Renal and cardiac effects of antihypertensive treatment with ramipril versus metoprolol in autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) affects ~12.5 million people worldwide. Forty percent of patients are diagnosed by 45 years of age. ADPKD is the fourth most common cause for end-stage renal disease (ESRD) worldwide and this disease accounts for 5–10% of renal transplant recipients [1,2]. Therefore, any therapeutic modality that can slow down the natural course history of this disease would have a significant impact on patients’ well-being and would be financially cost-effective. The manuscript by Zeltner et al. in this issue attempts to determine if there is a difference between an angiotensin-converting enzyme (ACE) inhibitor (ramipril) and a beta blocker (metoprolol) when employing first-line therapy in ADPKD patients with hypertension.

The study has a number of limitations; some of them recognized by the authors that could influence the conclusion are noted as follows:

1. Small number of study subjects that lead to a Type II error.
2. Short follow-up of only 3 years.
3. Almost no primary endpoints were reached; therefore, only secondary endpoints were analysed.
4. Blood pressure (BP) stratification groups were done retrospectively. The standard (MAP > 97 mmHg) and rigorous (MAP < 97 mmHg) groups were designated in a post hoc analysis. The lack of a prospective, randomized BP assignment creates bias because the low-BP group may have less severe disease, and therefore patients were self-selective.
5. Maximum dose of ramipril was low in contrast to the dose of metoprolol.
6. No assessment of whether the patients had ADPKD Type I or Type II.
7. No radiological imaging studies to assess total kidney volume/total cyst volume.

The impact of each of these issues is discussed below.

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The small number of study subjects makes the conclusion less than robust [3–5]. Twenty-three patients each were assigned to both the ramipril and metoprolol groups, but only 37 patients (80.4%) completed the 3-year follow-up. Therefore, a Type II error clouds every finding. With more study subjects, the differences in left ventricular mass index (LVMI) and urinary albumin excretion between the ramipril and the metoprolol groups could possibly have reached statistical significance based on trends noted.

A follow-up of 3 years is entirely too short a period of time to draw any conclusions in a PKD population that slowly develops disease progression over decades. Separation between study groups in several hypertension trials began to occur after 2 years of therapy and statistical significance was not reached until 3 years of treatment or longer [6–8].

Another issue of importance in the study is that there was no mention or attempt to define patients as having either Type I or Type II ADPKD. This designation would obviously impact the natural course history of the disease, cyst size and severity of hypertension [9–11].

With virtually no patient reaching a primary endpoint, the secondary endpoints became the focus of this paper. These endpoints were changes in serum creatinine, urinary albumin excretion and LVMI, with the conclusion being that there was no difference in the three measurements between those treated with ramipril or metoprolol, during 3 years of follow-up. Retrospective analysis in the small study cohort showed that 3 years of rigorous BP control (no matter which agent was used) was not associated with a change in LVMI. In contrast, the standard BP cohort had an increase in LVMI. Reduced urinary albumin excretion occurred in the rigorous BP group in contrast to the group that achieved standard BP control.

The Consortium for Renal Imaging Studies of Polycystic Kidney Disease (CRISP) Study has clearly shown that patients with ADPKD Type I have larger cysts, more hypertension and a more rapid decline in kidney function as compared to those with Type II ADPKD [12,13]. In the CRISP Study, changes in total kidney volume were due almost exclusively to changes in total cyst volume. Patients with total kidney volume of >1500 mL were at greater risk for worse hypertension and more severe impairment of kidney function, that progressed at a more rapid rate when
compared to those with less total kidney volume [14]. This study by Zeltner et al. lacks any radiological imaging information that could help categorize patient risk.

It required a post hoc analysis to determine that the lower (defined as vigorous) BP group had no increase in LVMi as compared to an increase in the LVMi group with a standard BP. Patients were stratified retrospectively and not prospectively. Therefore, these observational data carry much less weight when compared to a prospective, randomized study.

The ramipril and metoprolol groups may not be comparable because of the dosing schedule [15]. The 2.5-mg starting dose of ramipril is low and is not comparable to 50 mg of metoprolol. Limiting the maximum dose of ramipril to 5 mg per day is also not comparable to metoprolol 100 mg per day. Ramipril doses can be increased by up to 20 mg per day before reaching maximum therapeutic benefit. Therefore, the choice of dosage can be put into question. Furthermore, a short-term haemodynamic (and reversible) fall in kidney function is expected with blockade of the renin–angiotensin system [16]. This fact could blunt the eGFR (estimated filtration rate) difference between the ACE inhibitor and the beta blocker.

