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Renal Artery Revascularization: Updated Meta-analysis With the CORAL Trial

Arguments for renal artery revascularization include blood pressure control, stabilization of renal function, and reduction in adverse cardiovascular events. We previously reported on the randomized clinical trial data to 2009 regarding renal artery revascularization compared with medical therapy. However, revascularization was associated with marginal improvement in serum creatinine levels (P = .06) and no improvement in systolic blood pressure (P = .32), although there was need for fewer antihypertensive medications (P < .001). Since then, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) Trial has been published.2

Methods | Details of the previous meta-analysis have been described.1 Briefly, the MEDLINE database was searched for trials published from study inception through June 2010. We required that patients were randomized to percutaneous revascularization of a renal artery stenosis with or without stenting vs medical therapy alone. Three independent reviewers extracted data elements. Summary relative risks and 95% CIs were calculated for dichotomous variables using a DerSimonian and Laird random-effects model. For continuous variables, the weighted mean difference (WMD) and 95% CIs were computed using a random-effects model. The Begg funnel plot assessed for publication bias, while heterogeneity was assessed by the I² measure.

An updated search of the MEDLINE database was performed from June 2010 to November 2013, which revealed 2 additional trials.2-3 Data from these trials were extracted (by 2 of us: A.A.B. and D.J.K.) and added to our preexisting database. One minor discrepancy was resolved by discussion. Analyses were performed with STATA statistical software (version 12.0; StataCorp LP).

Overall, there were 8 studies in 2223 patients. The 5 later studies routinely used stents. The mean age ranged from 59 to 72 years, and the proportion of women ranged from 27% to 50%. At baseline, the mean number of antihypertensive medications was 2.43, and the mean systolic blood pressure ranged from 131 to 182 mm Hg. The mean duration of follow-up was 34.2 months.

Renal artery revascularization was not associated with a change in systolic blood pressure from baseline when compared with medical therapy (WMD, 0.12; 95% CI, −0.97 to 1.21; P = .83) but was associated with a reduction in the number of antihypertensive medications required at follow-up (2.96 vs 3.18; WMD, −0.23; 95% CI, −0.33 to −0.12; P < .001). There was no evidence of heterogeneity (I² = 0) or publication bias (P = .45 for change in systolic blood pressure; P = .85 for medications at follow-up). Revascularization was not associated with a reduction in adverse cardiovascular or renal outcomes compared with medical therapy (Figure). Results were similar when restricted to stent-only trials.

Discussion | Among patients with renal artery stenosis and hypertension and/or chronic kidney disease, revascularization was of marginal benefit. This therapy slightly reduced the need for antihypertensive medications. However, revascularization did not reduce adverse cardiovascular or renal outcomes compared with medical therapy over a mean follow-up of 34 months.

Patients enrolled in the CORAL Trial likely mirrored clinical practice in that the degree of renal artery stenosis was somewhat modest, and the frequency of bilateral renal artery stenosis was low.2 Also, in the CORAL Trial, the average blood pressure at baseline was 150 mm Hg, a value at which revascularization may be unlikely to provide much benefit. It still remains plausible that revascularization could benefit patients with severe bilateral stenoses, or a critical stenosis that supplies a solitary kidney; however, such a trial is unlikely to be performed. Currently, the only class I recommendation for
renal revascularization is in the setting of recurrent pulmonary edema.4

In conclusion, routine revascularization of a renal artery stenosis does not seem to be clinically beneficial.

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Invited Commentary: The Kidney Connection: Holy Grail or Wild Goose Chase?

The pathophysiologic mechanisms of renovascular hypertension are well described: Hemodynamically significant renal artery stenosis results in reduced renal perfusion pressure, which in turn leads to activation of the renin-angiotensin system and increased levels of angiotensin II, resulting in systemic vasoconstriction, aldosterone release, sodium retention, and expansion of extracellular fluid volume and blood volume. Logically, reversal of the restriction in flow and establishment of normal renal perfusion pressure should reverse the process and decrease blood pressure. Nevertheless, the clinical benefits of renal artery revascularization in the setting of refractory hypertension have been variable, and largely disappointing.

In this issue of JAMA Internal Medicine, Bavry et al present an update to their 2011 meta-analysis 4 of renal revascularization vs medical therapy for resistant hypertension. Their findings once again suggest no significant difference in systolic or diastolic blood pressure among patients randomized to renal artery revascularization or medical therapy. Important clinical outcomes such as death, stroke, congestive heart failure, or worsening renal function also did not differ between treatment groups. The only outcome measure that differed significantly between groups in the current analysis was the mean number of antihypertensive medications, which was lower in patients randomized to revascularization (2.96 vs 3.18; weighted mean difference, −0.23; 95% CI, −0.33 to −0.12; P < .001). These results are materially unchanged from those of their prior publication.

This update was undertaken owing to the recent publication of the much anticipated Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) Trial, 3 which reported only a modest reduction in blood pressure after a median of 43 months of follow-up in patients randomized to renal artery stenting (−2.3 mm Hg; 95% CI, −4.4 to −0.2; P = .03) compared with medical therapy, and no difference in death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy.

