# Renal Artery Stenting in Patients With Uncontrolled Hypertension: Should We? And to Whom?

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In this issue of the *Journal*, Chrysant and colleagues evaluated the longer-term efficacy of renal artery stenting with respect to blood pressure (BP) control by analyzing the results of the Safety and Effectiveness Study of the Herculink Elite Renal Stent to Treat Renal Artery Stenosis (HERCULES) trial after 36 months of follow-up.[1] The HERCULES trial was a multicenter, single-arm trial of 202 patients with uncontrolled hypertension caused by atherosclerotic renovascular disease (ARVD) treated by percutaneous renal artery dilatation and renal stent placement. In the original HERCULES trial, the authors found that the absolute reduction in systolic BP (SBP) after 9 months was related to the severity of the baseline hypertension before intervention. In ARVD patients with preprocedure SBP >180 mm Hg and a postprocedure reduction in SBP, the mean reduction recorded at 9 months was 48 mm Hg, while patients with ARVD with a baseline SBP between 140 mm Hg and 160 mm Hg had a decrease of only 23 mm Hg in SBP at 9 months. In addition, this trial demonstrated excellent procedure-related safety, with a 30-day composite safety endpoint rate of 1.5%.[2]

Chrysant and colleagues further hypothesized that if the renal stent used in the initial HERCULES trial maintained renal artery patency over time, then the clinical benefit confirmed in the initial trial should be sustained over time. Based on this hypothesis, the authors gave 3-year results.[1]

The included patients were those with uncontrolled hypertension defined as an SBP ≥140 mm Hg or a diastolic BP (DBP) ≥90 mm Hg despite maximal doses of at least 2 antihypertensive agents in appropriate combinations and with renal artery stenosis ≥60% (angiographic visual estimate). The suboptimal percutaneous transluminal balloon renal angioplasty (PTRA) result was defined as one of the following: ≥50% residual stenosis, a persistent translesional pressure gradient (mean 10 mm Hg, or peak systolic gradient of 20 mm Hg), flow-limiting dissection, or thrombolysis in myocardial infarction flow <3. Patients with either unilateral or bilateral atherosclerotic renal artery stenosis were included. Lesions representing in-stent restenosis following a prior endovascular revascularization were not eligible for enrollment. Patients with serum creatinine >2.5 mg/dL, recent myocardial infarction, stroke or transient cerebral ischemia, impaired left ventricular ejection fraction (≤25%), atherosclerotic renal artery stenosis and a solitary functioning kidney, or transplant renal artery stenosis were also ineligible for the study.

After 36 months, the mean±standard deviation SBP and DBP were 146±21 mm Hg (initially 162±19 mm Hg) and 75±11 mm Hg (initially 78±12 mm Hg), respectively. There was a statistically significant reduction in SBP and DBP compared with preintervention values. The reduction in SBP was 46 mm Hg—if the baseline SBP was >180 mm Hg, 27 mm Hg—if the baseline SBP was <180 mm Hg but ≥160 mm Hg and 26 mm Hg—if the baseline SBP was ≥140 mm Hg but <160 mm Hg. There was no change in the number of antihypertensive medication or renal function, as measured by estimated glomerular filtration rate (eGFR). In summary, this follow-up report of the HERCULES study offers an optimistic perspective with regard to control of BP. However, we believe that one must be careful while reaching firm conclusions.

Previous studies performed in 1998 and 2000 provided inconsistent results with respect to percutaneous transluminal renal angioplasty (PTRA) and BP control.[3–5] As a result of these studies, BP reduction was only evident in patients with bilateral renal artery stenosis although fewer antihypertensive drugs were used in the PTRA group compared with the medical treatment control groups. Most importantly in these "initial" clinical trials, typically balloon angioplasty without stenting was used. Besides, these trials were analyzed using an intention-to-treat design resulting in a substantial number of crossovers to balloon angioplasty (27%–44%) occurring after randomization in the medical therapy group (mostly caused by refractory hypertension or signs of progressive occlusive renovascular disease. A meta-analysis of these studies concluded that the effect of PTRA produces only a slight improvement in BP.[6,7] More recent randomized controlled trials have also failed to show a significant benefit from intervention with respect to BP control. The results of the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial were released in 2009. The ASTRAL trial was a multicenter, randomized, unblinded clinical trial including a total of 806 patients (1:1 medical: revascularization). The profile of patients considered for randomization included uncontrolled hypertension (SBP 155 mm Hg) as well as unexplained renal

