Influence of *ACE* (I/D) and G460W polymorphism of α-adducin in autosomal dominant polycystic kidney disease

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Abstract

**Background.** The deleterious effect of the DD genotype of *ACE* in autosomal dominant polycystic kidney disease (ADPKD) remains controversial. Small sample size, population admixture and lack of consideration of parameters modulating the effects of *ACE* genotype, such as gender or α-adducin (*ADD*) genotype, might explain the discrepancy.

**Methods.** We investigated the effect of *ACE* (I/D) polymorphism on the age at end-stage renal disease (ESRD) in a homogeneous population of 191 ADPKD patients, according to gender and genotype for the G460W polymorphism of *ADD*. Cumulative renal survival was assessed in 276 patients from the same families.

**Results.** Though no effect was detected in the whole population, analysis of the male subset (*n* = 97) showed that patients harbouring the DD genotype of *ACE* had a 5-year lower mean age at ESRD than DI + II patients ([47.8 ± 1.8](n = 31) vs [52.8 ± 1.1](n = 66), respectively) (*P* = 0.02). Furthermore, cumulative renal survival was lower in the corresponding pedigrees [47 ± 1 years, 95% confidence interval (CI) 45–49, vs 51 ± 1 years, 95% CI 48–54]. The G460W polymorphism of *ADD* had no effect on the age at ESRD and cumulative renal survival, either alone or in combination with the *ACE* (I/D) polymorphism.

**Conclusions.** In this large series of ADPKD patients, we found no effect of the *ACE* (I/D) polymorphism on the age at ESRD, either alone or in combination with the G460W polymorphism of *ADD*. However, a deleterious effect of the DD genotype of *ACE* on renal disease progression was observed in ADPKD males.

Keywords: adducin; ADPKD; angiotensin-converting enzyme; modifier gene; polymorphisms

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic hereditary diseases and the most prevalent inherited nephropathy. ADPKD is characterized by the development of multiple cysts in both kidneys. By the age of 60 years, about half of ADPKD patients have progressed to end-stage renal disease (ESRD) [1]. Mutations in *PKD1* are responsible for ~85% of ADPKD cases, whereas mutations in *PKD2* account for the vast majority of the remaining cases [1]. The proteins encoded by *PKD1* and *PKD2* (polycystin-1 and polycystin-2, respectively) probably interact in the plasma membrane to participate in a signal transduction pathway involving intracellular calcium concentrations and controlling renal tubular cell maturation [2].

One of the most striking features in ADPKD is the substantial variability in the severity of renal phenotype, primarily assessed by the age at ESRD. This variability is observed among families, family members and even dizygotic twins [3]. Interfamilial phenotypic variability may be related to genetic (*PKD1* vs *PKD2*) and allelic (nature of the mutation) variants. Indeed, *PKD2* is clinically milder than *PKD1* disease, and the location of mutations within *PKD1* and *PKD2* is associated with differences in renal disease progression [3,4]. Intrafamilial phenotypic variability could result from a combination of environmental and genetic factors, which might influence all the steps leading to the disease. In particular, modifier genes could affect the signal transduction pathway involving the polycystins; influence the rate of second hit and, potentially, cyst formation; play a role in cyst progression and cyst fluid accumulation; or influence factors involved in the...
polymorphism on cardiovascular diseases is mainly instance, there is evidence that the effect of tations [4]. Such conflicting results have also been a large series of patients characterized for (I/D) polymorphism on hypertension and other blood pressure (BP)-related phenotypes [7]. Potential explanations for this discrepancy include the small size of many series, ethnic differences and population admixture, and inclusion of related patients. Alternatively, the discrepancy could reflect differences in other factors modulating the effect of ACE. For instance, there is evidence that the effect of ACE (I/D) polymorphism on cardiovascular diseases is mainly observed in males [17]. Other genetic variants are also susceptible to modulate the effect of ACE. One such variant is the G460W locus of ADD, the gene that encodes α-adducin, a heterodimeric cytoskeletal protein which interacts with the sodium pump (Na+/K+-ATPase) in renal tubular cells [18]. In several studies, the deleterious effect of the DD genotype of ACE on parameters such as BP, BP response to salt loading and renal function was restricted to subjects harbouring the W allele of ADD [19,20].

In order to clarify the modifier role of the ACE (I/D) polymorphism in ADPKD, we studied its influence on the age at ESRD in males and females from a large series of unrelated ADPKD patients, either in single-gene analysis or in combination with the G460W locus of ADD.

