Approaches to Testing New Treatments in Autosomal Dominant Polycystic Kidney Disease: Insights from the CRISP and HALT-PKD Studies

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Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disease characterized by a prolonged subclinical course of gradual renal cyst expansion, resulting in massively enlarged kidneys and renal failure by the fifth to sixth decade. Renal cyst expansion results in intrarenal ischemia and activation of the renin-angiotensin-aldosterone system (RAAS) and relates to the development and maintenance of hypertension in ADPKD. Hypertension relates to disease progression in ADPKD with regard to renal volume, proteinuria, cardiovascular complications, and progression to end-stage renal disease. Novel magnetic resonance imaging methods developed in the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) provide accurate estimates of change in renal volume over a short period of time in ADPKD patients with intact renal function. In CRISP an increase in renal volume of 63.4 ml/yr was found. PKD1 status, male gender, hypertension, reduced renal blood flow, and proteinuria are associated with increased renal volume and change in renal volume over time. HALT-Polycystic Kidney Disease (HALT-PKD) is designed to test whether blockade of RAAS and/or rigorous blood pressure control play a role in slowing renal progression during early (using magnetic resonance imaging methods developed in CRISP) and during late (using measures, including composite of time to doubling of serum creatinine, onset of end-stage renal disease, or death) phases in ADPKD. Findings from CRISP and the rationale for interventions in ADPKD are described, and the design of the HALT-PKD clinical trial is outlined.

Recent significant advances have occurred in understanding the genetics and molecular pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Complex pathways regulating the formation and development of cysts are being elucidated. Primary ciliary dysfunction plays a universal role in cystic disorders. New, molecularly targeted therapies are available and can be tested in ADPKD, offering hope for a cure or impact in this disorder.

To determine the efficacy and reliably translate new therapies in ADPKD, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease study (CRISP) funded by the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases) was established to develop methods that reliably measure disease progression in ADPKD over a relatively short period of time. In tandem with the CRISP study, randomized clinical trials (RCTs) are now being performed in ADPKD using magnetic imaging methods developed in CRISP. Specifically, the HALT-PKD Network has been developed to assess the benefit of rigorous blood pressure (BP) control and maximal inhibition of the renin-angiotensin-aldo-

sterone system (RAAS) on progressive renal disease and cardiovascular manifestations in ADPKD. This review will highlight the observations from CRISP and describe the rationale for and study design of the HALT-PKD Network.

Clinical Hallmarks and Pathogenesis of ADPKD

ADPKD is the most commonly inherited autosomal dominant renal disease, occurring in 1:400 to 1:1000 individuals accounting for approximately 2.5% of end-stage renal disease (ESRD) in the United States. ADPKD is a heterogeneous disorder resulting from mutations in at least two genes, PKD1 and PKD2. A total of 85% of affected families are linked to a mutation in the PKD1 gene located on the short arm of chromosome 16 (16p13.3 region). Mutations in the PKD2 gene located on the long arm of chromosome 4 (4q21.2 region), accounting for 15% of affected families (1). Polycystin 1 and 2 colocalize in the primary cilium and are required for membrane-based calcium channels to operate properly (2). Cilia create a transmembrane calcium current in the presence of stretch or luminal flow, leading to a signaling cascade and multiple intracellular events. These pathways are altered or inhibited when a mutation in PKD1 or PKD2 takes place. In the absence of PKD1 or PKD2 function, cystic epithelia dedifferentiate, losing planar polarity, increasing cell division (3) and apoptosis (4), and losing reab-

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sorptive capacity. These events result in cyst growth and expansion, ultimately resulting in enlarged kidneys and progressive renal injury.

ADPKD is a systemic disease resulting in liver, pancreas, thyroid, subarachnoid, and seminal vesicle cysts in addition to inguinal hernias. The vascular phenotype of ADPKD includes intracranial aneurysms, early-onset hypertension with early reductions in renal blood flow, mitral valve prolapsed, and abnormalities in biventricular function. However, the clinical hallmark of ADPKD is gradual and massive cystic enlargement of the kidneys, ultimately resulting in renal failure (5).

