21) and 7 NRCSs (22–27, 29). Measures of kidney function did not statistically significantly differ between interventions in 5 of the trials (9, 10, 15, 16, 21) (**Table 1** and **Supplement Table 6**). Only 1 RCT (17) found a significant difference: The decrease in serum creatinine level exceeded 20% more often with PTRAS ($P < 0.001$). Among NRCSs reporting categorical kidney outcomes, 2 reported significantly more patients with improved (or not worse) GFR after PTRAS (25, 27), but 1 reported similar rates of GFR improvement and worsening (26). Three of 7 NRCSs reported larger improvements in serum creatinine level or GFR measures after PTRAS than with medical therapy alone (although statistical significance was not analyzed) (22, 23, 25), but 4 reported similar and nonsignificant changes in kidney function (24, 26, 27, 29).

BP Control

We found low strength of evidence of no difference in BP control among patients undergoing PTRAS compared with medical therapy alone; however, studies had heterogeneous findings. In 5 of 6 RCTs, treatments did not significantly differ in either categorical or continuous measures of BP (10, 15, 16, 19, 21) (**Table 1**; **Supplement Table 8** and **Appendix Figures 2** and **3**, available at www.annals.org). The CORAL trial (9) found small but statistically significant differences in changes in systolic BP (−2.3 mm Hg [95% CI, −4.4 to −0.2 mm Hg]) and the number of antihypertensive medications (0.2 fewer) after PTRAS. In a seventh RCT (17), significantly more patients were cured of hypertension (11% vs. 0%) after PTRAS versus medical therapy. Changes in BP reported in 7 NRCSs varied widely (22–27, 29), with significant reductions in systolic BP in 2 studies after PTRAS (25, 27). In 4 of 5 NRCSs, changes in the number of antihypertensive medications did not differ (22, 24, 25, 27, 29).

Adverse Events, Procedural Complications, and 30-Day Mortality

Adverse events related to PTRAS and medical therapy were inconsistently defined and reported across studies (**Supplement Table 9**, available at www.annals.org). In 3 RCTs, periprocedural deaths were rare, with

Table 1. Characteristics and Main Results of Comparative Studies of PTRAS Versus Medical Therapy

Study, Year (Reference)	Enrollment Dates	Mean Duration, *y*	Interventions*	Participants, *n*	Mean Stenosis Percentage	Bilateral Stenosis, %	Mean Blood Pressure, *mm Hg*
Randomized, controlled trials							
Bax et al, 2009 (15) (STAR)	2000–2005	2	PTRAS	64	NR	50	160/83
			ARB, statin, aspirin	76	NR	46	163/82
Cooper et al, 2014 (9) (CORAL)	2005–2010	3.6	PTRAS	459	67.3	22	150/NR
			CCB, statin, diuretic	472	66.9	18	150/NR
Marcantoni et al, 2012 (16) (RASCAD)	2006–2009	1	PTRAS	43	60	NR	133/73
			α-Blockers, β-blockers, CCB, diuretic	41	58	NR	131/74
Scarpioni et al, 2009 (19) (NITER)	NR	3.6	PTRAS	24	80	58	148/79
			Medication (NR)	28	80	46	150/79
Wheatley et al, 2009 (10) (ASTRAL)	2000–2007	5	PTRAS	403	76	NR	149/76
			α-Blockers, β-blockers, CCB, diuretic, statin, antiplatelet agent, warfarin	403	75	NR	152/76
Zeller, 2013 (21) (RADAR)	2008–2010	1	PTRAS	34	≥70	NR	NR
			Best medical treatment†	33	≥70	NR	NR
Ziakka et al, 2008 (17)	NR	4	PTRAS	36	NR	39	178/88
			α-Blockers, β-blockers, CCB	46	NR	30	175/90
Nonrandomized, comparative studies							
Arthurs et al, 2007 (22)	2001–2005	2.9	PTRAS	22	NR	55	142/73
			ACE inhibitor/ARB, β-blockers, diuretic	18	NR	61	162/75
Cianci et al, 2011 (23)	2004–2009	1	PTRAS	53	≥70	28	160/86
			ACE inhibitor/ARB, α-blockers, β-blockers, CCB, statin, clopidogrel, aspirin	40	≥50	20	155/83
Dichtel et al, 2010 (24)	1999–2007	3	PTRAS	47	NR	57	145/75
			Medication (NR)	71	NR	41	141/70

