Early Rapid Decline in Kidney Function as a Beneficial Sign After Starting Antihypertensive Medication

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In one of the latest online forums of the *American Society of Nephrology*, a user asked the following question: "Some of my patients have their albuminuria improved from A3 to A2 significantly on RAS [renin-angiotensin/aldosterone system] inhibition but the GFR [glomerular filtration rate] going down from stage G3 to G4 where we start education for ESRD [end-stage renal disease] management options and they get very concerned about whether these medications are hurting their kidneys. Should we be backing up on RAS inhibition or is it worth continuing it?" This important clinical situation is similar to what the authors of an article within the current issue of the *Journal of the American Heart Association* (*JAHA*) dealt with. Cooper et al published a post hoc analysis of the noninvasive arm (treated by medication, including RAS blockers) of the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial (randomized controlled trial), which tested the effect of stenting renal artery stenosis on top of medical therapy versus medical therapy alone.[1]

The CORAL trialists randomly assigned 947 participants with atherosclerotic renal artery stenosis and systolic hypertension or stage 3 chronic kidney disease (GFR not <30 mL/min) to medical therapy plus renal artery stenting or medical therapy alone. As a major result, "renal-artery stenting did not confer a significant benefit with respect to the prevention of renal function loss and other clinical events (35.1% versus 35.8%, respectively; hazard ratio with stenting, 0.94; 95% confidence interval [CI], 0.76–1.17; *P*=0.58). However, a modest difference in systolic blood pressure favoring the stent group (−2.3 mm Hg; 95% CI, −4.4 to −0.2; *P*=0.03) was notable."[2] These results of the CORAL trial were in line with other major randomized controlled trials on renal angioplasty and/or stenting of renal artery stenosis,[3–8] including the latest, but preterm stopped, RADAR (Randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis) study.[9] All such trials suggested no benefit of endovascular procedures to restore, protect, or increase renal function in patients with renal artery stenosis but favored medical therapy. Although overwhelming data of interventional evidence have been supplied, there is ongoing discussion about the usefulness of endovascular revascularization in certain situations, such as ostial stenosis, reduced perfusion patterns, or resistive indexes.

On the other hand, the alternative for endovascular procedures in renovascular hypertension, medical therapy alone, does convey a suspicious risk of temporary renal function deterioration as well, as many physicians (like our forum user) have noticed in their praxis and studies revealed.[10,11] This is not only true in situations when systemic or isolated glomerular hypovolemia and hypoperfusion is present, such as with (infectious) diarrhea, reduced drinking volume, bleeding, and resulting full-blown acute kidney failure. The randomized ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial investigated the effect of starting perindopril-indapamide (an angiotensin-converting enzyme inhibitor with thiazide) or placebo in kidney-stable patients on the occurrence of major macrovascular events, new or worsening nephropathy, and all-cause mortality. Interestingly, although an initial GFR decrease was associated with greater risk of cardiovascular end points, the frequency of nephropathy was not higher in patients in whom the study medication was continued, despite an early GFR decrease.[12,13] These study authors argued that "while initial short-term increases in serum creatinine beyond 30% (and indeed even 20%) are associated with less favorable prognosis, continuation of ACE [angiotensin-converting enzyme] inhibitor-based therapy in those who experience these levels of increase may be beneficial and reduce the long-term risk of major clinical outcomes."

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J Am Heart Assoc. 2019;8:e013145. DOI: 10.1161/JAHA.119.013145.

