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Do the Renin-angiotensin system inhibitors provide renoprotection beyond blood pressure lowering?

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Chronic kidney disease is associated with arterial hypertension (AHT) in more than 80%, the kidneys being both generators and culprits of AHT. Hypertension induces renal damage essentially by two mechanisms: vascular wall stress and increased expression of intrarenal pro-inflammatory cytokines, adhesion molecules and growth factors, that result in glomerular capillary injury and arteriolar sclerosis (nephroangiosclerosis). Large observational studies identified AHT as a major and independent risk factor for end-stage renal disease (ESRD) and intervention trials clearly showed that lowering the blood pressure (BP), by all means, can significantly reduce this risk. ❑

Angiotensin II is another well-demonstrated renal aggressor, promoting glomerular fibrosis by both hemodynamic and non-hemodynamic effects: intraglomerular hypertension, mesangial cell proliferation, increased expression of platelet-derived growth factor (PDGF), endothelin-1, transforming growth factor-beta (TGF-beta), monocyte chemo-attractant protein 1 (MCP-1) and plasminogene activator inhibitor 1 (PAI-1), stimulation of nuclear transcription factor NF-κB, oxidative stress, sodium reabsorbtion and aldosterone release. Therefore, drugs that inhibit the renin-angiotensin system (RAS) seem particularly interesting to nephrologists, as likely renoprotective agents.

Today, angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARBs) are advocated by several national and international guidelines as first-choice antihypertensives in patients with diabetic and non-diabetic nephropathies (1-4). This recommendation is based on the assumption that these drugs, compared to other antihypertensive agents, have specific renoprotective effects, beyond those resulting from lowering the BP alone.

To assess the evidence supporting this assumption, Juan P. Casas, M.D., and colleagues of the British Heart Foundation Laboratory at University College of London undertook a systematic review and meta-analysis of randomised controlled trials investigating the effect of antihypertensive drugs on renal outcomes. This work, published in the 2005, Dec. 10 issue of *The Lancet* (5), is one of the most remarkable recent nephrology papers and it has already driven many clinicians to reconsider some „well-established" therapeutic principles.

Searching three large electronic databases, from 1960 to 2005, the authors found 127

randomised controlled studies (n = 73,514; mean follow-up = 4.2 years) that looked at the effect of various antihypertensive drugs upon the progression of chronic renal disease. Effects on primary discrete endpoints – doubling of serum creatinine and ESRD – and secondary continuous markers of renal outcomes – creatinine, albuminuria, and glomerular filtration rate (GFR) – were calculated with random-effect models. The effects of ACEI or ARBs in placebo-controlled trials were compared with the effects seen in trials that used an active comparator drug (β blockers, diuretics, calcium-channel blockers, α blockers, or combinations of these).

The results of the meta-analysis showed that ACEI and ARBs were associated with a significant reduction in the risk of ESRD (by 13%), when compared with other antihypertensives ($p = 0.04$; RR = 0.87; 95%CI = 0.75 to 0.99). ACEI or ARB treatment also resulted in significant decreases in serum creatinine concentration (by 7 μmol/l; $p = 0.01$) and daily urinary albumin excretion (by 15.7 mg/day; $p = 0.001$). However, some doubts persisted in the interpretation of this data: first, ACEI and ARBs had no advantage over other agents in reducing the GFR decline (95%CI = – 0.76 to 1.32), and second, the benefit of ACEI/ARBs on reducing the risk of ESRD and doubling of creatinine was less obvious in larger trials ($n > 500$) than in smaller trials ($n < 500$). The authors suggest some possible explanations for this study-size effect. One explanation could be, for instance, the fact that in the largest trial, ALLHAT (6), patients assigned to thiazide diuretics had a 2 mm Hg lower BP than patients assigned to ACEI, and this difference in BP might have contributed to the absence of any beneficial effect of ACEI over thiazides on renal outcomes. Another explanation may be small-study bias, i.e. small negative studies often remain unpublished, and those small studies that are published are likely of lower quality and more prone to bias than large studies.

Surprisingly, but most importantly, in diabetic patients, ACEI and ARBs had no clear advantage over other antihypertensive agents upon renal outcomes. Although ACEI and ARBs reduced albuminuria more than other drugs (by 12 mg/day; 95%CI = – 21.68 to – 2.74), they showed no significant benefit on ESRD (RR = 0.89; 95%CI = 0.74 to 1.07), on doubling of creatinine (RR = 1.09; 95%CI = 0.55 to 2.15) and on GFR (- 1.19 ml/min; 95%CI = – 2.69 to 0.31).

When compared to placebo, ACEI and ARBs consistently demonstrated a significant benefit in reducing the risk of ESRD and doubling of creatinine, in both diabetic and non-diabetic patients. However, this benefit was clearly associated to the BP-lowering effect (by 2.3 to 6 mm Hg more than placebo). Again, greater benefit was seen in the small trials than in the large ones.

The authors conclude that views endorsed by guidelines of ACEI and ARBs as having specific renoprotective effects are mainly the result of small and placebo-controlled studies. Serious doubts are expressed whether these drugs should actually be indicated as first options, above other antihypertensive agents, in patients with chronic renal disease, and especially in those with diabetes. For the renal outcome, lowering the BP seems far more important than the class of drugs used for this purpose. Therefore, antihypertensive strategy should rely mainly on criteria of efficacy, tolerance and costs, rather than class.

However, Thomas D. Giles, M.D., president of the American Society of Hypertension and a professor of medicine at Louisiana State University, said the authors may be jumping to an unwarranted conclusion (7). He pointed out that a "meta-analysis is not the world's greatest instrument for evaluating clinical benefit." He added that "it's been known for quite some time that the key factor in renal protection is lower BP, so no argument there." But he said the vast majority of both basic science and clinical trials support the view that drugs that inhibit "the renin-angiotensin system have a beneficial effect on glomerular pressure." Moreover, while the authors suggested that price is a significant consideration, Dr. Giles said "there are already several generic ACEI available and some ARBs will soon be coming off patent, so price is really not a factor."

Nevertheless, controversies opposing RAS inhibitors to other antihypertensive agents are largely academic. The main issue in renoprotection is efficient lowering of BP and there is universal agreement that in most patients that means using several drugs, with an ACEI or an ARB part of that mix, especially in high-risk patients. Furthermore, the combination of an ACEI and an ARB seems to be beneficial in patients with chronic kidney disease: for example, in the COOPERATE study (in which the mean baseline GFR was about 38 ml/min/1.73 m^2), this combination slowed the progression of kidney disease more than did either drug alone (8). ❑

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