Clinical trials to slow progression of ADPKD

Definitive information on the potential role of blockade of the renin–angiotensin–aldosterone system (RAAS) to prevent progression of renal dysfunction in humans with ADPKD is lacking. Maschio et al. performed a prospective, randomized, double-blind placebo-controlled study to assess the benefits of ACE inhibition on renal progression in non-diabetic kidney disease (including patients with ADPKD). There was a lack of therapeutic efficacy in 64 ADPKD patients who were followed for ~3 years. Ramipril was the ACE inhibitor used and there was a doubling of serum creatinine with equal frequency when compared to a placebo-controlled group. One of the limitations was a reduced GFR at the onset of intervention (a mean creatinine clearance of 42 mL/min) in the study group [17]. Patients may have had advanced disease that was not amenable to any treatment.

In a 7-year prospective trial assessing both the level of BP control and the class of antihypertensive agent used, no advantage of an ACE inhibitor (Enalapril) versus a calcium channel blocker (Amlodipine) was found in reducing the rate of decline of renal function by the eGFR (using the MDRD equation) [18]. Proteinuria and left ventricular hypertrophy were significantly reduced in the group treated with Enalapril as compared to Amlodipine [19]. This difference was manifested after 5 years of intervention. Interestingly, increased proteinuria was observed when a diuretic was used for BP control as compared to an ACE inhibitor alone.

Activation of the RAAS in ADPKD

Clinical data support the hypothesis that the RAAS is activated in individuals with ADPKD [20–22]. Substantial data suggest that as renal cysts enlarge, they compress the renal vasculature, causing intra-renal ischaemia, attenuation of the renal vasculature and interstitial fibrosis [23–25]. Can interruption of RAAS activation impact the clinical course? Other non-ACE inhibition-dependent mechanisms for renal activation of the RAAS may also exist. Clinical studies show higher plasma renin and aldosterone concentrations in the supine and upright positions and also in response to ACE inhibition in subjects with ADPKD compared to matched subjects with essential hypertension [26]. Normalization of renal blood flow in hypertensive ADPKD individuals with ACE inhibitors is not complete, since these agents (or angiotensin receptor blockers) result in incomplete inhibition of the RAAS, as aldosterone and angiotensin II are generated via multiple pathways.

It is for the above reasons that the HALT PKD Study will determine the efficacy of aggressive RAAS blockade in preventing/slowing renal function decline in ADPKD [27]. This prospective randomized blinded study is being conducted at seven centres throughout the United States in 1018 patients. This 2 × 2 study will determine if the activation of the RAAS and hypertension play independent roles in structural progression of renal cysts (as measured by MRI) in ADPKD. It will also determine whether cyst growth correlates with a loss of renal function. Patients between the ages of 18 and 50 years with an eGFR of >60 mL/min/1.73 m² and a BP ≥130/80, or being treated with an antihypertensive medication will be assigned to receive an ACE inhibitor alone (Lisinopril) or in combination with an angiotensin receptor blocker (Telmisartan). A standard BP goal of 120–130/75–85 will be compared to a low-BP group of 95–110/65–75 in both medication groups. This 2 × 2 study will separate out the role of medication versus the impact of BP control alone. Secondary outcomes will include the rate of decline in kidney function using the MDRD equation for eGFR and rate of decline in renal blood flow by MRA. This study will continue for 5 years, so the follow-up period can be adequate. Hopefully this will provide definitive information about the specific role of ACE inhibitors and ARB medications, as well as the independent effect of BP in the treatment of patients with ADPKD.

Conflict of interest statement. None declared.

(See related article by Raoul Zeltner et al. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2008; 23: 573–579.)

References

Statins and small GTPases: Koch’s postulates and chronic kidney disease

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Introduction

Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) are attracting more and more attention as cardiovascular and renal protective agents. Evidence from in vitro and rodent experiments indicates that this is not mediated via cholesterol-lowering effects, simply because culture dishes and rodents do not respond to statins with a decrease in plasma cholesterol. However, these so-called pleiotropic effects of statins are much harder to prove in humans, where in secondary prevention trials even...