Subjects and methods

Study population

Patients were recruited from September 1998 to September 2001 in three academic institutions located in a restricted geographic area (<150 km radius): Saint-Luc Academic Hospital, Brussels (Belgium), UZ Gasthuisberg, Leuven (Belgium) and Necker Hospital, Paris (France). All Caucasian patients affected with ADPKD who were on renal replacement therapy (dialysis or renal transplantation) in the three centres were included, provided they were unrelated. The diagnosis of ADPKD was established on the basis of bilateral enlarged cystic kidneys and a family history suggestive of autosomal dominant inheritance [1]. The age at ESRD was defined as the age at starting renal replacement therapy. A detailed clinical follow-up for at least 2 years before ESRD was available for all patients. The study was extended further to affected relatives of the patients initially included, whether at ESRD or not. Linkage analysis for PKD1 and PKD2 was performed in informative families as described [6]. The use of DNA was approved by the Ethical Review Board of each centre involved, and informed consent was obtained from all patients included in the study.

DNA extraction and genotyping

DNA was extracted from peripheral blood samples (Gentra, Minneapolis, MN). Polymerase chain reaction (PCR) for both polymorphisms was carried out in a 20 μl volume with 100 ng of genomic DNA, 10 pM of each primer, 1.25 mM dNTP (Roche Diagnostics, Mannheim, Germany), 1 U of Tag polymerase (Roche) and 2 μl of 10× buffer containing 15 mM MgCl2 (Roche). Genotyping for the ACE (I/D) polymorphism was performed using primers and methods described previously [10]. Following denaturation at 94°C for 5 min, 30 cycles of denaturation at 94°C, annealing at 62°C and elongation at 72°C for 1 min were performed before a final elongation step of 72°C for 10 min. The insertion-specific PCR was performed on all individuals typed as DD in order to detect ID individuals mistyped as DD [9]. Following denaturation at 94°C for 5 min, 30 cycles of denaturation at 94°C, annealing and elongation at 72°C for 2 min were performed before a final elongation step of 72°C for 10 min. Amplified products were resolved on a 2% agarose gel.

Genotyping for G460W polymorphism of ADD was obtained by PCR followed by allele-specific oligonucleotide (ASO) hybridization using the primers, probes and PCR conditions described by Barlassina et al. [19]. Briefly, following denaturation at 94°C for 5 min, 30 cycles of denaturation at 94°C, annealing at 62°C and elongation at 72°C for 1 min were performed before a final elongation step of 72°C for 10 min. Each PCR product was blotted in duplicate on Zeta-Probe™ membranes (Biorad, Hercules, CA). The membranes were hybridized overnight at 42°C in a 7% polyethylene glycol (PEG), 10% sodium dodecyl sulfate (SDS) solution containing the 32P-radiolabelled probes, and then washed for 20 min in 2× SSC, 0.1% SDS at room temperature followed by 10 min in 1× SSC, 0.1% SDS at 42°C, rinsed in 1× SSC and exposed for 6 h to an X-ray film. Representative genotyping for both polymorphisms is shown in Figure 1.

Statistical analysis

All data were analysed using the SPSS statistical software (version 10.0, SPSS, Chicago, IL), and P-values <0.05 were considered as significant. The ages at ESRD were normally
distributed in males and females, and compared by two-tailed Student’s t-test. For each polymorphism, allele frequencies were calculated from the genotype. Allele and genotype distributions in male and female subsets were compared by χ² test. Hardy–Weinberg equilibrium was tested by a χ² test. Hardy–Weinberg equilibrium was tested by a χ² test.

Simple linear regression analysis was used to assess the individual effect of each polymorphism (independent variable) on age at ESRD (dependent variable). Multiple linear regression analysis was performed to investigate the joint effects of both polymorphisms on the same dependent variables. To deal with the categorical nature of a polymorphism, dummy variables were generated for each polymorphism. Cumulative renal survival analysis was performed using the Kaplan–Meier method; log-rank and Breslow tests were used to compare renal survival according to genotype. The Breslow test is more powerful if the event rate does not differ by a constant multiplier between the subsets harbouring different genotypes, i.e. late events are weighted less heavily by this test [21]. Differences in genotype distribution between patients having reached ESRD before 45 or after 60 years of age were tested by χ². Continuous variables were expressed as mean ± SEM.

