Update in Nephrology: Evidence Published in 2013

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This update summarizes 8 important studies in nephrology, transplantation, and hypertension that are relevant to primary care. The authors screened the literature by using ACP JournalWise to identify articles for inclusion and subsequently considered additional late-breaking publications. Studies were selected to emphasize the provision of high-value care to patients by primary care providers and key basic scientific and translational discoveries in nephrology.

This review examines a landmark trial in dual renin–angiotensin–aldosterone system (RAAS) blockade for treatment of diabetic nephropathy. The distribution and outcomes of hypertension among patients with kidney disease and a novel telemonitoring intervention to improve blood pressure (BP) control are also presented. Additional epidemiologic studies examining the determinants of the progression of chronic kidney disease (CKD) are shown to highlight novel risk factors, which may explain some of the racial disparity of CKD progression seen in the United States. One of the exciting trials of autosomal dominant polycystic kidney disease (ADPKD) demonstrated how breakthroughs in our understanding of basic disease pathophysiology translate into clinical trials. Recent landmark trials that explored the use of rituximab in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis are extended by a recent study that examined long-term follow-up of patients in the RAVE (Rituximab for ANCA-associated Vasculitis) trial.

Although it is widely known that patients with end-stage renal disease (ESRD) have a mortality rate similar to or greater than that of patients with many types of cancer, this update presents a report showing that patients with ESRD have expectations for long-term survival and that these expectations may frame their health care decisions. Finally, kidney transplant patients remain at high risk for cardiovascular disease, and this update presents a long-term study of RAAS blockade on cardiovascular and renal graft outcomes.

Hypertension

Combined Therapy With Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers Showed No Benefit in Treatment of Proteinuric Diabetic Nephropathy

Fried LF, Emanuele N, Zhang JH, et al; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-903. [PMID: 24206457]

Background: Diabetic nephropathy is the most common cause of ESRD in the developed world. The use of angiotensin-receptor blockers (ARBs) in reducing the rate of progression of CKD in patients with diabetic nephropathy has been critical to improving the outcomes of these patients. It has been posited that dual therapy with ARBs and angiotensin-converting enzyme (ACE) inhibitors would lead to further decreases in proteinuria and preserve renal function.

Findings: The VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) study was a multicenter, double-blind, randomized, controlled study designed to test whether combination therapy with ARBs and ACE inhibitors would significantly decrease the rate of progression of proteinuric diabetic nephropathy compared with ARBs alone. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end point events in the ARB group and 132 in the combination therapy group (hazard ratio with combination therapy, 0.88 [95% CI, 0.70 to 1.12]). Combination therapy did not provide a survival benefit (hazard ratio for death, 1.04 [CI, 0.73 to 1.49]) or reduction in cardiovascular events compared with ARB therapy. The combination therapy group also had an increased risk for hyperkalemia (6.3 vs. 2.6 events per 100 person-years with monotherapy; $P < 0.001$) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years; $P < 0.001$) compared with the ARB group.

Cautions: This study largely included men, which may limit generalizability of the findings to other populations. Although the data and safety monitoring board ended the study early, conditional power analyses suggested that the observed effects on the primary end point would not have been significant if the study had been completed as planned.

Implications: This study showed that dual therapy with ACE inhibitors and ARBs is not beneficial for proteinuric diabetic nephropathy. Given these findings and those from other clinical trials, physicians should avoid this therapy in patients with recent-onset proteinuric diabetic nephropathy. Physicians should review these study findings with patients who are stable and receiving dual therapy and consider withdrawing 1 of the agents. For patients who choose to continue the therapy, physicians should recommend avoiding potassium-rich foods and should have a low threshold for evaluating kidney function.

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Moderately Elevated Systolic BP Combined With Normal Diastolic BP Had Consistently Lower Mortality Rates Among U.S. Veterans With CKD

Kovesdy CP, Bleyer AJ, Molnar MZ, et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. Ann Intern Med. 2013;159:233-42. [PMID: 24026256]

Background: The BP targets for patients with CKD have been unclear and may differ by severity of proteinuria or diabetes status.