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Table 1–Continued

Mean eGFR or Creatinine Clearance, mL/min/1.73 m²	Mean Serum Creatinine Level, μmol/L (mg/dL)	Cardiovascular Disease, %	All-Cause Mortality	Kidney Function	Blood Pressure
Creatinine clearance: 45	154 (1.7)	NR	8.1%; HR, 0.99 (95% CI, 0.30–3.24)	Worse: 16%; HR, 0.73 (CI, 0.33–1.61) RRT: 1.8%	Change: −9/−6 mm Hg Refractory hypertension: 0% <140/90 mm Hg: 32%
Creatinine clearance: 46	145 (1.6)	NR	8.1%	Worse: 22% RRT: 0% (CI, 0%–12%)	Change: −8/−3 mm Hg Refractory hypertension: 4% <140/90 mm Hg: 29%
eGFR: 58	NR	MI: 27 CHF: 12	14%; HR, 0.80 (CI, 0.58–1.12)	Worse or stable: 17%; OR (worse), 1.15 (CI, 0.82–1.61) RRT: 3.5%; HR, 1.98 (CI, 0.85–4.62)	Change: −17/NR mm Hg
eGFR: 57	NR	MI: 30 CHF: 15	16%	Worse or stable: 19% RRT: 1.7%	Change: −16/NR mm Hg
Creatinine clearance: 65; eGFR: 68	NR	NR	5.3%; OR, 0.92 (CI, 0.12–6.88)	Change in GFR: −2 mL/min/1.73 m²	Change: −6/−2 mm Hg
Creatinine clearance: 58; eGFR: 60	NR	NR	5.7%	Change in GFR: −0.7 mL/min/1.73 m²	Change: −6/−6 mm Hg
eGFR: 40	150 (1.7)	CAD: 63 AAA: 25 PAD: 50	NR	NR	Cured: 0% *P* for systolic blood pressure = 0.53 *P* for diastolic blood pressure = 0.22
eGFR: 46	141 (1.6)	CAD: 64 AAA: 29 PAD: 43	NR	NR	Cured: 0%
eGFR: 40	179 (2.0)	CAD: 50 PAD: 41 CVA: 18	26%; HR, 0.90 (CI, 0.69–1.18)	Worse: 37%; OR, 0.94 (CI, 0.69–1.29) Improved: 29%; OR, 1.16 (CI, 0.83–1.63) AKF: 6.5%; OR, 1.12 (CI, 0.62–2.01) ESRD: 7.8%; OR, 0.99 (CI, 0.59–1.67)	Change: −8/−3 mm Hg
eGFR: 40	178 (2.0)	CAD: 48 PAD: 40 CVA: 19	26%	Worse: 38% Improved: 26% AKF: 5.9% ESRD: 7.9%	Change: −11/−6 mm Hg
NR	NR	NR	NR	Change in GFR: 4.0 mL/min/1.73 m²	141/79 mm Hg at 1 y
NR	NR	NR	NR	Change in GFR: −2.0 mL/min/1.73 m²	140/75 mm Hg at 1 y
NR	208 (2.4)	NR	NR	Worse: 36%; OR, 1.06 (CI, 0.43–2.64) Improved: 31% RRT: 22%; OR, 1.36 (CI, 0.45–4.06)	Cured: 11% Improved: 67%
NR	193 (2.2)	NR	NR	Worse: 30% Improved: 0% RRT: 22%	Cured: 0% Improved: 72%
NR	88 (1.0)	CAD: 50 CeVD: 27 PAD: 36	11%; OR, 1.25 (CI, 0.16–9.88)	Reciprocal serum creatinine slope: 0 dL/mg/mo at 4 y RRT: 0%	Change: 4/5 mm Hg at 4 y
NR	133 (1.5)	CAD: 47 CeVD: 29 PAD: 35	9%	Reciprocal serum creatinine slope: −0.05 dL/mg/mo at 4 y RRT: 0%	Change: −5/5 mm Hg
eGFR: 56	129 (1.5)	NR	NR	Change in GFR: 11 mL/min/1.73 m² Change in serum creatinine level: −22 μmol/L (−0.25 mg/dL)	Change: −5/−2 mm Hg
eGFR: 51	131 (1.5)	NR	NR	Change in GFR: 5 mL/min/1.73 m² Change in serum creatinine level: −11 μmol/L (−0.13 mg/dL)	Change: −7/1 mm Hg
eGFR: 38	NR	CAD: 46 CHF: 13 PAD: 26	43%; OR, 2.35 (CI, 1.06–5.21)	Change in GFR: 0.1 mL/min/1.73 m² ESRD: 21%; OR, 1.86 (CI, 0.69–5.00)	Change: −3/−1 mm Hg
eGFR: 37	NR	CAD: 67 CHF: 27 PAD: 38	24%	Change in GFR: −0.2 mL/min/1.73 m² ESRD: 13%	Change: −7/−1 mm Hg

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Table 1–Continued

Study, Year (Reference)	Enrollment Dates	Mean Duration, *y*	Interventions*	Participants, *n*	Mean Stenosis Percentage	Bilateral Stenosis, %	Mean Blood Pressure, *mm Hg*
Hanzel et al, 2005 (25)	NR	1.75	PTRAS	26	NR	50	162/82
			Antihypertensive (not specified), statin, aspirin	40	NR	20	154/77
Kalra et al, 2010 (26)	1995–2007	1	PTRAS (cohort from Germany)	472	NR	NR	144/78
			PTRAS (cohort from United Kingdom)	89	NR	NR	157/81
			ACE inhibitor/ARB, statin (cohort from United Kingdom)	347	NR	NR	156/80
Kane et al, 2010 (27)	NR	2.8	PTRAS	50	NR	53	154/NR
			ACE inhibitor/ARB	50	NR	38	148/NR
Ritchie et al, 2014 (28)	1995–2011	3.8	PTRAS	127	NR	NR	163/83
			ACE inhibitor/ARB, statin, aspirin	340	NR	NR	155/79
Sofroniadou et al, 2012 (29)	1997–2003	7.4	PTRAS	26	NR	77	177/90
			ACE inhibitor/ARB, statin, aspirin	10	NR	NR	146/77

AAA = aortic abdominal aneurysm; ACE = angiotensin-converting enzyme; AKF = acute kidney failure; ARB = angiotensin-receptor blocker; ASTRAL = Angioplasty and Stenting for Renal Artery Lesions; CAD = coronary artery disease; CCB = calcium-channel blocker; CeVD = cerebrovascular disease; CHF = congestive heart failure; CORAL = Cardiovascular Outcomes in Renal Atherosclerotic Lesions; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; NITER = Nephropathy Ischemic Therapy; NR = not reported; NYHA = New York Heart Association; OR = odds ratio; PAD = peripheral artery disease; PTRAS = percutaneous transluminal renal angioplasty with stent placement; RADAR = Randomized, Multi-Centre, Prospective Study Comparing Best Medical Treatment Versus Best Medical Treatment Plus Renal Artery Stenting in Patients With Hemodynamically Relevant Atherosclerotic Renal Artery Stenosis; RASCAD = Stenting of Renal Artery Stenosis in Coronary Artery Disease; RRT = renal replacement therapy; STAR = 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.

* For most studies, the list of medications was incomplete because of incomplete reporting and, implicitly or explicitly, the same medications were used in patients who underwent PTRAS.

† Optimal drug therapy for control of hypertension, hypercholesterolemia, and diabetes.

none in the CORAL trial and 4 of 839 (0.5%) total across the 3 trials (9, 10, 15). In 4 RCTs (9, 10, 15, 16) and 4 NRCSs (22, 25, 28, 29), other reported serious events occurred in fewer than 3.2% of patients and included pseudoaneurysms, distal embolization, groin hematoma, bleeding requiring transfusion, acute kidney injury, and renal artery occlusion. One NRCS reported a rate of (undefined) major periprocedural complications of 4.8% (28).

