Hot Off the Press

Thomas Kahan

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden; and Department of Cardiology, Danderyd University Hospital Corporation, Stockholm, Sweden

Antihypertensive treatment with thiazide type diuretics may prevent osteoporotic fractures

Hypertension and osteoporotic fractures are common in older persons and share several risk factors such as smoking, physical inactivity, postmenopausal status and older age. Indeed, there is an increased risk of osteoporotic fractures in hypertensive patients, as compared to persons with normal blood pressure. The effects of thiazide type diuretics on calcium balance have been taken to suggest that diuretic treatment may reduce the risk of osteoporotic fractures.

In a recent post hoc analysis of the ALLHAT study [1], Putnam et al show that chlorthalidone, a thiazide type diuretic, reduces the risk of osteoporotic fractures [2]. Patients eligible for participation in ALLHAT were women and men 55 years or older with mild-to-moderate hypertension (a systolic blood pressure of 140 mm Hg or above and/or a diastolic blood pressure of 90 mm Hg or above, or on drug treatment for hypertension) and with at least one additional risk factor for coronary artery disease. Mean age was 70 years, 43% were female, 50% were white non-Hispanic and 31% African American. The participants were randomized double blind to chlorthalidone, the dihydropyridine calcium channel blocker amlopidine, the angiotensin converting enzyme inhibitor lisinopril, or the alpha adrenergic receptor blocker doxazosin (this arm was stopped early and was not considered for the current analysis). The beta adrenergic receptor blocker atenolol was added if needed to achieve a blood pressure below 140/90 mm Hg, with additional medications to be added if required. For the purpose of the current study 10,174 patients on chlorthalidone and 12,006 on amlopidine or lisinopril were evaluated after a mean follow up time of 4.9 years. Hospitalized hip and pelvic fractures were chosen as outcome. An additional post trial follow up was performed on 7,631 and 8,991 patients, respectively, and a total mean follow up of 7.8 years. There were 34 pelvic fractures and 307 hip fractures during the trial, and the authors show a 21% (95% confidence interval 2–37%; P = 0.04) in trial risk reduction of fractures on diuretic therapy, as compared to other antihypertensive therapy, after adjustment for demographic and clinical potentially confounding factors [3]. The effects on fracture risk by amlopidine and lisinopril were similar, and atenolol did not seem to influence the risk of incident fractures. A similar, although not significant, benefit of diuretic treatment was seen with the prolonged post trial follow up.

That antihypertensive treatment with a diuretic can reduce the risk for osteoporotic fractures is supported by a recent large retrospective cohort study of hypertensive patients attending primary health care in Sweden by Bokrantz et al [3]. These authors used the Swedish Primary Care Cardiovascular database [4] to assess 57,822 hypertensive patients 45 years or older attending primary health care in 2006. Data on antihypertensive (and other potentially confounding) drug treatment was achieved from all pharmaceutical dispensations, obtained by data linkage to the Swedish Prescribes Drug Registry. Thiazide diuretics were taken by 54%. Other thiazide like diuretics (chlorthalidone, metazolone and amiloride) were used in 2% only. Mean age was 66 years, 55% were female, and 95% were of European ethnicity. The primary outcome was an osteoporotic fracture, which included hip, spine, distal forearm, and proximal humerus.

There were 2,345 incident osteoporotic fractures (1,210 hip fractures) during a follow up of 7 years. Patients with fractures were older, more often female and had lower socioeconomic status, had slightly higher blood pressure values, more comorbidity, and were on more medications. Current thiazide use was associated with an 11% (95% confidence interval 2–19%; P < 0.05) lower fracture risk, as compared to other antihypertensive therapy, after adjustment for demographic and clinical potentially
confounding factors [3]. Of note, the protective effect of diuretics appeared to increase with prolonged duration of use, and former use was associated with an increased risk up to 4 months after the last dispensed prescription. These two studies in consort suggest that treatment with a thiazide type diuretic reduces the risk for osteoporotic fractures in hypertensive patients. This makes the results clinically relevant and potentially important. The post hoc analysis of ALLHAT [2] is the first large randomised controlled study in hypertension to demonstrate a benefit of diuretic treatment on incident fractures. However, that study excluded several patients with high risk for osteoporotic fractures such as coronary artery disease, chronic heart failure, and chronic kidney disease. Second, ALLHAT studied chlorthalidone, a preferred thiazide type diuretic in the United States, whereas hydrochlorothiazide or other diuretics are preferred in many countries. Third, at least one out of five patients assigned to chlorthalidone, amlodipine, or lisinopril did not did not take their assigned drug class medication, and a similar proportion in the amlodipine and lisinopril group patients took a diuretic at their five year follow up. Thus, the magnitude of the potential benefit of diuretic treatment on fracture risk may be difficult to assess from these results. The large Swedish registry study [3] represents an unselected hypertensive population with more comorbidity than ALLHAT. Data were obtained from electronic health records and registries with minimal risk of selection bias; however, there was no formal protocol for data collection and follow up. Drug adherence was accounted for by use of data on dispensed drugs but, inherent to a retrospective cohort study there was no randomisation to treatment. Taken together, the results of these two studies extend previous findings of an association between antihypertensive treatment with thiazide type diuretics and an approximately 10-25% reduction in osteoporotic fractures [5, 6]. Furthermore, the association between duration and timing of thiazide exposure and fracture incidence [3] may be taken to suggest a causal relation.

REFERENCES:

- Thomas Kahan

**Hot Off the Press**

**Noriko Daneshtalab**
Professor (Assistant) and Researcher, School of Pharmacy and Cross-Appointment to the Division of BioMedical Sciences, Cardiovascular and Renal Group, Faculty of Medicine, Memorial University of Newfoundland, Newfoundland and Labrador, Canada

**Immune system regulation of hypertension evident in the homeostatic role of cyclooxygenase-2-derived PGE2 in response to increased dietary salt**

Hypertension on its own is a complex trait traditionally determined by both genetic and environmental factors with a high prevalence (~30% worldwide) and a major risk factor for other cardiovascular diseases. Interestingly, it is also a disease which patients with autoimmune diseases such as psoriasis and arthritis are more prone to having at a higher prevalence than the normal population (1). These patients also have a significantly