

Hydrochlorothiazide in hypertension

An acceptable first choice

● **A pharmacoepidemiological study of about 700 000 hypertensive patients exposed to either chlorthalidone or hydrochlorothiazide did not show any significant difference in the incidence of cardiovascular events and mortality between these two groups of patients. Electrolyte abnormalities and renal disorders were less frequent with hydrochlorothiazide.**

In adults with hypertension and no other cardiovascular risk factor, taking a blood pressure-lowering drug has a favourable harm-benefit balance once blood pressure reaches or exceeds 160/100 mm Hg. In countries where it is available, chlorthalidone is the first-choice thiazide diuretic. Its efficacy in preventing cardiovascular events has been reliably demonstrated (1). In France, where there is no available medicinal product containing chlorthalidone alone, the first-line thiazide diuretic is hydrochlorothiazide. Hydrochlorothiazide has been less well evaluated than chlorthalidone, although given the lack of any randomised trial directly comparing these two drugs in hypertension, there is no evidence that it has lower efficacy (1,2).

A retrospective pharmacoepidemiological study compared the incidence of cardiovascular events and adverse effects in hypertensive patients regularly exposed to chlorthalidone or hydrochlorothiazide (2).

The authors of this study analysed three US databases containing information on a total of about 730 000 hypertensive patients, aged 51 years on average. In these patients, blood pressure-lowering treatment was started with one of the two drugs between 2001 and 2018. About 37 000 patients were exposed to chlorthalidone and about 690 000 to hydrochlorothiazide. The regularity of exposure to these drugs was assessed on the basis of dispensed prescriptions. The primary outcomes, which were pre-specified, were hospitalisation for myocardial infarction, heart failure or stroke, and a composite outcome including these 3 outcomes and sudden cardiac death. The authors also looked for the occurrence of about fifty pre-specified potential adverse effects. In order to limit inherent bias from confounding factors due to the lack of randomisation (such as the presence of conditions in addition to hypertension, or treatment with drugs other than one of the two blood pressure-lowering drugs), analysis of the data was carried out after stratification according to so-called propensity scores (a)(2).

Based on this analysis, neither mortality nor the occurrence of cardiovascular events was statistically different between the group of patients regular-

ly exposed to chlorthalidone and those regularly exposed to hydrochlorothiazide (2).

The risk of hypokalaemia was 3-fold higher in patients exposed to chlorthalidone (a statistically significant difference), and the risks of hyperkalaemia, hyponatraemia, renal failure and type 2 diabetes were around 25% to 35% higher in patients exposed to chlorthalidone, compared to patients exposed to hydrochlorothiazide (statistically significant differences) (2).

In practice Despite the limitations of this retrospective study carried out using databases, there appears to be no clear difference in the incidence of cardiovascular events between hypertensive patients taking chlorthalidone and those taking hydrochlorothiazide. In the absence of a direct comparison with a higher level of evidence, these data support the pragmatic choice of hydrochlorothiazide as the first-line thiazide diuretic for most hypertensive patients in countries where chlorthalidone is not available, especially since this drug appears to cause fewer electrolyte abnormalities and renal adverse effects than chlorthalidone.

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a- The determination of a propensity score is based on a statistical method employed in observational studies, which aims to correct for intergroup differences, in the absence of randomisation, so as to limit bias due to confounding factors (ref 3).

Selected references from Prescrire's literature search

- 1- Prescrire Editorial Staff "Treating essential hypertension. The first choice is usually a thiazide diuretic" *Prescrire Int* 2014; **23** (152): 215-220.
- 2- Hripcsak G et al. "Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension" *JAMA Intern Med* 2020; **180** (4): 542-551.
- 3- Moulis G et Lapeyre-Mestre M "Score de propension: intérêts, utilisation et limites. Un guide pratique pour le clinicien" *Rev Med Interne* 2018; **39** (10): 805-812.