A total of 42 studies reported adverse events after PTRAS (9, 10, 15, 16, 22, 25, 28–59-60–63). Mortality within 30 days of PTRAS ranged from 0% to 3.2% in 17 studies (9, 10, 15, 22, 32, 34, 36–38, 42, 44, 45, 48, 51, 58, 59, 63), with a median of 0.8% (Table 2). In a sensi-

Table 1–Continued

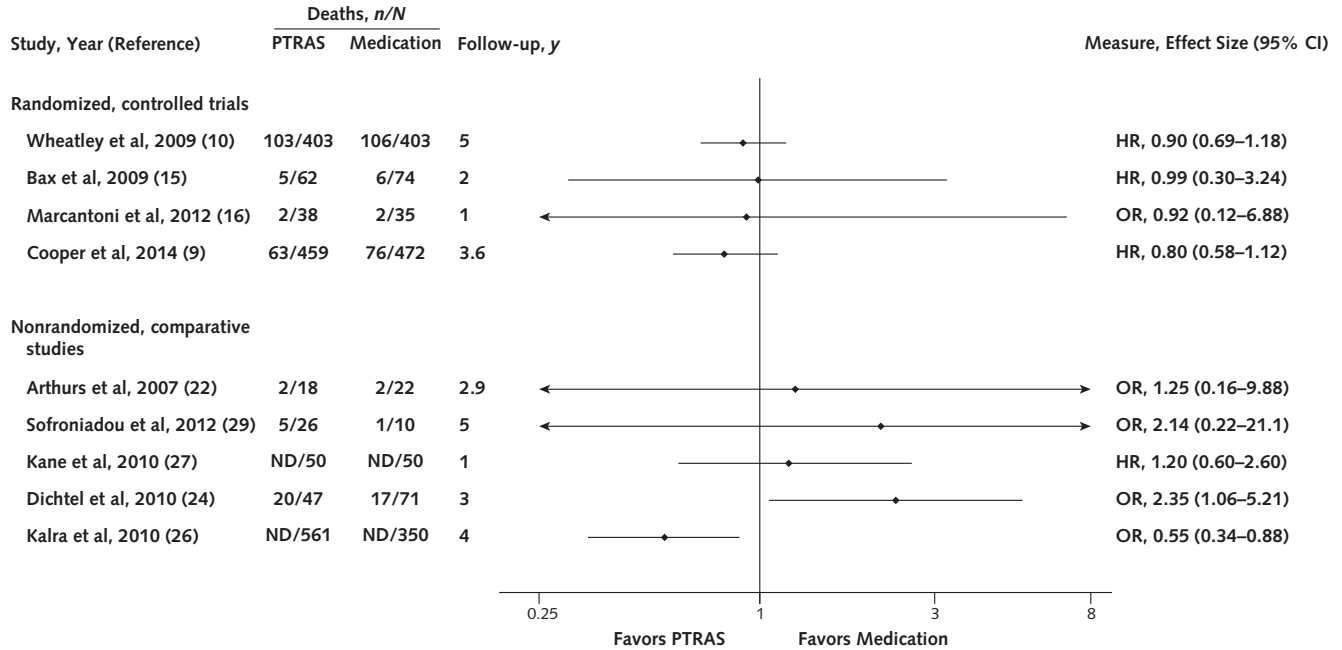
Mean eGFR or Creatinine Clearance, *mL/min/1.73 m²*	Mean Serum Creatinine Level, *μmol/L (mg/dL)*	Cardiovascular Disease, %	All-Cause Mortality	Kidney Function	Blood Pressure
GFR: 56	133 (1.5)	NR	NR	Change in GFR: 4.0 mL/min/1.73 m² Change in serum creatinine level: 0 μmol/L (0 mg/dL) GFR increase ≥10%: OR, 7.94 (CI, 2.29–27.60)	Change: −15/−8 mm Hg
GFR: 61	115 (1.3)	NR	NR	Change in GFR: −4.0 mL/min/1.73 m² Change in serum creatinine level: 9 μmol/L (0.1 mg/dL)	Change: −11/−5 mm Hg
eGFR: 60	NR	Angina: 80 CAD: 80 CeVD: 51	NR	Worse: 19% Improved: 26% Change in GFR: 0.7 mL/min/1.73 m²	Change: −10/−4 mm Hg
eGFR: 34	NR	Angina: 40 CAD: 38 CeVD: 25	NR; OR, 0.55 (CI, 0.34–0.88) at a mean of 4 y	Worse: 26%; OR, 0.71 (CI, 0.40–1.24) Improved: 28%; OR, 1.65 (CI, 0.92–2.96) Change in GFR: −1.0 mL/min/1.73 m²	Change: −13/−9 mm Hg
eGFR: 35	NR	Angina: 28 CAD: 28 CeVD: 27	NR	Worse: 33% Improved: 19% Change in GFR: −2.7 mL/min/1.73 m²	Change: −6/−5 mm Hg
eGFR: 40	NR	CHF: 94 CAD: 74 NYHA class III or IV: 66 CeVD: 54 PAD: 36	NR; HR, 1.2 (CI, 0.60–2.60)	Worse: 28%; OR, 0.28 (CI, 0.12–0.65) Improved: 26%; OR, 22.20 (CI, 6.88–71.80) Change in GFR: −9.0 mL/min/1.73 m² ESRD: 14%; OR, 1.87 (CI, 0.51–6.85)	Change: −28/NR mm Hg
eGFR: 37	NR	CHF: 84 CAD: 78 NYHA class III or IV: 62 CeVD: 48 PAD: 52	NR	Worse: 34% Improved: 8% Change in GFR: −7 mL/min/1.73 m² ESRD: 8%	Change: −9/NR mm Hg
eGFR: 37	NR	Angina: 39 MI: 39 PAD: 43	NR	ESRD: 18%; OR, 1.03 (CI, 0.61–1.75)	NR
eGFR: 35	NR	Angina: 34 MI: 30 PAD: 38	NR	ESRD: 18%	NR
GFR: 44; eGFR: 42	NR	CAD: 70 Carotid artery disease: 50 PAD: 60 CVA: 40	19%; OR, 2.14 (CI, 0.22–21.10) at 5 y	Change in GFR: −6 mL/min/1.73 m² ESRD: 12%; OR, 1.17 (CI, 0.11–12.80)	Change: −28/−13 mm Hg
GFR: 37; eGFR: 32	NR	CAD: 65 Carotid artery disease: 15 PAD: 58 CVA: 15	10% at 5 y	Change in GFR: −8 mL/min/1.73 m² ESRD: 10%	Change: −18/−9 mm Hg