Results

Characteristics of the ADPKD population studied

Two-hundred unrelated ADPKD Caucasian patients were recruited in the three centres: 114 (57%) in Saint-Luc Academic Hospital, Brussels; 49 (25%) in UZ Gasthuisberg, Leuven; and 37 (18%) in Necker Hospital, Paris. Because of the small size of most ADPKD families within this area, only 57 families were considered informative; linkage to PKD1 (n = 30) and PKD2 (n = 9) was established in 39 of these families. The nine patients linked to PKD2 were excluded from the analysis, which therefore included 191 unrelated ADPKD patients who had reached ESRD. Age at ESRD was ≤45 years (‘rapid progressors’) and ≥60 years (‘slow progressors’) in 26% (n = 50) and 24% (n = 46) of these 191 patients, respectively. Age at ESRD (52.1 ± 0.8 years) was similar to that described in Caucasian PKD1 populations in general [4,9] as well as in the 30 PKD1 patients in this series (52.5 ± 1.9 years). Gender did not significantly affect age at ESRD, both in the whole series and in the rapid/slow progressor subgroups. The main characteristics of patients included are shown in Table 1.

Distribution of the ACE (I/D) and ADD G460W polymorphisms

The distribution of the two diallelic polymorphisms is shown in Table 1. For each polymorphism, the observed genotype frequencies did not deviate from the Hardy–Weinberg equilibrium (I/D: χ²_1df = 0.04, P = 0.8; G460W: χ²_1df = 0.95, P = 0.3) and were similar to those previously described in Caucasians [19,22]. The genotype frequencies were not different according to gender (P = 0.9 and P = 0.3 for the I/D polymorphism of ACE and the G460W polymorphism of ADD, respectively) or centre (P = 0.3 and P = 0.6, respectively). As expected from the different chromosomal location,
the two polymorphisms were not in linkage disequilibrium ($P = 0.4$).

**Influence of the I/D and G460W genotypes on the age at ESRD**

The age at ESRD according to genotype is shown in Table 2. Although the I/D polymorphism of *ACE* had no effect on the age at ESRD in the whole population, male patients with ADPKD harbouring the DD polymorphism of *ACE* had a significant, 5-year lower mean age at ESRD than DI + II patients (recessive model). A similar trend was found in the subgroup of 15 ADPKD male patients belonging to *PKD1*-linked families (DD patients: 44.2 ± 4.0 years, $n = 5$ vs DI + II patients: 52.7 ± 3.2 years, $n = 10$, $P = 0.2$). Furthermore, the distribution of the I/D polymorphism of *ACE* was significantly different in the rapid (DD: 55%, $n = 16$; ID + II: 45%, $n = 13$) and slow progressors (DD: 19%, $n = 4$; ID + II: 81%, $n = 17$) subsets of ADPKD males ($P = 0.02$). The effect of the *ACE* (I/D) polymorphism on the age at ESRD in females (Table 2), and its distribution was similar in the rapid and slow progressor subsets of female patients (data not shown). The G460W polymorphism of *ADD* had no effect on the age at ESRD in the whole population or in the male and female subgroups (Table 2), and its distribution was not significantly different in slow and rapid progressor subsets of ADPKD patients (Table 1).

The effect of both polymorphisms on cumulative renal survival was assessed in a larger group extended to the affected relatives of the 191 patients initially included ($n = 276$). In the male subset, the cumulative median renal survival was lower in patients harbouring the DD genotype of *ACE* [47 ± 1 years, 95% confidence interval (CI) 45–49, $n = 40$] compared with patients harbouring the ID + II genotypes (51 ± 1 years, 95% CI 48–54, $n = 101$). This difference was significant ($P < 0.05$) by Breslow test but not by log rank test ($P = 0.3$) (Figure 2A). No effect was observed in the female subset (DD: 55 ± 2 years, 95% CI 52–58, $n = 50$ vs ID + II: 52 ± 2, 95% CI 48–56, $n = 85$, log rank test: $P = 0.8$; Breslow test: $P = 0.5$) (Figure 2B) or in the whole population (DD: 50 ± 2 years, 95% CI 46–54, $n = 90$ vs ID + II: 52 ± 1, 95% CI 50–54, $n = 186$, log rank test: $P = 0.7$; Breslow test: $P = 0.5$). There was no effect of the G460W polymorphism of *ADD* on cumulative renal survival, either in the whole population or according to gender (data not shown).