Epidemiology of ADPKD: Difficulty with Evaluating Potential Therapeutic Agents

In ADPKD, gradual cyst expansion results in renal enlargement and ultimate progression to renal failure with a mean age of onset of 59 yr (6). Although ADPKD children are usually asymptomatic, elevated BP, increased left ventricular mass, and hernias are common and are associated with cyst number and kidney size. Importantly, glomerular hyperfiltration is a common finding in ADPKD children, suggesting that there is a significant amount of compensatory glomerular hyperfiltration that occurs in association with cyst expansion and probable nephron loss. The average age of diagnosis of ADPKD is 27 yr and hypertension is 31 yr, before loss of renal function (7,8). Once renal dysfunction occurs, a universal rapid decline in renal function (~5.9 ml/min per yr) occurs (Figure 1). Importantly, almost all RCTs in ADPKD have been performed at this late stage in ADPKD and fail to demonstrate benefit.

Food and Drug Administration-acceptable outcome measures of progressive renal disease include frequency or time to ESRD, doubling of serum creatinine, or death. Other outcome measures are less favorably accepted and include change in rate of loss of renal function (serum creatinine, reciprocal of serum creatinine, or glomerular filtration rate [GFR]), change in proteinuria, or protocol biopsy. Regardless, all of these outcome measures are ineffective with little or no role in ADPKD given the long presymptomatic phase and late age of onset of renal dysfunction in this disorder.
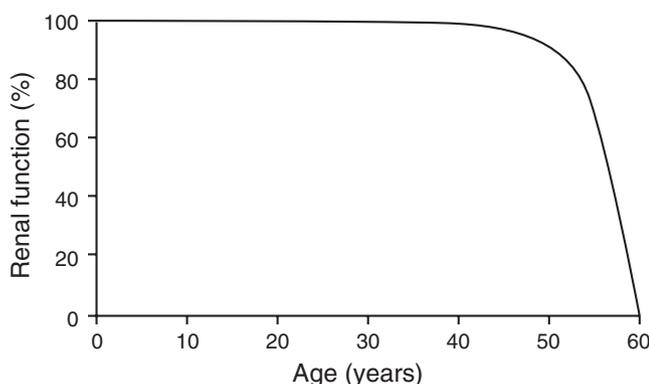

Figure 1. Renal survival curve in autosomal dominant polycystic kidney disease. These demonstrate a long duration of intact renal function before loss of renal function or entry into ESRD.

CRISP

The CRISP consortium, funded by National Institute of Diabetes and Digestive and Kidney Diseases, was developed to establish reliable measures of disease progression early in ADPKD (9). CRISP is an ongoing prospective observational study with 3 yr of annual cyst and kidney growth measurements available in 243 ADPKD patients with relatively intact initial renal function. Magnetic resonance imaging done annually initially included gadolinium enhancement. In total, there were 972 exposures in 726 patient-years and no reported cases of nephrogenic systemic fibrosis (10). Subsequent studies proposed in the current continuation (CRISP II) do not include gadolinium infusions. Significant findings from CRISP are summarized in Table 1.

The CRISP cohort demonstrated significant progression of renal cyst growth and renal enlargement before loss of kidney function (7,11). CRISP participants initially demonstrated age-associated increases in renal and cyst volumes. Hypertensive individuals demonstrated significantly greater renal and cyst volumes compared with their normotensive counterparts and PKD1 individuals demonstrated significantly greater renal and cyst volumes than PKD2 individuals. CRISP subjects most often demonstrated renal volumes in excess of 1000 ml, with normal being 150 ml. Renal volume associated inversely with

Table 1. Highlights of the observations obtained from the CRISP study program

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Liver cystic disease: 95% prevalence of liver cystic disease by age 35, women more often than men (9)