tivity analysis that assumed that the remaining studies that reported complications had no perioperative deaths, 0.4% of patients died within 30 days of PTRAS overall. Major bleeding due to PTRAS, which was variously defined in 11 studies (16, 25, 35, 41, 44, 46, 49, 53, 54, 59, 63), ranged from 0.8% (bleeding resulting in limb amputation [59]) to 16% (bleeding requiring transfusion [44]), with a median of 2.9%. Other reported serious events occurred in less than 1% to 13% of the study population (Table 2). No study reported on medication-related adverse events, although the STAR (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) trial reported that no patients in the medication group died within 30 days of the start of the trial (in contrast to 2 of 62 who died within 30 days of PTRAS [15]).

Patient and Disease Factors Related to Outcomes

The CORAL and ASTRAL trials found no differences in outcomes with regard to renal dysfunction (variously defined) or degree of ARAS (≥80% vs. <80% in the CORAL trial and bilateral vs. unilateral >70% in the ASTRAL trial) (9, 10). The CORAL trial also found no interaction between the intervention and sex, black race, global kidney ischemia, or diabetes with the composite outcome of death and myocardial infarction, and no significant differences in the outcome in subgroups based on stenosis percentage, systolic BP, or peak or mean systolic pressure gradient (15, 64). In 1 retrospective NRCS, patients with flash pulmonary edema had

Figure 1. Forest plot of effect size of death in adults with renal artery stenosis receiving PTRAS versus medical therapy alone.



HR = hazard ratio; ND = no data; OR = odds ratio; PTRAS = percutaneous transluminal renal angioplasty with stent placement.

decreased mortality with PTRAS (HR, 0.43 [CI, 0.20 to 0.91] vs. medical therapy), and patients with both rapidly decreasing kidney function and refractory hypertension had decreased mortality (HR, 0.15 [CI, 0.02 to 0.94]) and CVD events (HR, 0.28 [CI, 0.10 to 0.79]) with PTRAS (28). In contrast, patients who presented at low risk with either rapidly decreasing kidney function or refractory hypertension alone had statistically similar rates of death or cardiovascular events regardless of treatment choice.

Results were mixed in the 24 PTRAS studies reporting patient or disease characteristics associated with the outcomes of interest (22, 27, 31, 43, 46, 49, 52, 54, 56–59, 65–77) (Supplement Table 10, available at www.annals.org). Overall, the studies did not provide adequate evidence that any baseline characteristic consistently predicts post-PTRAS outcomes. Among predictors analyzed in at least 3 studies, those with at least some indication of an association with favorable outcomes included worse pre-PTRAS kidney function (8 of 19 studies, although 1 found worse outcomes with worse kidney function), bilateral stenosis (5 of 12 studies), higher BP before PTRAS (5 of 8 studies), higher grade of stenosis (2 of 5 studies), higher resistive index (2 of 5 studies), and younger age (2 of 7 studies). Results were inconsistent across 8 studies of preexisting CVD. Patient sex (9 studies), history of diabetes (9 studies), and smoking (3 studies) were not associated with outcomes. None of these analyses suggest whether PTRAS is more beneficial than continuing medical therapy for any subgroup of patients.

Three studies reported analyses of patient-level predictors of clinical outcomes in patients treated medically (28, 78–80). Two studies found that statin use was associated with a lower risk for death or cardiac or renal events, and 1 found that use of angiotensin-converting enzyme inhibitors was associated with a lower risk for adverse clinical outcomes.

