The VA NEPHRON-D study in diabetic nephropathy: The experiment was a success, but the patient got sicker

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Study acronyms

ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints

IDNT = Irbesartan Diabetic Nephropathy Trial

ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

VA NEPHRON-D = Veterans Affairs Nephropathy in Diabetes

The renin angiotensin aldosterone system (RAAS) plays a pivotal role in the initiation and progression of renal disease in diabetes. In animals, its activation leads to an increase in glomerular capillary pressure, which eventually leads to glomerulosclerosis. Blockade of the RAAS in these models can prevent and slow progression of experimental nephropathy (Zatz et al, 1986).

Before the VA NEPHRON-D study

The first class of agent to block the RAAS was the angiotensin-converting enzyme inhibitors, and, in early studies, they reduced albuminuria and slowed progression of nephropathy (Lewis et al, 1993). Since then, the development of angiotensin receptor blockers (ARBs) and direct renin inhibitors (e.g. aliskiren), together with aldosterone receptor blockers, means that the RAAS can be inhibited at multiple levels. These agents also reduce albuminuria, and ARBs slow progression to end-stage renal disease (ESRD) in type 2 nephropathy (Brenner et al, 2001; Lewis et al, 2001).

Post hoc analysis of these studies suggested that the greater the reduction of albuminuria, the slower the progression (Evans et al, 2012), so investigators explored methods of maximising the albuminuria response. One idea was to block the RAAS at multiple levels, and short-term studies suggested that this reduced albuminuria further. Several large trials of combination therapies were then undertaken (ONTARGET [Mann et al, 2008], ALTITUDE [Parving et al, 2012]) and, most recently, the VA NEPHRON-D study, where lisinopril was added to losartan (Fried et al, 2013).

The VA NEPHRON-D study

The VA NEPHRON-D study investigated just under 1500 people with type 2 diabetes with a baseline urinary albumin-to-creatinine ratio of >300 mg/g and an estimated glomerular filtrate rate (GFR) of 30–89.9 mL/min/1.73 m^2. After a 4-week run-in on losartan 100 mg/day, participants were randomised to be additionally administered with lisinopril or placebo. The study was terminated early because of an excess in acute kidney injury (AKI) and hyperkalaemia. The VA NEPHRON-D study, therefore, joins ONTARGET and ALTITUDE, in that they showed no clinical benefit and had an excess of adverse events, despite all achieving a significant reduction in albuminuria. Why should this be?

Progression of diabetic renal disease is much slower nowadays. In the original captopril trial, the rate of loss of creatinine clearance (a proxy for GFR) was >11 mL/min/1.73 m^2/year (Lewis et al, 1993). By the time of IDNT (Lewis et al, 2001; Evans et al, 2012) and the RENAAL trial (Brenner et al, 2012) 10 years later, this was down to <3 mL/min/1.73 m^2/year. Thus, the VA NEPHRON-D trial would have had to wait 10 years for its primary end-point, and was terminated after a median duration of 2.2 years.

The RAAS preserves renal blood flow and protects the kidney at times of physiological stress. Complete blockade renders the kidney vulnerable, so it is not surprising that more episodes of AKI occurred in those on combination therapy (there were a large number of cardiovascular events in study participants, more than 18% of whom had heart failure, an acute myocardial infarction or stroke during the trial).

Practical implications

What does this mean for clinical practice? The VA NEPHRON-D study shows why suitably powered trials with hard clinical end-points are necessary to confirm findings from short-term studies. We still need therapies to slow and prevent the development of diabetic ESRD since diabetes as a comorbidity was reported in 35% of those on renal replacement therapy in the UK in 2011–12 (Renal Association, 2013). However, multiple-level RAAS blockade is neither effective nor safe, and currently has no place in the management of individuals with diabetic nephropathy. ■