**Discussion**

Previous studies investigating a potential effect of the I/D polymorphism of *ACE* on renal disease progression in ADPKD yielded conflicting results (summarized in Table 3). These discrepancies may be due, at least in part, to small sample size, population admixture and over-representation of large families. In addition, they could reflect the variable distribution of genetic or clinical parameters likely to modulate the influence of *ACE* (I/D) polymorphism, such as gender [17] and *ADD* genotype [19,20].

In an effort to clarify this issue, we investigated the effect of the *ACE* (I/D) polymorphism and its modulation by gender and *ADD* genotype in a large number of unrelated Caucasian ADPKD patients at ESRD recruited within a restricted geographic area. No effect of the *ACE* (I/D) polymorphism was found in the whole population, either in single-gene analysis or in

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**Table 2. Age at ESRD according to the ACE (I/D) and ADD G460W genotypes**

<table>
<thead>
<tr>
<th></th>
<th>Total ($n = 191$)</th>
<th>Males ($n = 97$)</th>
<th>Females ($n = 94$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Age at ESRD (mean ± SEM)</td>
<td>$p**$</td>
</tr>
<tr>
<td><em>ACE</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-dominant*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>64</td>
<td>51.3 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>100</td>
<td>52.5 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>27</td>
<td>51.9 ± 2.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Recessive*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>64</td>
<td>51.3 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>ID + II</td>
<td>127</td>
<td>52.4 ± 0.9</td>
<td>0.5</td>
</tr>
<tr>
<td><em>ADD</em></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Co-dominant*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>121</td>
<td>51.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>GW</td>
<td>63</td>
<td>52.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>WW</td>
<td>7</td>
<td>57.0 ± 4.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Dominant*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>121</td>
<td>51.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>GW + WW</td>
<td>70</td>
<td>52.7 ± 1.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Mode of inheritance. **$P$-value obtained by ANOVA. All values are expressed as mean ± SEM.
combination with the G460W polymorphism of ADD. The latter also had no influence per se on the age at ESRD. However, a deleterious effect of the ACE DD allele was demonstrated in male patients, as it was associated with a significant, 5-year mean lower age at ESRD compared with the ID + II genotypes. Accordingly, the DD genotype was almost three times more frequent in the rapid vs slow progressors subset of ADPKD males. Analysis of renal survival extended to the affected relatives of the 191 ADPKD patients confirmed that the influence of the DD genotype of ACE was confined to the subset of male patients.

A deleterious effect of the DD genotype of ACE in ADPKD may be explained by the increased ACE plasma levels detected in such patients [15]. The subsequent increase in systemic AngII could result in earlier and more severe arterial hypertension, a factor well known to hasten the progression of renal failure in ADPKD [1]. Furthermore, since increased ACE plasma levels might be associated with increased levels of ACE and AngII at the tissue level, this could lead to

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**Table 3.** Main results of previous studies looking for an effect of ACE (I/D) polymorphism on the age at ESRD in ADPKD

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients at ESRD (n)</td>
<td>52</td>
<td>48</td>
<td>33</td>
<td>68</td>
<td>152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>NR</td>
<td>24 (50%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at ESRD</td>
<td>48 ± 1</td>
<td>48 ± 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>44 ± 2</td>
<td>48 (45–51)</td>
</tr>
<tr>
<td>ACE genotypes</td>
<td>DD</td>
<td>25 (48%)</td>
<td>15 (31%)</td>
<td>6 (18%)</td>
<td>20 (29%)</td>
<td>64 (30%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>ID</td>
<td>14 (27%)</td>
<td>26 (54%)</td>
<td>14 (43%)</td>
<td>35 (52%)</td>
<td>108 (50%)</td>
<td>6 (31%)</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>II</td>
<td>13 (25%)</td>
<td>7 (15%)</td>
<td>13 (39%)</td>
<td>13 (19%)</td>
<td>44 (20%)</td>
<td>11 (58%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>ID/II</td>
<td>67 (88%)</td>
<td></td>
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<td></td>
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<tr>
<td>Age at ESRD according to genotype</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>44 ± 2</td>
<td>48 (45–51)</td>
<td>56 ± 7</td>
<td>55 ± 2</td>
<td>52</td>
<td>52 ± 2</td>
<td>52 ± 5</td>
</tr>
<tr>
<td>ID</td>
<td>49 ± 2</td>
<td>53 (48–62)</td>
<td>56 ± 2</td>
<td>35</td>
<td>52</td>
<td>56 ± 4</td>
<td>55 ± 3</td>
</tr>
<tr>
<td>II</td>
<td>54 ± 2</td>
<td>51 (43–54)</td>
<td>55 ± 3</td>
<td>52 ± 3</td>
<td>54</td>
<td>51 ± 4</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>ID/II</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P-value*</td>
<td>0.013^c</td>
<td>0.025^c</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*The distribution was calculated for a larger group including non-ESRD patients (n = 216).