Why have we been unable to demonstrate a benefit with renal artery revascularization? Prior critiques have focused on patient selection because some studies have included patients with less-than-severe renal artery stenosis and unilateral disease. Logically, stricter inclusion criteria may allow for better identification of patients most likely to benefit from renal artery revascularization. However, while prior studies included patients withstenoses of 50% or greater, 4 patients enrolled in the CORAL Trial were required to have at least 80% diameter stenosis or at least 60% stenosis with a pressure gradient of at least 20 mm Hg. We must also acknowledge the high interobserver variability in visual estimation of angiographic lesion severity. In the setting of coronary artery disease, we have learned that revascularization of lesions with objective evidence of ischemia results in improved outcomes compared with the previously standard practice of revascularization of lesions based on angiographic criteria alone. The same might hold true for renal artery stenosis, and accordingly, measures such as fractional flow reserve or the renal resistive index might be useful in identifying patients who truly have a renovascular component to their hypertension and who might benefit from revascularization. 5

Furthermore, the technical challenges of treating predominantly aorto-ostial disease must be addressed, and the potential impact of adjunctive technologies, such as intravascular ultrasonography, have not been evaluated in contemporary studies of renal artery revascularization. Finally, restenosis (as high as 15% in prior studies) may temper the clinical benefits of renal artery revascularization, and current-generation drug-eluting stents are not available in the large sizes typically needed for renal artery stenting.

There is, however, a deeper reason to question the renal-hypertension connection. Another recent publication, the Sympli city 3 HTN (hypertension) study, 6 surprisingly demonstrated no significant reduction in blood pressure in patients undergoing renal artery denervation and has generated an uproar in the field of interventional treatment of resistant hypertension. Prior, nonrandomized, studies 7,8 suggested signifi-

Letters

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cant decreases in blood pressure following renal denervation, but this sham-controlled study identified no such benefit. While these findings also may be influenced by patient selection, they should concern those inclined to recommend interventional treatment of resistant hypertension presumed due to renovascular causes. Keeping in mind that blood pressure reduction can only be considered a surrogate for “hard end points” such as death, myocardial infarction, stroke, congestive heart failure, and renal failure, we seem to be very far removed from any convincing evidence that renal artery interventions reduce cardiovascular or renal morbidity or mortality.

With these issues in mind, where do we go from here? While awaiting further studies to investigate the possibility of a clinical benefit to renal artery interventions, we must focus on aggressive medical management of patients with refractory hypertension. We should not overlook the consistent evidence that sodium restriction, increased potassium intake, exercise and weight loss are associated with blood pressure reduction in patients with hypertension. Furthermore, the recent Eighth Joint National Committee guidelines9 suggest that for nonblack patients, first-line therapy for hypertension should consist of 1 or a combination of thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. For black patients, first-line therapy should consist of thiazide diuretics and calcium channel blockers. Emphasis on the importance of lifestyle measures and medication compliance, and consideration of secondary causes such as sleep apnea, drug-induced hypertension, hypercortisolism, hyperaldosteronism, hyperthyroidism or hypothyroidism, or hyperparathyroidism is warranted in patients with resistant hypertension. Focus on proven therapies while we await more concrete data supporting the use of interventional procedures for resistant hypertension is the most reasonable approach, at least until the next big thing comes along.

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LESS IS MORE

Altering Overuse of Cardiac Telemetry in Non–Intensive Care Unit Settings by Hardwiring the Use of American Heart Association Guidelines

Arrhythmia detection is reported to affect the clinical management of care in 3.4% to 12.7% of patients.1 The American Heart Association’s (AHA’s)2 published recommendations addressing the use of non–intensive care unit (non-ICU) cardiac telemetry stratify patients into 3 categories: cardiac telemetry is indicated, may provide benefit, or is unlikely to provide benefit. Clinical-effectiveness studies of implementing these guidelines have either reported the use of labor-intensive strategies3 or nonsustained decreases in non-ICU cardiac telemetry use.4 Various efforts to reduce the perceived overuse of cardiac telemetry at Christiana Care Health System, a 1100-bed tertiary care system, were unsuccessful. In August 2012 we convened a team to increase the appropriate use of non-ICU cardiac telemetry through the integration of AHA guidelines into our electronic ordering system (EOS). This effort was validated in March 2013 when non-ICU use of cardiac telemetry appeared on the Society of Hospital Medicine’s top 5 list for the Choosing Wisely campaign.5

Methods | Approval for this study was received from the institutional review board of Christiana Healthcare System; need for patient consent was waived. Our interdisciplinary team redesigned and standardized all cardiac telemetry orders within our EOS. Cardiac telemetry orders were removed from order sets for clinical conditions for which monitoring was not supported by the AHA guidelines.2 The remaining orders for cardiac telemetry required providers to select from a list of clinical indications, each with its AHA guideline–based predetermined telemetry duration (Box). bedside nurse assessment guidelines were embedded in the EOS to facilitate safe, timely, and automatic discontinuation of cardiac telemetry. When telemetry discontinuation was believed to be unsafe, such as in a patient with unstable blood pressure, the nurse was required to contact the physician, and telemetry could be reordered when appropriate.