Genotype: PKD1 individuals demonstrate larger kidneys with more cysts than age-matched PKD2 individuals; rate of change in cyst growth are similar between PKD1 and PKD2 individuals (11,12)

Hypertension: Hypertensive ADPKD individual demonstrate larger kidney volumes than age-matched normotensive ADPKD individuals that grow at a faster rate (5,47)

Kidney volume: Increases over time with growth due to cyst expansion; associated with proteinuria and reduction in GFR (8)

Renal blood flow: Is reduced early in ADPKD, before loss of renal function, and is associated with increased renal size (10,48)

Ultrasound *versus* MRI: Demonstrates reduced reliability and reproducibility with ultrasound and decreasing correlation with MRI-based estimates of renal volume as kidney size increases (49)

MDRD estimates of GFR in ADPKD individuals with intact renal function: are less reliable than other regression models using serum creatinine concentration (50)

MRI, magnetic resonance imaging.

iothalamate clearance (GFR) and correlated with urinary protein excretion, both significant predictors of poor renal outcome in ADPKD. Liver cystic volume was measured and liver cystic disease was highly prevalent (>85% of CRISP participants) (12). Women were more often affected than men, particularly early (<25 yr of age); however, in those >35 yr of age, >95% of the entire CRISP cohort demonstrated liver cysts.

Renal growth occurred in almost all CRISP participants with a mean rate of increase of 5.3% (−5.3, −17%) or 63.4 ml/yr (11). Changes in total renal and cyst volumes were similar (204 ± 246 versus 218 ± 263 ml), indicating that cyst expansion accounts for the increased renal volume estimates found in ADPKD. Younger individuals with larger kidneys (>1500 ml, <30 yr) demonstrated the greatest growth rates (12.7%/yr). Overall, change in total renal volume was associated reciprocally with change in GFR. In participants with kidneys >1500 ml, GFR declined (−4.3 ml/min per yr). In a subset of 131 CRISP participants, quantitative renal blood flow measures were obtained during magnetic resonance imaging studies (13). A significant inverse relationship was found between renal volume and renal blood flow and reduction in renal blood flow significantly correlated with increases in renal volume, before loss of GFR. Importantly, when accounting for age, gender, hypertension status, renal volume, and renal blood flow, age and renal blood flow were the most significant predictors of loss of renal function. These finding suggest that vascular change associated with cyst expansion and alterations in renal vascularization are a central problem related to loss of renal function in ADPKD.

Using denaturing high performance liquid chromatography, direct sequencing, and large deletion detection methodologies, mutations in PKD1 or PKD2 were found in 89.1% of tested CRISP individuals (14,15). Overall, 15% were PKD2 and 85% PKD1, consistent with other reported ADPKD populations. The spectrum of mutations included frameshift (31.1%), nonsense (26.1%), missense (24.4%), splicing (12.2%), or in-frame deletions or insertion (6.1%) mutations. Previously reported mutations were found in 30% of families in the CRISP cohort.

In general, PKD2 is a less severe form of polycystic kidney disease than PKD1 with a later age of onset of ESRD and hypertension (1,7,16). Less severe disease was also found in PKD2 CRISP participants. PKD2 subjects demonstrated significantly smaller renal volumes compared with PKD1 subjects. However, the rate of renal growth was similar between PKD1 (5.7%/yr) and PKD2 (5.0%/yr) (P = not significant). When cyst numbers in PKD2 and PKD1 individual renal images were determined, fewer cysts were found in PKD2 individuals (11.3 versus 22.1 cysts/image, P < 0.01) (15). These findings indicate, therefore, that cystogenesis rather than the rate of cyst expansion accounts for the differences in renal volume observed between PKD genotypes.

