EDITORIAL

Long-term cardiovascular outcome after renal revascularization

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Percutaneous stenting of the renal artery for the treatment of presumed renovascular hypertension due to atherosclerotic renal artery stenosis (RAS) remains a controversial issue. From dilating and stenting every renal stenosis in the 1990s, the approach changed to conservative therapy following the landmark trials in the field. Indeed, both the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) and ASTRAL (Angioplasty and Stent for Renal Artery Lesions) trials, and some other randomized controlled trials failed to show improvement in blood pressure (BP) control as well as renal function.[1] However, all these trials have been criticized for lack of power, nonstandardized inclusion criteria, also with the inclusion of patients with only mild stenosis, and inadequate selection of patients that led to the exclusion of high-risk individuals.[1,2] On the other hand, clinical experience and observational studies do show a beneficial effect of revascularization on BP, renal function, and even cardiovascular (CV) events in patients with progressive but reversible renal failure, resistant or refractory hypertension, or circulatory fluid overload.[1] The uncertainty about the effectiveness of revascularization in the management of CV events is reflected in the 2005 American College of Cardiology / American Heart Association guidelines,[3] which provide a class I–II recommendation with the level of evidence B for percutaneous transluminal angioplasty (PTA) with stenting in these high-risk patients, and the 2013 European Society of Hypertension / European Society of Cardiology guidelines,[4] where the procedure has a class III recommendation with the level of evidence B.

Besides, atherosclerosis is a progressive condition and patients with atherosclerotic renal artery disease are at high risk of end-stage kidney disease as well as CV morbidity and mortality, which also depends on the stage of chronic kidney disease.[5-8] Moreover, medical therapy in RAS conveys a risk of a temporary decline in renal function due to the inhibition of the renin–angiotensin–aldosterone system (RAAS) per se or due to BP lowering. However, reducing intraglomerular pressure may not necessarily be unfavorable and may appear to be nephroprotective in the long run. In a recent post hoc analysis of the noninvasive arm of the CORAL trial, the clinical outcome of patients with an early rapid decline in renal function (≥30% decrease in the estimated glomerular filtration rate [eGFR] from baseline to 3 and / or 6 months) was comparable to that of individuals in whom such a decline was not observed. The authors suggested that "the best medical therapy (without stenting) should be continued in those patients."[9]

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), a retrospective study by Rosławiecka et al[10] was published, in which the authors evaluated not only the direct impact of percutaneous transluminal renal angioplasty (PTRA) on BP and renal function, but also its long-term effect on CV events. They included 211 consecutive patients with symptomatic RAS (stenosis ≥60% or of 50%–69% with a mean transstenotic pressure gradient >10 mm Hg at rest or hyperemic systolic pressure gradient >20 mm Hg, or renal fractional flow reserve ≤0.8) with difficult-to-treat arterial hypertension and / or known progressive renal function impairment. Difficult-to-treat arterial hypertension was defined as accelerated arterial hypertension (systolic BP [SBP] >160 mm Hg or hypertensive crisis despite treatment with at least 3 antihypertensive drugs, including a diuretic), drug-resistant arterial hypertension (SBP >140 mm Hg and / or diastolic BP [DBP] >90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic), or hypertensive crisis (SBP >220 mm Hg and / or DBP >140 mm Hg) with no target organ damage. While a critical degree of RAS (at least 70%) is needed to cause renal ischemia sufficient to activate the RAAS and thereby lead to

hypertension, as in many other papers,[1] the authors included a proportion of patients with less severe RAS. However, these patients had to meet additional inclusion criteria for PTRA with stent placement. Yet, even low-grade (<30%) atherosclerotic RAS has been associated with a poorer CV outcome.[11] There is also evidence that low-grade atherosclerotic RAS is already related to pathophysiological alterations in the renal and systemic vasculature.[12] In addition, timely identification and treatment of atherosclerotic RAS might modify the natural history of kidney disease at least in some patients. Unfortunately, the authors do not report data on concomitant medical treatment with antihypertensive, lipid-lowering, and antiplatelet drugs, while there is ample evidence that angiotensin-converting enzyme inhibitors, statins, and antiplatelet agents have a beneficial effect on atherosclerotic CV and renal disease.