Findings: This cohort study examined outcomes among patients with CKD in U.S. Veterans Affairs health facilities who were not dependent on dialysis. Various combinations of lower systolic and diastolic BPs were associated with lower mortality rates as long as the diastolic BP remained greater than approximately 70 mm Hg. Patients with systolic BP of 130 to 159 mm Hg and diastolic BP of 70 to 89 mm Hg had the lowest mortality rates. Patients with "ideal" BP (<130/80 mm Hg) had increased mortality rates because the study included patients with low systolic and diastolic BPs.

Cautions: The study cohort comprised U.S. veterans who were almost exclusively men; hence, the findings may not apply to women or the general population. In this observational study, no causal relationships could be established between BP and survival.

Implications: This study challenges guidelines recommending lower BP targets for patients with CKD. However, these findings are consistent with the Eighth Joint National Committee recommendations. Further information on BP targets will be provided by SPRINT (Systolic Blood Pressure Intervention), an ongoing trial by the National Institutes of Health that examines BP targets in older adults with and without CKD.

Home BP Telemonitoring and Pharmacist Case Management Led to Better BP Control

Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013;310:46-56. [PMID: 23821088]

Background: Although hypertension generates a substantial number of office visits for primary care physicians, many patients have uncontrolled BP in this care model. This study tested whether a combined intervention of telemedicine and pharmacist-led care was effective for improving BP control.

Findings: In this cluster randomized clinical trial, 8 clinics were randomly assigned to provide usual care to patients and 8 were randomly assigned to provide a telemonitoring intervention. Home BP telemonitoring and pharmacist case management provided significantly better systolic BP control than usual care during the 12-month intervention, and these positive effects persisted during 6 months of postintervention follow-up. At 18 months (6-month postintervention follow-up), BP was controlled in 71.8% of patients in the intervention group and 57.1% of those in the usual care group.

Cautions: This trial was done in highly selected populations. Most participants had more than a high school diploma (82.6%) and a household income greater than $30 000 per year (83%).

Implications: The telemonitoring intervention provided significant and sustained improvements in BP control. This study suggests that different care models play a role in improving BP control in primary care patients.

Chronic Kidney Disease

Apolipoprotein L1 Risk Variants Linked to Increased CKD Progression

Parsa A, Kao WH, Xie D, et al; AASK Study Investigators. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369:2183-96. [PMID: 24206458]

Background: Compared with white persons, black persons have a 2-fold higher rate of progression to ESRD. Several factors have been posited as the source of this racial disparity, including genetic differences. A region on chromosome 22 containing the genes encoding apolipoprotein L1 (APOL1) has been implicated in the increased risk for progression to ESRD among black patients with nondiabetic CKD. This work examined the relationship between APOL1 risk variants and long-term CKD progression in 2 prospective, multicenter studies.

Findings: In AASK (African American Study of Kidney Disease and Hypertension), the effects of APOL1 risk variants on CKD progression were examined among black patients with CKD due to hypertension. In the CRIC (Chronic Renal Insufficiency Cohort) study, the effects of APOL1 risk variants were tested in black and white participants with CKD. The primary composite end point in AASK was ESRD or a doubling of serum creatinine levels, which occurred in 58.1% of patients in the APOL1 high-risk group (hazard ratio, 1.88; $P < 0.001$) and 36.6% of those in the low-risk group. In the CRIC study, black patients in the APOL1 high-risk group had a faster decrease in estimated glomerular filtration rate and a higher risk for either ESRD or a 50% reduction in estimated glomerular filtration rate from baseline than white patients.

Cautions: The mechanism of how APOL1 influences kidney disease progression is unknown. Therefore, the observed relationship among APOL1 variants may be due to other tightly linked genes.

Implications: The influence of APOL1 risk variants on CKD outcomes among black and white persons may explain some of the disparities in CKD outcomes in the United States. In addition, this work provides the research community with an important new target for understanding factors determining CKD progression. The potential

influence of genotyping individual APOL1 risk variants on clinical management requires further investigation.