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failure with significant ARVD (>60%) identified by renal artery imaging (computed tomography, magnetic resonance imaging, or renal ultrasonography). However, of all patients included, 40% had low-grade ARVD (between 50% and 70%) at the time of angiography. The study was negative: by the end of the 5-year follow-up period, SBP decreased to the same degree in both study groups; renal and cardiovascular end points were also similar. The main issue in the ASTRAL trial was the safety. The ASTRAL trial had a number of adverse procedure-related complications, including 2 deaths in the group randomized to stents, resulting in an overall complication rate of 17%. The authors concluded that when compared with medical therapy, revascularization carries a substantial risk, without adding benefit with respect to renal function, BP control, cardiovascular events, or mortality.[8]

The largest randomized controlled trial to date, the Benefits of Medical Therapy Plus Stenting for Renal Atherosclerotic Lesions (CORAL) trial, was designed to test whether renal artery stenting, when added to optimal medical therapy including blockade of the renin-angiotensin system, improves cardiovascular outcomes in individuals with ARVD. It included 947 participants randomly assigned to stenting plus medical therapy (467 patients) or medical therapy alone (480 patients). Patients, at baseline, had an average eGFR of 58 mL/min/1.73 $m^2$. Patients were considered hypertensive if they were taking ≥2 antihypertensive agents. After a mean of 43 months of follow-up, no difference was identified in the primary composite end point (death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal replacement therapy) between the stent group and the medical therapy group (35.1% and 35.8%, respectively; hazard ratio, 0.94; 95% confidence interval [CI], 0.76–1.17; *P*=.58). The SBP averaged 150 mm Hg at baseline in both groups and decreased over time, associated with an increase in the number of antihypertensive drugs. Final SBP was slightly lower in the revascularization arm (−2.3 mm Hg; 95% CI, −4.4 to −0.2 mm Hg; *P*=.03). This difference persisted throughout the follow-up period but did not translate into a significant improvement in clinical outcomes.[9] In the CORAL trial—unlike in the ASTRAL trial—the complications rate was smaller and similar to the HERCULES trial. Thus, both the ASTRAL and CORAL trials showed no/only modest benefits with respect to BP, which was notably different when compared with HERCULES.

In light of these findings, can we ignore the previous data and encourage intervention in patients? The response is obviously no. One should not forget that although the ASTRAL and CORAL studies have limitations, they were the largest randomized controlled trials in this context. The authors also acknowledge that care must be taken not to mislead the scientific community with contradictory results from weaker levels of evidence, especially when strong evidence exists. Indeed the major limitation of the current study is lack of a control group.

Importantly, the HERCULES trial showed good examples of methodology and safety. One of the most important advantages of the HERCULES trial was the unique inclusion of patients with hemodynamically significant ARVD, as reflected by the mean visual percent stenosis of 81% and core laboratory quantitative measurement of 66%. It is likely that many of these lesions were below the threshold of 75% occlusion usually required to cause a rise in BP and a reduction in renal function. The difference in operator-estimated and core laboratory–adjudicated findings reported herein confirms how the visual estimation of stenosis overestimates lesion severity and further raises concerns about suboptimal patient selection in the ASTRAL trial where no core laboratory was used. The ASTRAL study aimed to involve significant ARVD (>60%) identified by renal artery imaging (computed tomography, magnetic resonance imaging, or renal ultrasonography). However, at the end, 40% of the patients had low-grade ARVD (between 50% and 70%) and with mild hypertension at the time of angiography. Thus, patients in the ASTRAL trial and, to a lesser extent, in the CORAL trial may in fact represent a group with only moderate atherosclerotic disease, limiting treatment efficiency. This issue is particularly relevant since a recent meta-analysis of 901 patients enrolled in 5 US Food and Drug Administration investigational device exemption trials found that the only predictor of clinical benefit following renal artery stent revascularization was significant hypertension at baseline.[10]

Thus, the long-term success of the HERCULES trial may rely on proper initial patient selection. Stent revascularization should be considered for true resistant hypertension, with failure of adequate medical therapy, hemodynamically significant ARAS, and flash pulmonary edema. With regard to hypertension, revascularization is deemed reasonable for BP control in the presence of accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication. With regard to renal function, revascularization is reasonable in the presence of progressive chronic kidney disease with bilateral RVD or RVD of a solitary functioning kidney.[11]

The second important issue of the HERCULES trial is the safety record, with only 1.5% of adverse events. The current trial has shown that in the hands of experienced operators, using suitable techniques and equipment, the procedure is safe. In conclusion, the HERCULES trial confirms that with proper stringent patient selection and suitable methodology, stenting offers good BP control with minimal complications.

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