In the study by Rosławiecka et al,[10] progressive renal function impairment was defined as a decrease in the eGFR of at least 30% or an increase in the serum creatinine concentration that exceeded 0.5 mg/dl over the last 3 to 6 months of follow-up. Patients with acute decline in renal function following the RAAS blockade were also included, but no details were reported. Patients with flash pulmonary edema, congestive heart failure, and acute coronary syndrome without coronary stenosis were included as well. A small kidney length (<7 cm in women and <8 cm in men) was an exclusion criterion for PTRA with stenting.

Procedural success was defined as residual diameter stenosis of less than 30%, and successful hypertension treatment, as BP of less than 140/90 mm Hg with no antihypertensive drugs.

In this high-risk population, mean SBP decreased by 12 mm Hg and DBP, by 5 mm Hg after 12-month follow-up without a decrease in the mean number of antihypertensive drugs. Hypertension was cured in a minority of patients (1.9%), while an improvement was observed in 18.4%. However, as no 24-hour ambulatory BP measurement was performed and no control group was recruited, the results might have been influenced by placebo and Hawthorne effects, regression to the mean, and other patient- and physician-related biases. Therefore, a true benefit of PTA on BP remains elusive.

At 12 months after PTA, the eGFR was significantly lower (4 ml/min/1.73 m^2), and no considerable change was noted in serum creatinine concentrations. Serum creatinine is a marker of renal function, commonly used in atherosclerotic RAS, although it is limited because of opposing hemodynamics observed in the kidney with stenosis and the contralateral organ.[13] A better method for evaluating the effect of PTRA with stenting on renal function is to look at its effect on renal blood flow and measured GFR in both kidneys separately. However, nowadays, the measured GFR of a single kidney is measured by renal scintigraphy, which carries a radiation burden. In the near future, functional magnetic resonance imaging may be useful in the clinical evaluation of RAS.[14]

Rosławiecka et al[10] searched for potential associations between the risk of CV death and changes in BP and renal function. Cardiovascular risk was associated with male sex, atherosclerotic lesions greater than 50% of the lumen diameter in at least 2 arterial territories in addition to RAS, previous PTA of the other arterial territories, history of hypertensive crisis, and concomitant atherosclerotic lesions greater than 30% present in the contralateral renal artery. At the 12-month follow-up after PTA, an increase in eGFR calculated with the MDRD formula of at least 11 ml/min/1.73 m^2 and a decrease in DBP of at least 5 mm Hg were noted. Both results were independently associated with a lower risk of developing CV disease and ischemic stroke. The procedural success rate was high and resulted in a considerable reduction in the severity of stenosis. Periprocedural complications occurred in less than 3% of patients, including 1 case of death due to acute limb ischemia with multiorgan failure. Other major in-hospital complications were acute renal artery occlusion reported in 3 patients and resulting in renal infarction in 1 patient, as well as massive bleeding requiring blood transfusion in 2 patients. This complication rate is comparable with the one reported in a systematic review by Raman et al.[15]

Rosławiecka et al[10] state that an improvement of kidney function of at least 11 ml/min/1.73 m2 or a decrease in DBP of at least 5 mm Hg after PTRAS in high risk patients with ARAS, improves CV prognosis. However, the authors' conclusion that they identified the subgroup of patients with atherosclerotic RAS who have an obvious clinical benefit following PTA, that is, a reduced risk of major adverse CV events and CV death, should be tempered with the caveat that no medically treated control group was included in the study. We do not know if PTRA with stenting had an effect on CV and renal outcome, as better BP control per se has an impact on target organ damage as well. Moreover, before the procedure is performed, we still do not know which patients will benefit from revascularization and which will not.

All things considered, we are still awaiting an "ideal" randomized clinical trial to test the benefits of revascularization in patients with atherosclerotic RAS. In the meantime, clinicians must be aware that indications for renal artery revascularization do exist.[1]

ARTICLE INFORMATION

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