HOT OFF THE PRESS: CLINICAL

Chlorothalidon or hydrochlorothizide for treatment of hypertension?

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The thiazides and the closely related phtalimidine derivates introduced more than 50 years ago have remained a mainstay of antihypertensive therapy. Hydrochlorothiazide is the most commonly prescribed member of this class of thiazide and thiazide like diuretics in many parts of the world including Europe, where chlorthalidone have been little used during the last decades due to more frequent metabolic side effects (including electrolytes, lipids, glucose).

In contrast, chlorthalidone has been claimed to have a longer half-life, greater blood pressure lowering effect and better proven effect on outcome in clinical trials, and remains the favoured diuretic of this class to treat hypertension according to US guideline recommendations. However, there are no direct comparisons between hydrochlorothiazide and chlorthalidone on morbidity and mortality in the treatment of hypertension.

Recently, Hripcsak and collaborators set out to compare the effectiveness and safety of hydrochlorothiazide and chlorthalidone as newly initiated first line therapy for hypertension[1]. The authors used a retrospective observational comparative cohort design to performe an analysis across three large disparate US databases that each had at least 2500 patients with exposures to each drug and information on outcome. Primary outcomes were acute myocardial infarction, stroke, heart failure hospitalization, and a composite of the three events and sudden cardiac death. Also 51 safety outcomes were collected.

A large number of baseline covariates were used for balancing the two cohorts by propensity scores. The study included 730 225 individuals (62% women, mean age 52 years); 69 337 received hydrochlorothiazide and had 3089 composite outcome events, and 36 918 received chlorthalidone and had 149 composite events from 2001 through 2018.

The results show no significant difference in risk for acute myocardial infarction, stroke, heart failure hospitalization or the composite outcome (hazard ratios with 95% confidence limits; lower hazard ratios favour chlorthalidone): 0.92 (0.64; 1.31), 1.10 (0.86; 1.41), 1.05 (0.82; 1.34), and 1.00 (0.85; 1.17), respectively. Chlorthalidone was associated with an increased risk for hypokalaemia, hyponatremia, acute renal failure, chronic kidney disease, and type 2 diabetes; and a lower risk for abnormal weight gain.

This study shows no difference in cardiovascular outcome between hydrochlorothiazide and chlorthalidone as first line newly initiated antihypertensive therapy. However, chlorthalidone was associated with more frequent electrolyte and glucose metabolic abnormalities, and deterioration renal function. The results are in agreement with some indirect meta-analyses, whereas other indirect meta-analyses and observational studies suggest a reduced risk for cardiovascular event with chlorthalidone. Differences in study design, patient populations, and doses studied may contribute to these differences.

Taken together, current results do not support the use of chlorthalidone over hydrochlorothiazide. Of note, a randomized controlled study of hydrochlorothiazide versus chlorthalidone (ClinicalTrials.gov Identifier: NCT02185417) is currently in progress[2] and may clarify matters.

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HOT OFF THE PRESS: CLINICAL

Renal denervation lowers blood pressure – now what?

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The controversies around renal denervation over the last decade have undoubtedly shaped the hypertension world and have brought to light some hidden truths, stimulated extensive research efforts into the phenotype of "resistant hypertension", and helped to advance our approaches to diagnose and manage this complex aspect of hypertension medicine. Therapeutic drug monitoring revealed that a large proportion of patients requiring poly-pharmacy are indeed non-adherent with prescribed medication. The importance of 24-hour ambulatory blood pressure (BP) monitoring as a primary endpoint measure, adequate study designs including sham-procedures, optimization of procedural aspects, and the relevance of patient selection became apparent. While Symplicity HTN-1 and HTN-2 demonstrated a substantial reduction in BP, Symplicity HTN-3, the largest and first study to include a sham control failed to demonstrate a BP lowering effect beyond that observed in the sham control group and thereby questioned the utility of catheter-based renal denervation[1].

Since then, three sham-controlled studies using either radiofrequency ablation technology[2,3] or high frequency ultrasound[4] in both drug-naïve[2] or treated hypertensive patients[3,4] demonstrated clinically relevant reductions in ambulatory BP compared to respective sham control groups.

Most recently, results from the SPYRAL HTN-OFF MED Pivotal trial, an international, prospective, randomised controlled trial on the effects of renal denervation in unmedicated patients were reported[5]. In a cohort of 331 patients with hypertension assigned to either radiofrequency ablation (n=166)