VIEWPOINTS

Vini Vidi Stenti

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In a recent issue of the *Journal of the American Heart Association* (*JAHA*), Reinhard and colleagues presented an interesting cohort series of people enrolled at 2 Danish centers undergoing renal artery stenting.[1] As described by the authors, they established their registry after the reporting of the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), ASTRAL (Angioplasty and Stenting for Renal Artery Lesions), and STAR (Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery Stenosis) randomized trials and enrolled people with ≥70% renal artery stenosis in predominantly 3 groups: those with hypertension not yet controlled; those with declining renal function; and, finally, a subgroup with heart failure. Of the 102 patients, 5 were not treated because of an occluded renal artery, and there were 12 procedure-related complications, including 4 significant renal artery injuries, 2 renal artery emboli, 2 respiratory events requiring intensive care, and 4 access site pseudoaneurysms. Over a median of 2 years, the serious adverse event rate was high. Ten died and 5 initiated renal replacement therapy, including 1 who started dialysis 2 days after stenting, and another 5 underwent contralateral nephrectomy for blood pressure control. Furthermore, of the 5 patients who had unsuccessful attempts at stenting, 4 died within 6 months, and the other required renal replacement therapy.

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The authors carefully measured blood pressure using 24-hour ambulatory monitoring and observed a 20-mm Hg decline in systolic pressure at 3 months, which was sustained to the 24-month follow-up period. Also observed was a reduction in the number of antihypertensive medications. The use and type of antihypertensive medications was not specified before and after stenting, and there was a relatively low use of renin-angiotensin system antihypertensives.

The current study should be viewed in the context of a long history of investigation in the treatment of people with atherosclerotic renal artery stenosis. Some 90 years ago, Goldblatt[2] observed that partial ligation of a renal artery resulted in increasing blood pressure. Later, it was determined that activation of the renin-angiotensin system was important in the pathogenesis of hypertension, and this was subsequently augmented by work demonstrating the importance of other mechanisms including sympathetic activations.[3–5]

Importantly, there is a mature body of work evaluating surgical renal artery bypass,[6] renal artery angioplasty,[7] and nephrectomy,[8] with limitations of these therapies including high surgical mortality,[9] restenosis,[10] and loss of kidney function for each of these treatments, respectively. With the advent of the Palmaz balloon-expandable stent, there emerged a percutaneous treatment that was highly effective in opening an obstructed renal artery and had lower rates of restenosis. In 1998, Gerald Dorros and colleagues published their center's experience with 163 people with atherosclerotic renal artery stenosis treated with the

Key Words: ischemic nephropathy ■ nephrectomy ■ renal artery stenosis ■ renovascular hypertension ■ stent

Palmaz stent.[11] Dorros's result was a heady affirmation of what we believed: find renal artery stenosis, stent renal artery stenosis, improve blood pressure and kidney function, improve clinical outcomes.

At the center of this belief was that (1) the improvements in blood pressure after stenting were caused by stent treatment; (2) medical therapies, while important, were insufficient to achieve this outcome; and (3) a reduction in blood pressure or improvement in estimated glomerular filtration rate would necessarily translate into improved clinical outcomes. In many of these observational studies, we noted that preprocedural rapid declines in renal function were associated with stabilization or even improved renal function in follow-up, and elevated blood pressures also improved. What we did not contemplate included phenomena such as regression to the mean where blood pressure and kidney function vary over time and high values tend to regress toward normal values simply because of variation and not because of treatment, and that concomitant attention to effective medical treatment also resulted in improved blood pressure and stabilized kidney function.

Importantly, there have been a number of high-quality cohort studies that followed Dorros's seminal publication. These are generally quite similar: average age 70; half being women; visual estimates of "severe" renal artery stenosis averaging ≈80%; modest numbers of people with stage 4+ chronic kidney disease; a subset of people with heart failure, with some having pulmonary edema. With the large number of observational studies demonstrating impressive reductions in blood pressure and "stabilization" of kidney function, it seems quite obvious that if we come to the interventional suite and see "severe" renal artery stenosis, we should treat it; *vini vidi stenti*, or I came, I saw, I stented. However, the best evidence, the published randomized trials, fails to support this approach.

To Reinard's credit, in the current cohort series, they have enriched the proportion of several high-risk subgroups including people on dialysis at enrollment, those with relatively high blood pressures at baseline, and those with baseline heart failure or pulmonary edema. Reinhard and colleagues contend that the people in their cohort study were different from those in randomized trials, which is partly true. Specifically, people hospitalized with acute heart failure and those on hemodialysis were excluded from the randomized studies. The organizers of the randomized trials did so because of the challenges of disentangling clinical events that were actively occurring that were also study end points, that is, adjudicating the occurrence of kidney disease requiring renal replacement therapy in a person being treated with dialysis and adjudicating heart failure when the person is in heart failure at the time of treatment. Consequently, these small subsets of patients are not represented in the randomized studies, and clinicians need better data to sort out

when to treat these critically ill patients since the risks and rewards are significant.