A large variation in the rate of renal-volume evolution is evident in the CRISP cohort. Gender, hypertension status, and genotype play major roles in the variation seen. Mathematical modeling using CRISP renal volumes and demographic data demonstrate a curvilinear or exponential renal growth curve. By estimating the relative contributions of cyst number, age of cyst appearance, and rate of cyst growth to overall cyst burden

and renal volume in CRISP, our understanding of cyst kinetics in ADPKD is now expanded. If one assumes an initial cyst size <2 mm (0.0042 ml), given all originate from a parent nephron, varying degrees of cyst burden at birth (500 versus 2000 cysts) and varying rates of cyst growth (5% to 25%), while using the established CRISP renal volume measures, improved understanding of cyst kinetics in ADPKD are obtained (17). Cyst growth rates of at least 20% to 25%/yr are required to reach the magnitude of renal volume observed in the CRISP cohort. If late initiation of renal cysts predominate (i.e., age >20 yr), little subsequent total renal growth over the next 20 yr occurs with renal volume estimates significantly less than those observed in CRISP. These data suggest that early cystogenesis is required in ADPKD, accompanied by a moderate rate of cyst expansion as opposed to continued cystogenesis throughout adulthood. By this analysis, new cyst formation in adulthood has little or no impact on increases in renal volume in ADPKD.

Testing Therapeutics in ADPKD: The Rationale for the HALT-PKD Clinical Trial

Cardiovascular disease is a major cause of mortality in ADPKD. Hypertension contributes to the development of cardiovascular disease and is a significant predictor of renal progression in ADPKD (18). At the mean age of 44 yr, 48% of hypertensive ADPKD adults have left ventricular hypertrophy (19). More than 70% of ADPKD subjects initiating dialysis have left ventricular hypertrophy (20). Microalbuminuria and proteinuria correlate with progression of renal disease in ADPKD (7,21) and are amenable to inhibition of the RAAS.

Hypertension occurs early and before loss of renal function, and clinical data support evidence for activation of RAAS in patients with ADPKD. Activation of the RAAS has been found in normotensive and hypertensive ADPKD subjects. As cysts enlarge, they compress the renal vasculature and attenuate the renal vessels causing intrarenal ischemia and activation of the RAAS (19,22,23) The RAAS contributes to hypertension in ADPKD but may also independently accelerate renal cyst growth. Renin is synthesized by the tubular epithelium in individuals with ADPKD and is found in increased quantities in juxtaglomerular apparatus and the afferent arterioles (22). Renal volume, significantly associated with cyst growth and enlargement, as seen in CRISP, is increased in hypertensive adults and children compared with their normotensive counterparts before loss of renal function (8,24,25). Increased circulating levels of plasma renin activity and aldosterone are present in hypertensive ADPKD patients with normal renal function compared with well-matched essential hypertensive individuals (23). Importantly, short-term therapy with angiotensin converting enzyme inhibitors (ACEIs) in hypertensive ADPKD individuals is associated with a relative improvement in renal blood flow compared with essential hypertensives.

These data suggest that drugs that block the RAAS (renin inhibitors, ACEIs, angiotensin receptor blockers [ARBs], or aldosterone antagonists) should play a reno-protective role in ADPKD. However, definitive information on the potential role of complete blockade of the RAAS to prevent progression of renal dysfunction in ADPKD is lacking. Maschio et al. have

performed the only prospective randomized double-blind, placebo-controlled study to assess the benefits of ACEI on renal progression in nondiabetic kidney diseases (26). This study included 64 ADPKD individuals with mean creatinine clearance of 42 ml/min followed over 3 yr (26). A doubling of serum creatinine concentration occurred with equal frequency in the ACEI ramapril (27%) and the placebo group (26%). In the Modification of Diet in Renal Disease (MDRD) study, which was designed to assess the role of dietary protein and phosphorous intake and level of BP control on renal disease progression, 221 of 840 subjects had ADPKD (27). Overall, there was no significant reduction in GFR decline in those treated with either the low-protein diet or low BP, and ACEIs were used in approximately 40%. In a 7-yr prospective trial of 72 ADPKD patients assessing both level of BP control and class of antihypertensive agent used, no advantage of the ACEI enalapril *versus* the calcium channel blocker amlodipine was found in reducing the rate of decline of estimated GFR (19). Proteinuria and left ventricular hypertrophy were significantly reduced in the enalapril-treated group. In addition, albumin creatinine ratios were higher in the amlodipine group *versus* the enalapril group (148 ± 74 *versus* 14 ± 6) after 5 yr of intervention.

