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 regularly 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.