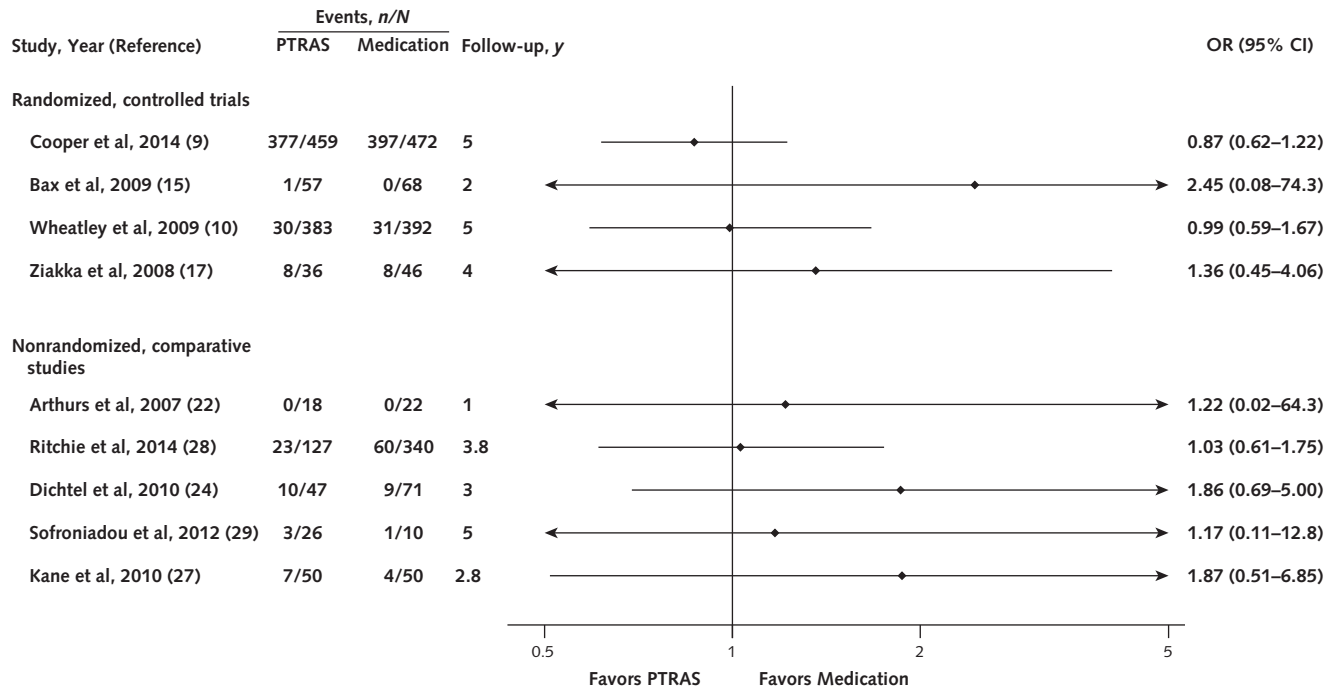
Treatment Factors Related to Outcomes

Four studies of PTRAS compared different cotreatments (Supplement Table 11, available at www.annals.org). No differences in BP or kidney function outcomes were found with use of gold-coated stents (31), sirolimus-eluting stents (62), intraluminal brachytherapy (81), or embolic protection devices (31, 35). A factorial study found that the platelet inhibitor abciximab was superior overall to placebo in preventing decreases in GFR; however, only the combined intervention group had stable GFR at 1 month ($P < 0.01$ vs. other groups) (35).

Acute Decompensation Case Reports

Few studies evaluated patients with acute decompensation. Twenty recently published case reports of management of patients with ARAS and acute decompensation (as manifested by rapid worsening of kidney function, recent severe or difficult-to-control hypertension, flash pulmonary edema, or related symptoms) found that all patients improved after PTRAS (82–101) (Supplement Table 12, available at www.annals.org). One case report described a patient who was successfully managed medically for 5 years after acute ARAS decompensation until she had a second episode of decompensation, at which point she was successfully treated with PTRAS (98).

Figure 2. Forest plot of effect size of incident renal replacement therapy in adults with renal artery stenosis receiving PTRAS versus medical therapy alone.



OR = odds ratio; PTRAS = percutaneous transluminal renal angioplasty with stent placement.

DISCUSSION

Taken together, the 7 RCTs and 8 NRCSs that compared PTRAS plus continued medical therapy versus medical therapy alone failed to support a beneficial effect of PTRAS on clinical outcomes for most patients with ARAS. There was low strength of evidence of no difference between PTRAS and medical therapy alone in mortality, RRT, cardiovascular events, and BP control and low strength of evidence of possible improvement in kidney function after PTRAS (Table 3). However, these conclusions are subject to several caveats due to important limitations in the studies.

The RCTs were limited mostly by their relatively small sample sizes, such that analyses of long-term clinical outcomes (mortality, RRT, and cardiovascular events) were underpowered to find statistically significant differences. They also were generally restrictive in their eligibility criteria and are applicable mostly to patients with a moderate degree of stenosis (50% to 70%), moderately controlled hypertension, and relatively sta-

Table 2. Periprocedural Complications With PTRAS

Complication*	Studies Reporting Complication, *n*†	Patients With Complication, *reported n/N (%)*	Median Patients With Complication (Range), *reported %*	Patients With Complication, *implied n/N (%)*‡
Death in ≤30 d	17	15/2155 (0.7)	0.8 (0–3.2)	15/4211 (0.4)
Major bleeding event	11	34/847 (1.3)	2.9 (0.8–16)	–
Renal replacement therapy	2	6/258 (2.3)	1.5/3.1§	–
Acute kidney failure	6	19/670 (2.8)	2.1 (1–13)	–
Renal artery dissection/perforation	6	25/884 (2.8)	3.0 (1–10)	25/3749 (0.8)
Renal artery thrombosis/obstruction	5	20/1222 (1.6)	1.3 (0.4–3.8)	20/3749 (0.5)
Femoral artery pseudoaneurysm	5	11/821 (1.3)	2.0 (0.3–5.9)	11/3749 (0.3)
Major complication (total or composite)	15	111/1557 (7.1)	3.3 (0–33)	–

PTRAS = percutaneous transluminal renal angioplasty with stent placement.
* Other reported complications included stent dislocation, thrombus or cholesterol embolization, contrast nephropathy, cerebrovascular event, pulmonary edema, and myocardial infarction.
† Eligible studies included those with ≥10 participants per group (for comparative studies of PTRAS vs. medication) or ≥30 total participants (for single-group studies of PTRAS). No single-group study of medication alone (with ≥10 participants) reported adverse events.
‡ Denominator assumed that studies not reporting complications had 0 events. All 42 studies reporting any complication were included for perioperative death. For arterial complications, the 5 studies that reported only perioperative death (and not any other complication explicitly) were excluded. For complications without "total" estimates, some studies likely included patients with these complications that were unreported, so these analyses were omitted.
§ Percentages of patients in the 2 studies.

