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CORRESPONDENCE

Revascularization for atherosclerotic renal artery stenosis: another flawed son of the ASTRAL Study

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The ASTRAL Study was widely criticized on several grounds,[1–3] which led to questioning its main conclusion that percutaneous transluminal renal artery angioplasty plus stenting (PTRAS) offered no advantage over medical treatment in patients with atherosclerotic renal artery stenosis for whom the 'patient's doctor was uncertain that the patient would definitively have a worthwhile clinical benefit from revascularization'.[4] The recent publication of a report on patients undergoing renal revascularization by means of PTRAS outside the ASTRAL trial from a center that participated in the main study[5] provides, in our view, another straightforward example of evidence-unbased conclusions. In a retrospective survey of 127 patients with angiographically significant stenosis, defined as a luminal narrowing on biplane angiography between 70% and 90% and a kidney length >7–8 cm, Valluri *et al.*[5] compared the rate of decline of renal function between the periods leading up to and following PTRAS.

Beside the many limitations of the paper that were acknowledged by the authors, a crucial issue regards the choice in their study, as in all other major trials in this field thus far, of the slope of reciprocal serum creatinine (sCr) as the major endpoint. It is widely known that in the ischemic kidney glomerular filtration rate (GFR) is lowered by the stenosis whereas it is raised in the contralateral kidney by the high blood pressure (BP). Hence, after PTRAS, an increase of GFR could be expected in the ischemic kidney along with a fall of GFR in the contralateral kidney as a consequence of BP lowering. The net result can thus be no change in overall GFR as assessed by indexes such as the slope of the reciprocal sCr examined by Valluri *et al.*[5] The failure to show any improvement in such an index of renal function could therefore easily be anticipated. For these reasons, a multicenter randomized clinical trial, the METRAS study (Medical and Endovascular Treatment of atherosclerotic Renal Artery Stenosis), was recently designed with the main aim of determining the effect of PTRAS on GFR in the ischemic and contralateral kidney.[6]

Moreover, Valluri *et al.* assessed the decline of renal function by the reciprocal of sCr slope constructed for each patient but, unfortunately, scant details were given on how it was actually calculated, and on how many time points and sCr values were used for such calculation, hence the precision remains undefined.

The effect of antihypertensive drugs on this parameter, which was overlooked by Valluri *et al.*,[5] is another major issue. This point is not negligible as effective PTRAS can allow use of drugs, such as angiotensin-converting-enzyme inhibitors, angiotensin receptors blockers or renin inhibitors, which should be avoided before revascularization because of the possibility of inducing acute renal failure, but can be prescribed afterward to improve BP control. These drugs are likely to decrease GFR in patients with incomplete revascularization and it is surprising that Valluri *et al.*[5] provided no information on the proportion of patients with unsuccessful PTRAS.

The importance of paying due attention to on-going medical treatment when assessing the outcome of PTRAS on renal function is also suggested by the findings of recent meta-analyses of all major randomized clinical trials, where PTRAS was associated with a greater reduction of drug treatment as compared with medical therapy alone.[7,8] Hence, it is likely that the number and/or doses of antihypertensive drugs, which can raise GFR, such as calcium channel blockers and other vasodilators, could have been lowered after successful PTRAS in the patients recruited in this study[5] with ensuing underestimation of the effect on eGFR.

Nowhere in their manuscript did Valluri *et al.* report the success rate of PTRAS in their study. Likewise, they provided no information on the predictors of improvement of renal function in their patients as determined by the resistivity index[9] and/or by angiography (renal parenchymogram, global or focal ischemia, progressive narrowing of the renal artery, and so on).[10] Surprisingly, they also declared that the assessment of a major goal of revascularization, for example, the BP outcome, was beyond the scope of their study. Instead they defined response retrospectively as 'those who responded positively in any way to revascularization in terms of improvement in the mean slope' and nonresponders 'those with a negative or neutral response'. By these definitions they split their 127 into 79 responders and 48 non responders. This means that 38% of their patients showed no improvement in renal function.[5] Notwithstanding the aforementioned limitations in the assessment of renal function, one wonders if the success rate of the PTRAS achieved by Valluri *et al.* was high enough to warrant their conclusions. In all the studies on renal revascularization, a grading system should be exploited and reported, as was done by cardiologists for the TIMI score in the 90 s. Assessment of the patency is crucial in that it allows distinguishing between the true effect of revascularization and that of a poor technical success. In our experience, in patients with features similar to those enrolled by Valluri *et al.*, the recurrence of intra-stent restenosis was about 12%, which suggests that a better strategy for preventing this untoward effect, possibly entailing drug eluting stent and/or use of double antiplatelet strategy, should be undertaken.[11]

Some further issues need to be raised concerning the subgroups analyses performed by Valluri *et al.* based on the premise that a more prominent benefit could be demonstrated in these patients. They first analyzed the subgroup with tight atherosclerotic renal artery stenosis (ARAS) in a single functioning kidney or with bilateral ARAS and compared the median rate of change in renal function before and after PTRAS in these patients. They concluded that there was no benefit,[5] but they did not report the duration of the follow-up in this group. It is altogether obvious that a proper control for this subgroup of patients, who, according to the American Heart Association (AHA) guidelines,[12] should be revascularized, would be patients submitted to medical therapy only. Valluri *et al.*[5] also reported that there was no improvement in terms of renal replacement therapy (RRT)-free survival or overall mortality, but unfortunately this finding was not supported by their data. They had 39 patients with tight ARAS of a single functioning kidney/bilateral ARAS and given the (unreported) length of their follow-up it is quite likely that the analysis was underpowered to provide any solid conclusions. Looking at the median time to death, which was 2.4 (1.1–3.3) years in this most severely diseased group and 2.2 (1.2–3.5) years in those with less severe renovascular disease, one could argue that some benefit was in fact achieved with PTRAS.

In a second subgroup analysis, Valluri *et al.*[5] examined the effect of PTRAS in those whose kidney function was rapidly declining before intervention. They found a median rate of change in renal function before revascularization of -1.5×10^{-3} l mmol^{-1} per year and following revascularization, of $+0.03 \times 10^{-3}$ l mmol^{-1} per year. Moreover, the median time to RRT was doubled (1.6, 0.8–3.6 *vs.* 0.9, 0.5–2.2) and the median time to death was also increased (3.5, 1.3–4.3 *vs.* 2.1, 1.0–3.0, $P = 0.06$) as compared with those with more gradually declining renal function.[5] In our view, this is a comparison of 'apples and pears' as the proper control group for this comparison should be medically treated patients with rapidly declining renal function. Moreover, even though there was a high (48%) mortality rate, the analysis was likely underpowered to demonstrate any benefit as there were only 29 patients in this group and the duration for follow-up was probably too short.

Therefore, if any lesson could be learned from this subgroup analysis, one should conclude that a trend toward a clear-cut benefit with PTRAS is evident, thus reinforcing the AHA guidelines recommendations for this subgroup of patients.[12]

In conclusion, it is undoubtedly challenging to establish 'evidence-based medicine' regarding the treatment of renal artery stenosis through randomized clinical trials as responsible clinicians never enroll their renal artery stenosis patients that are more likely to benefit from renal stenting in such trials as White pointed out.[13] However, nonrandomized retrospective observational studies, like that by Valluri *et al.*,[5] have far too many limitations to provide solid conclusions. Moreover, the results of subgroups analyses are often questionable as are their conclusions. Unfortunately, this type of evidence-unbased medicine could lead physicians to deny an effective treatment to these high-risk patients and therefore should be taken with great caution.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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