However, if initial worsening of kidney function after medication initiation is long-term beneficial (and not only hazard free) has not been proved definitely in all RAS trials yet. This question looks like the key idea of the current post hoc CORAL trial analysis. Authors analyzed 359 patients from the medical therapy group for occurrence of rapid decline of renal function (at 3 and 6 months or at both time points) and what happened in 66 of these 359 patients (18%). They analyzed baseline parameters and further course of renal function (up to 5 years) for examination of risk factors associated with rapid decline. Baseline renal function, age, and logarithmic urine albumin/creatinine ratio discriminated between patients experiencing rapid decline at 3 or 6 months or not, and decline "was associated with an improvement in eGFR [estimated GFR] at 1-year (6.9%, P=0.04), as was baseline logarithmic urine albumine/creatinine ratio (−1.8%, P=0.007), and baseline cystatin C (14.2%, P<0.001)."[1] This is an intriguing effect, but does not answer the extended question, if GFR decline is advantageous compared with having no decline because patients in whom GFR declined were compared with their own baseline and not with the group in whom GFR did not decline. Moreover, nephroprotection exerted by reduced transmembrane glomerular pressure, as it is supposed in these patients, should be accompanied by reduced proteinuria, an issue that was not investigated in the study but is well known in clinical practice. Anyhow, the rapid declining group reconstituted their baseline function after a period of 6 to 12 months and up to a time period of 5 years in some patients. A complex, but important, figure providing GFR course in every single patient shows virtually no patient experiencing exaggerated GFR loss during follow-up, despite declining from baseline to 3 or 6 months. Interestingly, few patients restored their baseline GFR as late as 2 years after decline. Other long-term clinical outcomes (cardiovascular and renal death and cardiovascular events) were similar between GFR-declining and nondeclining patients as well. The authors conclude "that patients continuing medical treatment after declining kidney function often experience a [later] improvement in kidney function" and take such proof to advise that an "early rapid GFR decline in renal function with medical treatment may not be an indication for stenting." Although this statement can be agreed on, a further issue of clinical relevance apart from the stenting question could be added: Without regard to endovascular therapy and although having a renal artery stenosis, decline of (excretory) renal function after initiation of medications affecting glomerular perfusion is not unfavorable per se. Physicians should consider that diminishing intraglomerular perfusion pressure (by RAS blockers or simply blood pressure reduction) might result in decreased GFR but at the same time may convey nephroprotective effects in the long run by reducing transmembrane glomerular injury.

Such effects have been shown in the trials of gliflozins to treat diabetes mellitus and reduce cardiovascular end points as well.[14–16] These inhibitors of the sodium-dependent tubular glucose-(re)transporter reduce osmotic pressure against the glomerular basement membrane by abandoning glucose reabsorption. Typically, patients receiving this new class of drugs experience modest early GFR decline, but a favorable renal outcome thereafter. Using gliflozins, the early GFR decrease is nowadays discussed as an advantageous sign of nephroprotection.[17] Following this reasoning, a growing clinical community might agree that there is no need to skip RAS blocker, antihypertensives, or gliflozins in all patients experiencing initial therapy-induced GFR decrease. Instead, the key to find the appropriate treatment algorithm is to consider the particular clinical and pathophysiological situation. Only when GFR decrease is accompanied by significant and sustained systolic blood pressure decrease to <110 mm Hg (eg, caused by hypovolemia with acute kidney failure), we recommend discontinuation of this medication until blood pressure has normalized. On the other hand, conditions associated with activated RAS (diabetes mellitus, congestive heart failure, and nephrotic syndrome) do compose additional arguments to sustain RAS blockade. In any case, after getting through critical phases, to maintain or reconstitute such medication should be a prioritized goal. To answer the colleague′s opening web forum question: When a GFR decrease is certifiable, physicians should carefully monitor GFR and albuminuria (at least 3 months, following the presented study of Cooper et al[1]). If albuminuria decreases, systemic blood pressure is not critically reduced, and no additional hypovolemia is present, most patients with stage 3 chronic kidney disease are likely to restore their baseline function and to benefit from this mechanism of expedient reduced intraglomerular pressure in the long-term.

Disclosures

None.

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Key Words: Editorials • antihypertensive therapy/angiotensin-converting enzyme and renin inhibitors/angiotensin II receptor blockers • chronic kidney disease • hypertension • intraglomerular pressure • kidney function • renal artery stenosis