Table 3. Strength of Evidence

Outcome	Strength of Evidence	Design and Number of Studies	Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Findings
Death	Low	RCTs: 4 NRCSs: 5	Moderate	RCTs: direct NRCSs: indirect	Inconsistent	Imprecise	Undetected	Important*	No evidence of a difference
Renal replacement therapy/end-stage renal disease	Low	RCTs: 4 NRCSs: 5 Case reports: 18	Moderate	RCTs: direct Others: indirect	Consistent	Imprecise	Undetected	Important*	Comparative studies: no evidence of a difference Case reports: renal replacement therapy averted with revascularization
Cardiovascular event	Low	RCTs: 5 NRCSs: 3 Case reports: 18†	Moderate	RCTs: direct Others: indirect	Consistent	Imprecise	Undetected	Important*	Comparative studies: no evidence of a difference Case reports: cardiovascular symptoms resolved immediately with revascularization
Kidney function	Low	RCTs: 6 NRCSs: 7 Case reports: 18	Moderate	RCTs: direct Others: indirect	RCTs: consistent NRCSs: inconsistent Case reports: consistent	Imprecise	Undetected	Important*	RCTs: no evidence of a difference NRCSs: heterogeneous effect on kidney function favoring PTRAS Case reports: improvement with revascularization
Blood pressure control	Low	RCTs: 6 NRCSs: 6 Case reports: 18	Moderate	RCTs: direct Others: indirect	Comparative studies: inconsistent Case reports: consistent	Imprecise	Undetected	Important*	Comparative studies: inconsistent Case reports: improvement with revascularization
Adverse events	Low	RCTs: 4 NRCSs: 4 Cohort studies (PTRAS): 34 Cohort studies (medical therapy alone): 0	Moderate	RCTs: direct Others: indirect	Consistent	Imprecise	Suspected	Important‡	Severe adverse events were rare and were reported only in PTRAS studies

NRCS = nonrandomized, comparative study; PTRAS = percutaneous transluminal renal angioplasty with stent placement; RCT = randomized, controlled trial.
* RCTs were of limited applicability to typical patients choosing PTRAS, NRCSs were inadequately adjusted, and case reports were applicable to patients with acute decompensation.
† Congestive heart failure/pulmonary edema symptoms and angina.
‡ Noncomparable adverse events between PTRAS and medical therapy; poorly reported.

ble kidney function who do not have symptoms, such as pulmonary edema. Both the CORAL and ASTRAL trials required substantive protocol changes during patient enrollment to reach their recruitment goals, which highlights a concern that patients with ARAS who enrolled in the trials were not typical of those seen in clinical practice (102). Also, all patients were treated with the current standard of care (antihypertensives, a statin, and an antiplatelet drug [103]) in only 3 RCTs: CORAL (9), RASCAD (Stenting of Renal Artery Stenosis in Coronary Artery Disease) (16), and STAR (15).

The NRCSs may have included a more generalizable population of patients but were also relatively small, which limited their ability to detect differences in long-term clinical events. They also failed to adequately control for intrinsic differences between patients who received different interventions. Thus, the NRCSs may have been substantially biased toward finding more favorable outcomes in patients who underwent PTRAS. The larger RCTs have fully published their results, but the degree of possible publication and reporting bias among the NRCSs is unclear. Adverse event reporting

was generally incomplete. No study reported medication-related adverse events, and only about half of the RCTs, NRCSs, and potentially eligible single-group studies reported procedural complications. No specific adverse event was explicitly reported in more than 17 of the 42 studies reporting complications. Nevertheless, while rates of PTRAS complications varied across studies, complication rates were low (although 30-day all-cause mortality after PTRAS was about 0.5%) in the RCTs, which used rigorous criteria for enrolling patients and implementing PTRAS and prospectively collected adverse event data.

Analyses of predictors of outcomes after PTRAS yielded inconsistent findings. The CORAL (9) and ASTRAL trials (10) failed to find a definable subset of patients who benefited from PTRAS versus medical therapy. The single NRCS that included patients with decompensated ARAS (28) found that those presenting with flash pulmonary edema or with both rapidly decreasing kidney function and refractory hypertension (but not those with either of the latter conditions alone or those at low risk) had reduced relative rates of death compared with those treated medically. This finding comports with the generally good and rapid outcomes after revascularization seen in case reports of patients with acute decompensation. However, the case reports were highly biased toward reporting of success after revascularization. Nevertheless, they do highlight that revascularization is highly beneficial for some patients. The evidence was conflicting on whether the effects of PTRAS differed in patients with bilateral and unilateral stenosis. The most consistent finding was that, as expected, those with worse cardiovascular risk factors, including worse kidney function, or a history of CVD were more likely to die or have future cardiovascular events. Whether different intervention techniques (different stent types, brachytherapy, or embolization protection devices) improve outcomes is unclear, and the evidence does not support any specific PTRAS-related technique.

We searched PubMed and the Cochrane Database of Systematic Reviews for recent pertinent systematic reviews. Since publication of the CORAL trial, 3 systematic reviews have evaluated only RCTs through 2014 or early 2015, focusing only on comparative effects (that is, not on outcome predictors or high-risk patients) (104–106). All included angioplasty without stenting, an intervention no longer used in clinical practice because of high rates of restenosis. They each included only 4 or 5 of the RCTs included in our review. Findings on comparative effectiveness of clinical outcomes (and procedural complications in the Cochrane review) from RCTs were similar. However, the Cochrane review (104) concluded that the evidence was mostly insufficient, with small improvements in diastolic BP and the number of antihypertensive drugs required after angioplasty, whereas the other reviews concluded more definitively that the interventions were equally effective (105, 106).

Future studies should focus on patients who are putatively most likely to benefit from PTRAS, namely those with proven hemodynamically significant ARAS or those who have signs of decompensation. In contrast to most existing NRCSs, future observational studies should adequately control for underlying differences between patients who undergo PTRAS and those who continue medical therapy, ideally with propensity score–adjusted analysis (107–109). Although they are not simple, well-conducted observational studies should be easier to implement and less resource-intensive than the larger, complex recent RCTs.

Overall, the evidence does not support a benefit with PTRAS over medical therapy alone in most patients with ARAS. Observational studies, however, suggest that "high-risk" patients—specifically, those with worse kidney function (variably defined), higher BP (variably defined), or flash pulmonary edema—may be more likely to have improved kidney function and BP with PTRAS. Whether these patients have benefits in survival and avoidance of cardiovascular events and RRT compared with those who continue medical therapy remains unclear. Anecdotal evidence from case reports confirms that some patients with acute decompensation due to ARAS benefit clinically from revascularization. Reanalyses of existing databases or future large observational data sets using propensity score–adjusted or similar analyses may allow for relatively unbiased analyses to determine the comparative effectiveness of PTRAS and medical therapy.