Although a definitive study to demonstrate efficacy of ACEIs on renal progression in ADPKD is not available, there is a wealth of evidence that ACEI is of benefit in slowing renal progression in nondiabetic kidney disease. Clinical practice guidelines from the National Kidney Foundation and the Joint National Committee on Prevention Detection Evaluation and Treatment of High BP call for ACEI as the first line agent for treatment of hypertension in patients with chronic kidney disease (28–30). In addition, ACEIs or ARBs have renoprotective effects (antiproteinuric) in the progression of diabetic and nondiabetic renal disease independent of antihypertensive effects (26,31–35).

A recent meta-analysis from 11 randomized clinical trials in nondiabetic kidney disease, including 145 ADPKD individuals, reported a 25% (but nonsignificant) relative risk reduction in the composite endpoint of ESRD, doubling of serum creatinine in individuals on ACEI *versus* other antihypertensive agents (36,37). These findings were from secondary analyses, performed in relatively small numbers of subjects with limited follow-up. Therefore, a rigorous clinical trial, adequately powered to assess the effect of ACEI on renal progression in ADPKD, has not been performed.

As in other renal diseases, complete blockade of the RAAS using ACEI does not occur in ADPKD. Angiotensin II (ANGII) contributes to the decreased renal plasma flow and increased systemic vascular resistance found in hypertensive ADPKD subjects (38,39). In addition, normalization of renal blood flow in hypertensive ADPKD individuals with ACEIs is not complete (23,40). Systemic ANGII levels do not suppress with chronic ACEIs in ADPKD, and systemic and renal hemodynamic responses to intravenous angiotensin I (ANGI) and ANGII persist in the presence of ACEIs (38,39).

Other non–ACE-dependent mechanisms for renal activation of the RAAS may exist in ADPKD. ANGII activity through chymase pathways has been demonstrated in polycystic kidneys (41). If one considers use of ACEIs in the setting of other inhibitors of the RAAS, the sustained benefit from increased bradykinin activity related to ACEIs and decreased ANGII at the tissue level through combination therapies is possible.

Addition of ARBs to ACEIs helps to prevent the escape phenomenon from ACEIs and reduces action of ANGII produced independent of the ACE pathway (Figure 2). Combination of ACEI and ARB also allows for the potential activation of the vasodilatory ANGII type 2 receptor while preventing the detrimental effects of ANGIV.

ARB therapy prevents action of ANGII in the systemic and renal circulations by binding with ANGII 1a receptors. However, ANGII levels also increase with chronic ARB therapy in ADPKD; systemic and renal hemodynamic responses to intravenous ANGII administration are not completely suppressed in the presence of ARB, and tissue penetration of ARB differs across local tissue beds (38,39). Given that ANGII level and action are important in regulating BP and renal plasma flow and appears to promote cyst growth in ADPKD, combination therapy with ACEIs and ARBs to maximally block ANG II production and action may be warranted.

To date, <20 good-quality studies involving 654 subjects with chronic renal insufficiency, either crossover or parallel designed, are available to determine the efficacy of combined ACEI and ARB therapy in proteinuric renal diseases (42–48). In general, the combination of an ACEI with ARB reduces BP by −4/3 mmHg compared ACEI or ARB administered as monotherapy. In many of these studies, BP is lower in drug combination groups, making it difficult to establish benefits due to drug combination or to differences in BP obtained. The COOPERATE trial (43) in 263 patients over 2.9 yr in nondiabetic patients with proteinuric renal disease using fixed doses for ACEIs and ARBs together demonstrated long-term renoprotection compared with either agent alone. Combined ACEI/ARB therapy reduced proteinuria by 30% compared with ACEIs and by 29% compared with ARBs. Doubling of serum creatinine or ESRD was reached by 11% of subjects receiving combination therapy compared with 23% on monotherapy with an ACEI or ARB alone (hazard ratio = 0.38 to 0.4 for combination *versus* ACEI or ARB, respectively). In another study, fosinopril or irbesartan therapy showed a reduction in proteinuria of 35%, whereas combination therapy reduced proteinuria by 60% *versus* placebo (44).