The critical question that the current study is unable to address is whether these patients would have had similar or even better outcomes had the study group simply treated them with aggressive and optimal medical therapy. What we know is that this high-risk group had some clinical improvements, such that 2 of 4 on dialysis no longer required dialysis. What we also know is that the other 2 on dialysis at the time of enrollment did not recover renal function; an additional 5 patients ended up on dialysis, including 1 who initiated treatment 2 days after stenting; 4 of 5 with failed revascularization required dialysis; and 10 died within 2 years. In the era of surgical revascularization, Hallett[12] observed that ≈1 in 4 people with azotemia preoperatively improved kidney function, half were stable, and 1 in 4 worsened after surgery. As a clinician in a conversation with a very ill patient, is an attempt at revascularization warranted, knowing that the rewards are potentially significant and the risks are also high?

To underscore this point, CORAL enrolled 364 patients with stenoses >80%, and there was no difference in clinical outcome between medical therapy alone and medical therapy with stent revascularization.[13] Similarly, although systolic blood pressure was predictive of clinical outcomes, stent treatment did not modify the effect, including in those with systolic blood pressures >180 mm Hg at study entry.[14] Similarly, the presence of global renal ischemia, defined as bilateral stenosis or a stenosis in a solitary functioning kidney, which was documented in 140 CORAL patients, was not associated with a difference in clinical outcomes. Of note, these subgroups are larger than many of the observational studies including the current Reinhard cohort.

Stenting to improve blood pressure has a limited role when clinicians are committed to assuring that their patients receive optimal medical therapy. Effective medical therapy is critically important since renal artery stenosis occurs in the setting of systemic risk factors and systemic atherosclerosis, which is oftentimes widespread. Optimal medical therapy includes aggressive medical therapy to define blood pressure thresholds using long-acting renin-angiotensin blockade and calcium antagonists with excellent trough-to-peak blood pressure ratios, intensive lipid lowering, smoking cessation, and antiplatelet therapy. In CORAL, stent treatment did lead to statistically significantly better blood pressures than medical therapy alone; however, the difference was modest (2 mm Hg better) and was not associated with fewer adverse cardiovascular or renal events.[13]

There are some people who will experience an increase in serum creatinine with effective blood pressure control (with or without renin-angiotensin inhibition); however, this should not be mistaken for "kidney failure" and most often does not necessitate cessation of treatment. Reinhard reported that 41% of people enrolled had

renin-angiotensin inhibition treatment discontinued because of a ≥30% increase in plasma creatinine. People treated with medical therapy alone who have an acute rise in creatinine often improve renal function absent any intervention, and importantly, their clinical outcomes are not impacted.[15] This phenomenon is so common that many studies of progression of chronic kidney disease exclude changes observed in the first few months of therapy and calculate the real effect of therapy on glomerular filtration rate beginning at ≥3 months after blood pressure is controlled.[16] Consequently, if a patient's creatinine rises from 1.0 to 1.3 mg/dL, or from 2.0 to 2.6 mg/dL with effective blood pressure control, the majority will do quite well without changing medical treatment and will improve or stabilize kidney function without revascularization.

Reinhard and colleagues suggest in their concluding remarks about the potential value of a randomized trial and highlight the difficulties of conducting such a study. As clinicians who are invested in providing the best possible care for our patients, additional cohort studies are unlikely to improve the situation. The core challenge is that high-risk patients have the potential for high-yield outcomes, such as the 2 patients who no longer required renal replacement therapy after stenting, and are at high risk of serious or fatal outcomes, such as seen with the current study.

What should busy clinicians remember? The vast majority of people with atherosclerotic renal artery stenosis need to be treated with aggressive and optimal medical therapy alone and do not benefit from stenting: *vini vidi optimus medicamentum*. There remains a modest group of people who were not represented in the randomized trials such as those with stage 5 or end-stage kidney disease and acute heart failure, for which difficult conversations must be had about the potential benefits and risks of revascularization. Finally, blood pressure control is rarely a reason to implant stents in renal arteries when we commit to ensuring optimal medical therapy, understand that an increase in creatinine during optimization of blood pressure control does occur, and in most people does not necessitate revascularization. Exceptional cases in which medical therapy fails to achieve blood pressure control should be evaluated by clinicians experienced with managing patients with complicated renal artery stenosis. When revascularization is performed, invariably these patients require ongoing medical therapy to achieve and maintain optimal blood pressure control.

ARTICLE INFORMATION

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Disclosures
None.

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