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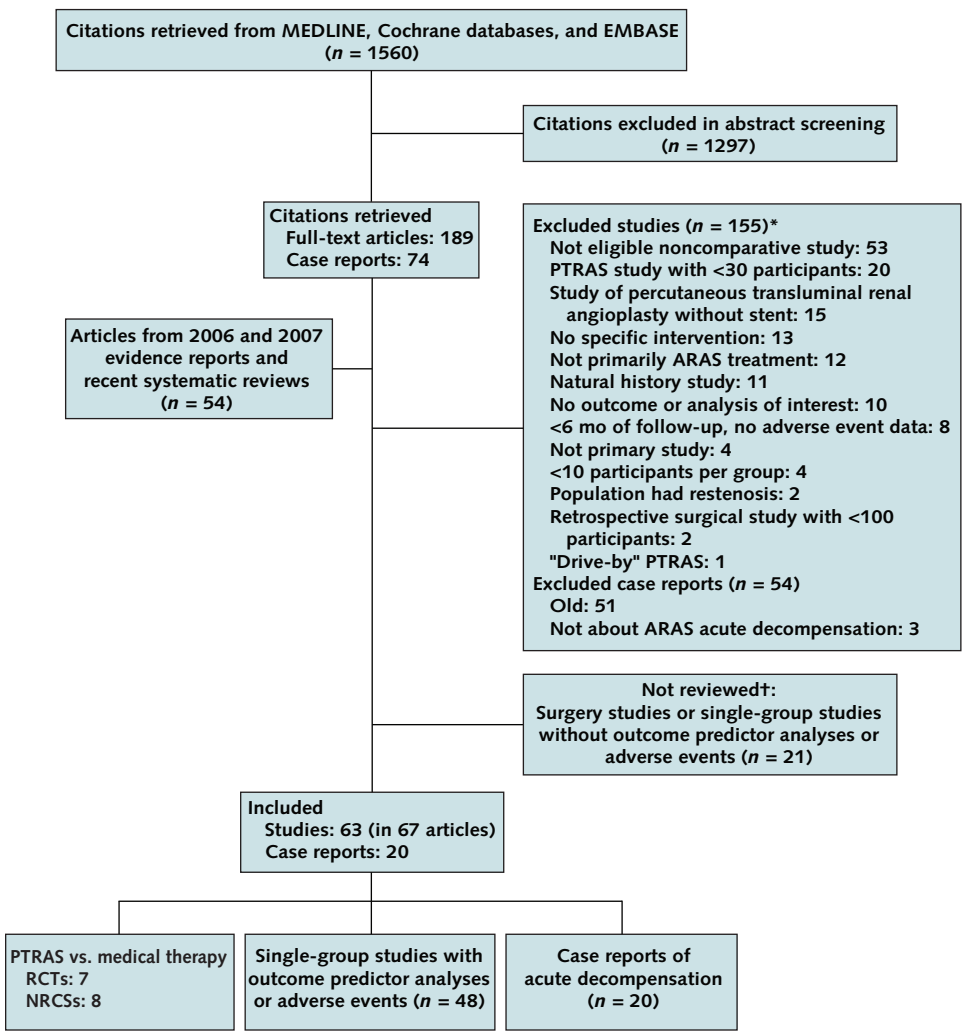
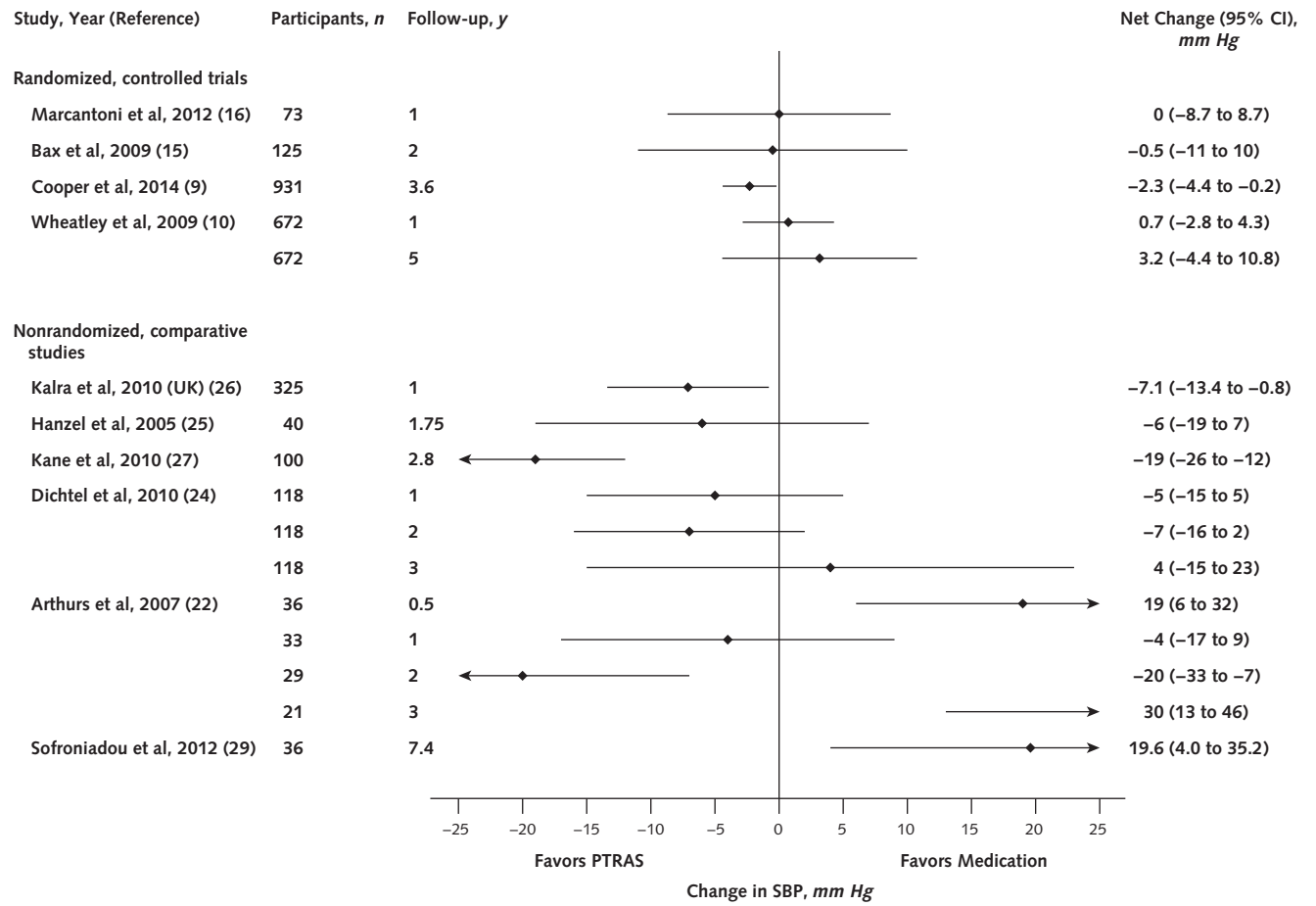
Appendix Figure 1. Literature flow diagram.