HALT-PKD: Study Design and Organization

The HALT-PKD study is the first prospective clinical interventional study sponsored by the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases) for adults with ADPKD. The hypothesis will be tested that intensive blockade of the RAAS with combination ACEIs and ARBs will delay the progression of renal disease independent of BP control in participants compared with ACEI monotherapy alone. In addition, the hypothesis will be tested that rigorous *versus* moderate BP control will be more effective in slowing progression of renal disease in early ADPKD.
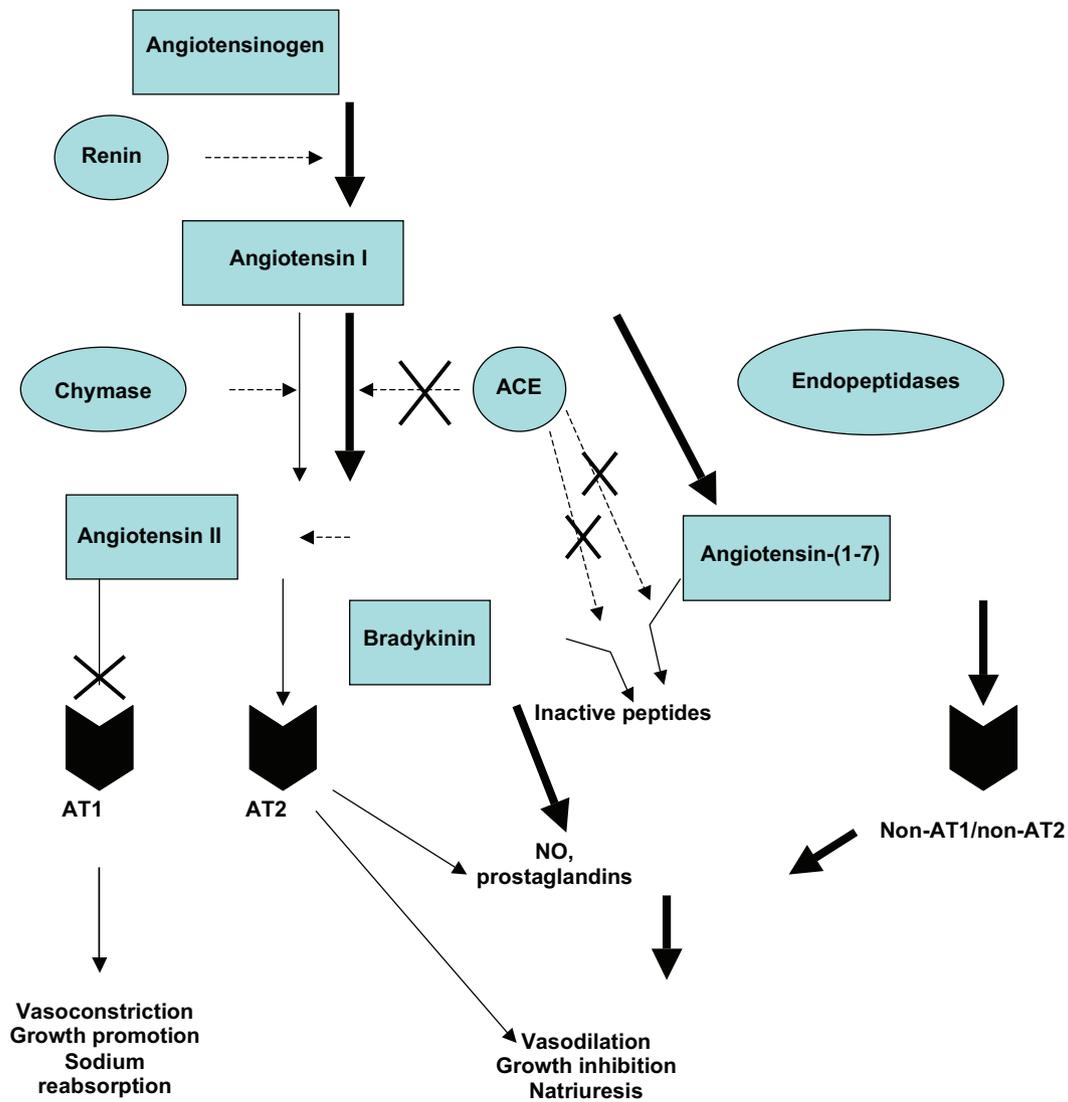
Figure 2. The cascade of the renin-angiotensin aldosterone system with respect to administration of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blocking agents. Note increased activation of the AT2 and the Non-AT1/NonAT2 pathways with administration of angiotensin receptor blockers.

