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COMMENTARY

WILEY

Treatment of hypertension in CKD patients with azilsartan/chlorthalidone vs olmesartan/hydrochlorothiazide

Walter M van der Merwe MBChB, FRACP

Hypertension Clinic, Auckland, New Zealand

Correspondence
Walter M van der Merwe, MBChB, FRACP, Hypertension Clinic, Auckland, New Zealand.
Email: waltervandermerwe7@gmail.com

In this issue of the journal, Bakris et al[1] published an open-label, long-term study evaluating the safety and tolerability of azilsartan medoxomil/chlorthalidone (AZL-M/CLD) verses olmesartan/hydrochlorothiazide (OLM/HCTZ) in hypertensive individuals with stage 3 chronic kidney disease (CKD). It was a multicenter study conducted in the USA and Europe. Hypertensive patients with stage 3a and 3b CKD (eGFR 30-60 mL/min/1.73 m^2) were randomised to receive AZL-M/CLD or OLM/HCTZ. Target was office blood pressure <130/80 and AZL-M/CLD was initiated at 20/12.5 mg and titrated to 40/25 mg. OLM/HCTZ was initiated at 20/12.5 mg and titrated to 40/25 mg (USA) and 20/25 mg (Europe). Additional agents were added if required to achieve target blood pressure. The study ran for 52 weeks and the primary endpoint was proportion of participants with ≥1 adverse event (AE) through week 52.

Seventy-seven participants were randomised to the AZL-M/CLD arm and 76 to the OLM/HCTZ arm. Average age in both arms was 68 years and eGFR 48 mL/min/1.73 m^2. 42% of individuals in both arms were diabetic. Mean untreated blood pressure in both arms was similar ~150/85 as was mean blood pressure in both arms at the end of the 52-week study ~124/74. However, significantly more participants in the OLM/HCTZ group required uptitration to the maximum dose, as well as addition of supplementary agents in order to achieve target blood pressure. AE were mostly minor (dizziness, headache, etc.) and not significantly different in both groups. Incidence of significant (> 50%) creatinine elevation was similar in both groups (12% AZL-M/CLD and 13.5% OLM/HCTZ). Most settled without requiring treatment discontinuation and was not associated with serious hyperkalemia. Serious (principally cardiovascular) adverse events were similar in both groups and are unlikely to have been treatment-related. There was only 1 death, which was judged unrelated to the study protocol. Detailed proteinuria data are not provided, although it is stated that significant creatnine elevation was associated with more rapid blood pressure drop and a reduction in proteinuria.

This is a relatively small 52 week efficacy-and-safety, rather than outcome, study of hypertension treatment in patients with CKD, which demonstrates similar antihypertensive efficacy and safety, with regimes based on either AZL-M/CLD or OLM/HCTZ. However, significantly more patients in the OLM/HCTZ group required titration to the maximum dose and addition of supplementary antihypertensives to acheive target blood pressure. Also, although mean blood pressure in both groups was similar at 52 weeks, target blood pressure was achieved significantly sooner in the AZL-M/CLD group. The authors argue that, for the practicing physician, AZL-M/CLD may be preferable to OLM/HCTZ in this situation for 3 principal reasons: (1) earlier achievement of target blood pressure, (2) requirement for fewer total medications in a group generally already on significant number of drugs (aiding compliance), and (3) the superior record of CLTD verses HCTZ in large hypertension outcome trials, including those involving CKD patients.

All of these points are highly relevant. Early achievement of target blood pressure was shown in the VALUE[2] and ASCOT[3] trials to predict long-term outcome, and although blood pressure at 52 weeks was similar in both groups, in the community setting, several additional physician titration visits would be required to achieve the same result with an OLM/HCTZ-based regimen. There are likely to be financial and other barriers to this in the non-clinical trial context. Similarly, in the real world, the requirement for additional medications and a more complex regimen may tend to mitigate against optimal blood pressure control in these patients.

It should also be noted that although similar office blood pressure measurements (used in this trial) were similar in both groups at 52 weeks, we have evidence that overnight blood pressure may be lower in CLD than HCTZ-treated patients, even when daytime office blood pressures are similar.[4] This, in turn, may have substantial implications for long-term cardiovascular outcome, particularly in individuals with CKD who often have blunted of absent overnight dipping of blood pressure.[5]

Part of the apparent lesser antihypertensive efficacy of HCTZ, in this study in particular, may be related to the participants' reduced eGFR (mean 48 mL/min/1.73 m^2). Diuretic effect with HCTZ is progressively reduced below GFR 50 mL/min,[6] whereas

CLTD has efficacy at GFR down to and below 30 mL/min/1.73 mL/min/1.73 m^2.[7] In other words, the increased requirement for additional antihypertensive drugs in the OLM/HCTZ group may suggest that some individuals in that group may be deriving little or no antihypertensive benefit from the HCTZ component of their combination pill.

Based greater efficacy and superior cardiovascular outcomes, over the past decade there has been a modest trend towards regarding CLD as the thiazide antihypertensive of choice, rather than HCTZ.[8-11] There seems even less reason in the CKD hypertension population than in the general hypertensive population not to use CLD as the thiazide of choice. Given that the vast majority of CKD patients with hypertension will require combination therapy to achieve target blood pressure, and that guidelines mandate a renin-angiotensin system (RAS) blocker-based regimen (for most), an angiotensin receptor blocker (ARB)-chlorthalidone combination pill is a logical basis for therapy. The study of Bakris et al confirms that the AZL-M/CLD combination pill is a safe and effective option in individuals with CKD 3 and hypertension.

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