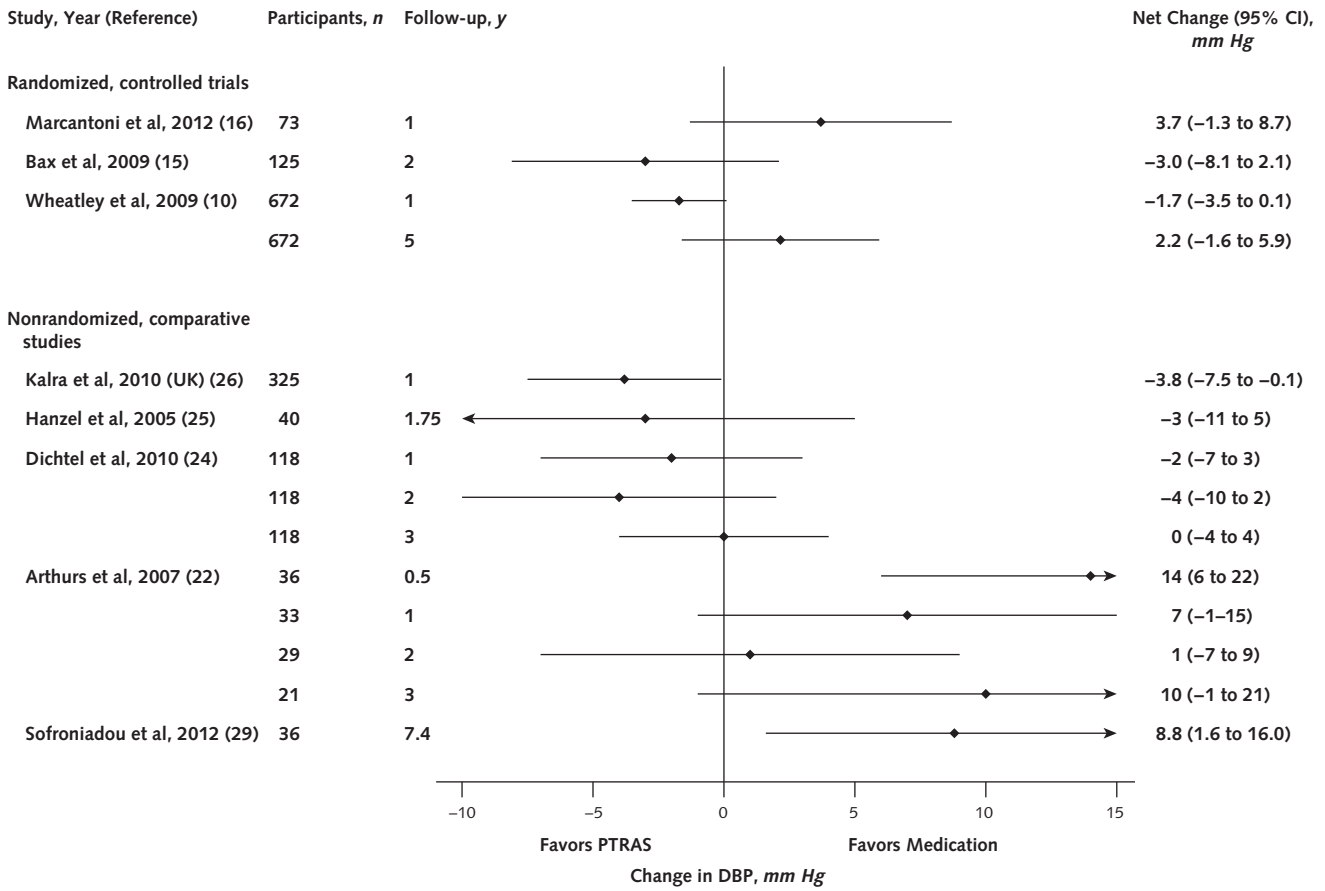
ARAS = atherosclerotic renal artery stenosis; NRCS = nonrandomized, comparative study; PTRAS = percutaneous transluminal renal angioplasty with stent placement; RCT = randomized, controlled trial.
* Does not include studies that were screened and excluded for the 2006 report.
† Studies of open surgical revascularization and other noncomparative studies are reported elsewhere (11).

Appendix Figure 2. Forest plot of net change in SBP in adults with renal artery stenosis receiving PTRAS versus medical therapy alone.



PTRAS = percutaneous transluminal renal angioplasty with stent placement; SBP = systolic blood pressure; UK = study cohorts from the United Kingdom.

Appendix Figure 3. Forest plot of net change in DBP in adults with renal artery stenosis receiving PTRAS versus medical therapy alone.



DBP = diastolic blood pressure; PTRAS = percutaneous transluminal renal angioplasty with stent placement; UK = study cohorts from the United Kingdom.