HALT-PKD involves seven clinical centers and a Data Coordinating Center with plans to recruit 1020 subjects between January 2006 and December 2008. HALT-PKD is a prospective RCT designed to determine the independent effects of renin-angiotensin system blockade using both ACEIs and ARBs as well as BP lowering on renal disease progression in early study A (GFR, >60 ml/min; n = 548) and more advanced renal disease study B (GFR, 25 to 60 ml/min; n = 472). The ACEI lisinopril is prescribed for all patients in HALT (both study A and B). It is not known whether the addition of an ARB, telmisartan, will provide renal or cardiovascular protection in ADPKD patients. Thus, patients in both study A and study B will be randomized to lisinopril plus placebo *versus* lisinopril plus telmisartan. In study A, hypertensive and borderline hypertensive (>130/80 mmHg) ADPKD subjects 15 to 50 yr of age are randomized in a 2 × 2 factorial design to lisinopril (ACEI) and placebo *versus* ACEI and telmisartan (ARB) and two levels

of BP control: standard (120 to 130/70 to 80 mmHg) *versus* rigorous goal (95 to 110/65 to 75 mmHg). Study A uses a primary structural endpoint, change in total kidney volume over 4 yr by MRI, as developed in CRISP and will be the first study to assess kidney volume change as a primary endpoint in a RCT. Secondary outcomes in study A include the rate of change in estimated GFR using the 4-point Modification of Diet in Renal Disease equation (49), change in renal blood flow and left ventricular mass using magnetic resonance imaging, change in albuminuria, and PKD-related symptoms.

In study B, hypertensive and borderline hypertensive ADPKD subjects 18 to 65 yr of age with GFR 25 to 60 ml/min are randomized to ACEI and placebo *versus* ACEI and ARB therapy with a single BP goal of 110 to 130/<80 mmHg. The primary outcome is time to the composite endpoints of doubling of serum creatinine, ESRD, or death.

The HALT-PKD trial will provide important information

related to disease progression in ADPKD given the large number of subjects to be studied and the design of the trial.

With the completion of the HALT study, we will establish the relative benefits of BP control and inhibition of the RAAS in both early and late stages of ADPKD, which will guide clinicians regarding best practices for ADPKD patients. Data from the HALT-PKD study will establish treatment standards and provide the necessary information to allow for the design of specific molecularly targeted therapies in ADPKD. Given the number of novel measures to be performed in this RCT, valuable structural information regarding cardiac and renal outcomes in ADPKD will guide future interventions when considering other inhibitors of the RAAS in ADPKD, including renin inhibitors and aldosterone receptor antagonists.

Acknowledgments

Disclosures

None.

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Erratum

Correction

Approaches to Testing New Treatments in Autosomal Dominant Polycystic Kidney Disease: Insights from the CRISP and HALT-PKD Studies. *Clin J Am Soc Nephrol* 3: 1197–1204, 2008

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Footnote to the Author[1]

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