^Median renal survival time.

^Recessive model: DD vs. ID + II.

All values are expressed as mean ± SEM. NR, not reported; NS, not significant.

The study by van Dijk et al. [16] is not included in the table, due to its different design (comparison of the distribution of ACE genotypes in slow and rapid progressors).
alteration of intrarenal haemodynamics and ultimately renal injury.

The restriction of the deleterious effect of the DD genotype of ACE to the male subset of ADPKD patients is in agreement with previous studies showing that genetic polymorphisms of the RAS display more profound effects on BP and cardiovascular diseases in men than women [17]. For instance, in a population study including 3095 participants of the Framingham heart study, the DD genotype was associated with diastolic BP in men, but not in women. In two recent, large sib-pair studies, ACE influenced systolic and diastolic BP in men, but not in women. Furthermore, in mice harbouring an inactivated ACE gene at the heterozygous state, the observed decrease in BP was restricted to males [17]. Such a gender difference might be explained by the influence of oestrogens on almost all steps of the RAS. As the influence of ACE genotype on ACE activity is present in females as well as in males, it may be hypothesized that oestrogens modulate the downstream effects of AngII, for instance through downregulation of AT$_1$ receptors or post-receptor signalling [17].

Genetic heterogeneity is an important factor in renal disease progression in ADPKD. Since PKD2 patients have a less severe disease than PKD1 patients, with a median age at ESRD of 74.0 years vs 54.3 years, respectively [3,4], an over-representation of the former could contribute to the higher age at ESRD in the (ID + II) subset. However, the latter hypothesis appears unlikely, as the mean age at ESRD in our population (52.8 years) is similar to that found in PKD1-linked patients in general [3,4], and the PKD1 subset in this study (52.7 years). Furthermore, an 8-year difference in the age at ESRD was found between DD and (ID + II) patients belonging to the PKD1-linked subgroup analysed here. Finally, the difference in cumulative renal survival between ADPKD males (Figure 2A) is present across all age categories with the exception of slow progressors (more likely to include less severe, PKD2 patients). This observation may explain why the Breslow test, which weights less heavily late events [21] more likely to be found in PKD2 patients, was more powerful than the log rank test to detect a difference between renal survival curves. Our results may also reflect an imbalance in other factors accounting for inter-familial variability in ADPKD, such as the nature of the PKD1 mutation itself [4], or differences in environment or medical care. The affected sib-pair method which fixes the effect of PKD1 mutations and minimizes the contribution of environment would be worthwhile to confirm these results. However, hundreds of affected siblings at ESRD would be required to achieve a sufficient statistical power [23].

Recent studies have shown that the G460W polymorphism of ADD modulates the deleterious effect of the DD genotype of ACE on salt sensitivity and hypertension [19,20]. Furthermore, the W allele of the G460W polymorphism has been associated with renal disease progression in patients with various nephropathies [24]. This deleterious effect is thought to be due to increased tubular reabsorption of sodium, leading to increased BP and accelerated renal function degradation [18]. However, our studies reveal a lack of influence of the G460W polymorphism of ADD on the age at ESRD in ADPKD, either alone or in conjunction with the ACE polymorphism.

In ADPKD patients harbouring the W460 allele of ADD, the deleterious effect of increased BP could be compensated by decreased cyst volume, a factor associated with slower renal disease progression [25], thus explaining the absence of a net effect of the G460W polymorphism on renal outcome. Indeed, α-adducin and Na$^+$/K$^+$-ATPase co-distribute in normal [18] and cyst-lining epithelial cells (A. Persu and O. Devuyst, unpublished data), and point mutations of α-adducin have been shown to activate Na$^+$/K$^+$-ATPase [18]. It is thus tempting to speculate that the 460W allele may be associated with an activation of the Na$^+$/K$^+$-ATPase in cyst-lining epithelia, leading to increased sodium reabsorption and decreased cyst fluid volume.

In conclusion, in this large, homogeneous series of ADPKD patients, we find no effect of the ACE (I/D) polymorphism on the age at ESRD. However, in the male subset, the DD genotype is associated with a worse renal outcome. This effect is not influenced by the G460W polymorphism of ADD, possibly reflecting opposite effects of increased tubular sodium reabsorption on BP and cyst fluid volume.

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