Long-Acting Octreotide Reduced Kidney and Cyst Growth in ADPKD

Caroli A, Perico N, Perna A, et al; ALADIN study group. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet. 2013;382: 1485-95. [PMID: 23972263]

Background: Autosomal dominant polycystic kidney disease is the most common monogenetic renal disorder. It progresses over the course of decades to ESRD and may affect patient quality of life by causing extraordinarily large kidneys and, in some cases, enlarged liver. No effective ADPKD therapy exists; however, the basic scientific findings showing pathways important to the progression of ADPKD cysts in animal models have led to many completed and ongoing clinical trials. The ALADIN (A Long Acting somatostatin on DIsease progression Nephropathy due to autosomal dominant polycystic kidney disease) study examined the effect of treatment with octreotide long-acting release (LAR) on renal function decline and kidney growth among patients with ADPKD.

Findings: This randomized, single-blind, placebo-controlled, parallel-group trial randomly assigned adult patients with ADPKD to 3 years of treatment with two 20-mg intramuscular injections of octreotide LAR or 0.9% sodium chloride solution every 28 days. The primary end point was change in total kidney volume, which was measured by non–contrast-enhanced magnetic resonance imaging, at 1 and 3 years of follow-up. A key secondary end point was the change in kidney function as measured by the change in iohexol plasma clearance. Total kidney volume increased significantly less in the octreotide LAR group than in the placebo group. A significant but small attenuation of the rate of decrease in kidney function occurred in the octreotide LAR group.

Cautions: This study was limited by small sample size and relatively short follow-up. It only included white patients, which may limit generalizability of the findings to other populations. Furthermore, the study did not assess patient-reported outcomes that may be particularly important in ADPKD given the effect of the cysts on such factors as pain, appearance, and appetite.

Implications: To our knowledge, this is the first trial to show reduction of total kidney volume and preservation of renal function with octreotide LAR. Although there is currently no effective therapy for ADPKD, this pilot study provides hope that our understanding of ADPKD pathophysiology will be translated to therapeutic interventions. However, many barriers to the application of new therapeutics for ADPKD remain. The disease typically runs its course over decades, and this study examined the effect of octreotide LAR over only 3 years. In addition, it remains unclear whether total kidney volume should be viewed as an adequate surrogate outcome or whether attenuation in the rate of kidney failure be the sole primary outcome. Furthermore, ADPKD affects patients' psychological and functional status. Thus, outcomes that are important to patients should be the key outcomes of future trials of agents that slow cyst growth.

Rituximab Versus Cyclophosphamide–Azathioprine for the Treatment of Severe ANCA-Associated Vasculitis

Specks U, Merkel PA, Seo P, et al; RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369:417-27. [PMID: 23902481]

Background: Most patients with ANCA-associated vasculitis have relapse. Although several studies have examined the use of rituximab in achieving complete remission of ANCA-associated vasculitis, the longer-term outcomes were unknown, particularly given that rituximab depletes B cells and the B-cell populations reconstitute over time. Therefore, this study examined the 18-month efficacy of rituximab compared with conventional immunosuppression in patients with severe ANCA-associated vasculitis.

Findings: This report presented results from the long-term follow-up of the RAVE trial. This double-blind, randomized trial compared rituximab (375 mg/m^2 once a week for 4 weeks) followed by placebo with cyclophosphamide administered for 3 to 6 months followed by azathioprine for the balance of 18 months. Both groups were treated with an identical glucocorticoid tapering regimen. As reported previously, 64% of patients in the rituximab group and 53% in the cyclophosphamide–azathioprine group had complete remission by 6 months. At 12 months, 48% of patients in the rituximab group and 39% of those in the cyclophosphamide group had maintained complete remission; at 18 months, the rates were 39% and 33%, respectively. No significant between-group difference was found in any efficacy measure, including the duration of complete remission, frequency or severity of relapses, kidney function as estimated with creatinine clearance, and health-related quality of life.

Cautions: This was a small trial to examine noninferiority, with only 146 participants at risk for relapse after complete remission. Patients with more acute illness were excluded, such as those with acute kidney injury and those requiring ventilatory support. Estimates of kidney function obtained by using the Cockcroft–Gault equation are imprecise, which weakens any inferences of the effects of rituximab on long-term kidney function compared with cyclophosphamide.

