Advancing understanding of treatment through clinical trials

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Three late-breaking studies presented during the American Society of Nephrology's Annual Kidney Week provide new information on drugs being tested in patients with diabetes or kidney disease.

Hans-Henrik Parving, MD (University of Copenhagen, in Denmark) and his colleagues investigated whether the drug aliskiren might improve the prognosis of patients with type 2 diabetes who are at high risk for developing heart and kidney problems. The randomized double-blind ALTITUDE trial included 8561 individuals who received aliskiren (300 mg once daily) or placebo on top of a drug that blocks the renin-angiotensin-aldosterone system (RAAS), a complex hormone system that regulates blood pressure and fluid balance. (Drugs that target the RAAS have limited effectiveness in part due to feedback responses, such as compensatory increases in an enzyme called renin. Aliskiren is a direct renin inhibitor and may help overcome these shortcomings because it suppresses the reactive rise in renin activity stimulated by other RAAS blockers.) After an average follow-up of 32.9 months:

- 17.9% of patients receiving aliskiren and 16.8% of those receiving placebo experienced a heart attack or stroke, developed kidney disease, or died of cardiovascular disease.
- Stroke occurred in 3.4% of patients taking aliskiren, compared with 2.7% of patients taking placebo.
- Patients taking aliskiren experienced significantly increased blood potassium levels and hypotension.

"The trial does not support administration of aliskiren on top of standard therapy with RAAS blockade in type 2 diabetic patients at high risk for cardiovascular and renal events, and may even be harmful," the authors concluded.

Another team led by Vicente Torres, MD, PhD (Mayo Clinic) tested the potential of a vasopressin V2 receptor antagonist (tolvaptan) to inhibit cyst growth and slow kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD). This condition causes kidney cysts often associated with pain, hypertension, and kidney failure. The phase 3, multi-center, double-blind, placebo-controlled, 3-year trial included 1445 ADPKD patients who were randomized 2:1 to split dose tolvaptan (45/15, 60/30 or 90/30 mg daily as tolerated) or placebo.

- Total kidney volume increase over 3 years was halved in patients treated with tolvaptan compared to placebo (2.80%/year versus 5.51%/year).
- Patients taking tolvaptan were 61% less likely to experience a certain level of worsening kidney function and 36% less likely to experience kidney pain requiring treatment.
- Tolvaptan slowed the rate of kidney function decline compared with placebo.

"Tolvaptan demonstrated clinically meaningful disease-specific benefits for ADPKD patients which may be clinically meaningful," said Dr. Torres. While the trial findings are encouraging, tolvaptan has not yet been approved for this indication.

A third trial, called EVOLVE, was designed to test the hypothesis that treatment with cinacalcet compared with placebo reduces the risk of premature death or non-fatal heart-related events among dialysis patients with secondary hyperparathyroidism. (Secondary hyperparathyroidism,

when the parathyroid gland produces excess amounts of parathyroid hormone, arises in most patients with chronic kidney disease as their disease progresses. It can lead to a number of complications, including cardiovascular problems.) Results from analyses using multivariable adjustment and censoring data 6 months after patients stopped taking the drug will be presented, along with safety data, by Glenn Chertow, MD (Stanford University School of Medicine).

More information: Study co-authors for "The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)" (abstract 6313) include Barry M. Brenner, MD, John Mcmurray, Dick de Zeeuw, MD, PhD, Steven Mark Haffner, MD, Scott D. Solomon, MD, Nish Chaturvedi, Frederik I. Persson, MD, Akshay Suvas Desai, Maria Nicolaides, and Marc A. Pfeffer, MD, PhD.

Study co-authors for "Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease: The TEMPO 3:4 Trial" (abstract 6357) include Arlene B. Chapman, MD, Olivier Devuyst, MD, PhD, Ron T. Gansevoort, MD, PhD, Jared J. Grantham, MD, Eiji Higashihara, MD, Ronald D. Perrone, MD, Holly B. Krasa, John Ouyang, PhD, Osamu Sato, and Frank S. Czerwiec, MD, PhD.

Study co-authors for "Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) trial" (abstract 6450) include Geoffrey A. Block, MD, Ricardo Correa-Rotter, MD, Tilman B. Drueke, MD, Jurgen Floege, MD, William G. Goodman, MD, Christian Mix, MD, Marie-Louise Trotman, Yumi Kubo, Charles A. Herzog, MD, Gerard M. London, MD, Kenneth Mahaffey, MD, Sharon M. Moe, MD, David C. Wheeler, MD, and Patrick S. Parfrey, MD.

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