Implications: In this follow-up of the landmark RAVE trial, the long-term findings showed that rituximab was noninferior to the standard cyclophosphamide-based approach to treating severe ANCA-associated vasculitis. These findings provide patients and providers with more

information on the 18-month outcomes of a novel approach to the management of ANCA-associated vasculitis.

Hemodialysis

Perceptions of Prognosis Among Patients Receiving Hemodialysis

Wachterman MW, Marcantonio ER, Davis RB, et al. Relationship between the prognostic expectations of seriously ill patients undergoing hemodialysis and their nephrologists. JAMA Intern Med. 2013; 173:1206-14. [PMID: 23712681]

Background: Patients with ESRD have a mortality rate of nearly 20% despite marked improvements in dialysis technology. This mortality rate reflects, in part, a selection of older persons with multiple chronic health conditions for dialysis therapy. Although patients with cancer have been shown to overestimate their likelihood of survival, little is known about whether patients with ESRD accurately perceive their prognosis. Patients' understanding of their prognosis is important because their perceptions may shape care goals, such as seeking evaluation for kidney transplantation or the use of hospice services.

Findings: The objectives of this cohort study were to compare perceptions of prognosis and the likelihood of transplantation among patients receiving hemodialysis and their nephrologists, to follow actual survival, and to explore the relationship between patients' expectations and their care goals. Patients were significantly more optimistic than their nephrologists about 1- and 5-year survival ($P < 0.001$ for both) and were more likely to believe that they were transplant candidates (66% vs. 39%; $P = 0.008$). Of the 81% of patients reporting a 90% or greater chance of being alive at 1 year, 44% preferred care focused on extending life, even if it meant more discomfort, compared with 9% of patients reporting a lower chance of survival ($P = 0.05$).

Cautions: This study was limited by its small sample size and highly selected patient population. The patients' responses to a hypothetical scenario may not reflect the choices they would make in real life.

Implications: To our knowledge, this was the first study to show discordance between perceptions of patients receiving hemodialysis and observed outcomes. The study further demonstrated that these perceptions were associated with aggressiveness of care in hypothetical situations. Given these findings, nephrologists and primary care physicians should discuss prognosis with their patients who have ESRD. Research into whether findings from this work extend to other noncancer chronic conditions with high mortality rates would be of interest.

Kidney Transplantation

ACE Inhibitors Were Effective in Improving Outcomes of Renal Transplant Recipients With Posttransplantation Subclinical Cardiomyopathy

Paoletti E, Bellino D, Marsano L, et al. Effects of ACE inhibitors on long-term outcome of renal transplant recipients: a randomized controlled trial. Transplantation. 2013;95:889-95. [PMID: 23380881]

Background: Patients who have had kidney transplantation often have substantial gains in survival and quality of life compared with patients who continue dialysis, yet transplant recipients remain at high risk for cardiovascular disease. Whether the benefits of RAAS blockade that have been shown for heart disease and most types of CKD extend to kidney transplant patients has been unclear. The long-term safety of RAAS blockade in patients with a kidney transplant is also uncertain.

Findings: This randomized trial tested the effects of ACE inhibitors on left ventricular hypertrophy and the incidence of cardiovascular events on kidney transplant recipients. It also reported renal graft outcomes over the 3-year study period. Thirty-six patients were allocated to receive lisinopril, and 34 served as control patients. During a 10-year follow-up, the lisinopril group had significantly better survival free of the combined end point (death, major cardiovascular events, renal graft loss, or creatinine doubling) ($P = 0.01$) and of major cardiovascular events ($P = 0.003$) without significant differences in renal outcome compared with the control group.

Cautions: This study was limited by its small sample size and highly selected patient population. It excluded patients with diabetes and living-donor kidney transplant recipients.

Implications: This small randomized trial showed a long-term benefit of lisinopril among kidney transplant patients. Although the study was not powered to evaluate renal graft function, there was no evidence that lisinopril was detrimental for long-term renal graft function.

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