Chlorthalidone vs Hydrochlorothiazide for Hypertension–CV Events: Did the Design Influence the Outcome?

Anil Pareek1*, Franz H Messerli2, C Venkata S Ram3

Received: 12 May 2023; Accepted: 22 June 2023

ABSTRACT

The Diuretic Comparison Project (DCP) was a real world study planned to evaluate in a pragmatic manner whether Chlorthalidone (CTD), as compared with Hydrochlorothiazide (HCTZ), would reduce the risk of major nonfatal cardiovascular disease outcomes in elderly hypertensive patients ≥65 years of age (older patients) who were receiving HCTZ (25 or 50 mg) at baseline. This study being a real world study lacks the robustness of a randomized controlled trial. The principle limitation being unequal exposure of the two diuretics, prolonged unknown duration of exposure to HCTZ vs a short exposure to CTD (Median 2.4 years). In the high risk population with history of MI/Stroke, CTD conferred a lower risk of primary outcome as compared to low risk population where no significant difference in outcome was seen in both diuretics. Other factors included, lack of established dose equivalency of the two diuretics and absence of use of 12.5 mg HCTZ in older hypertensives.

BACKGROUND

The DCP1 was a pragmatic real-world study done to compare CTD and HCTZ. The primary aim was to evaluate which of the two diuretics reduces the risk of major adverse CV events (MACE) in hypertensive patients above 65 years of age (older patients) who were taking HCTZ (25 or 50 mg) at baseline. The patients were randomly assigned to continue HCTZ or were switched to CTD at a dose of 12.5 or 25 mg.1 We think that this study has a few limitations in its design and dose used in the study population.

DOSE CONSIDERATIONS

Equivalent daily doses in this study were 25 mg hydrochlorothiazide (HCTZ) and 12.5 mg chlorthalidone (CTD). However, the usual dose at which HCTZ should be started is 12.5 mg in older patients and 25 mg in younger patients. The usual dose at which CTD should be started is 6.25 mg in older patients and 12.5 mg in younger patients.2 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (BP) VI and the Canadian hypertension guidelines (1995) suggest that HCTZ be initiated at 12.5 mg daily. A 2018 meta-analysis found that the equivalent doses of HCTZ and CTD have a ratio of 3:1.3 An ambulatory BP monitoring study noted that 6.25 mg CTD produced a significant decrease in 24-hour and night-time BP than did 12.5 mg HCTZ.4 More hypokalemia in the CTD arm also indicates that CTD potency was more than two times higher than HCTZ.

DESIGN LIMITATIONS

This trial, in a pragmatic manner, aimed to answer a pertinent question. This trial had many flaws in the design, which included its open-label nature, which cannot match the accuracy of randomized controlled trials. In this study, 95% of all patients were taking HCTZ 25 mg before being randomized either to continued HCTZ or to CTD. Patients with a history of myocardial infarction (MI) and/or stroke comprised 10.8% of participants in the CTD group and 10.7% of participants in the HCTZ group. In this high-risk population, CTD conferred a lower risk of primary outcome than HCTZ [hazard ratio (HR) 0.73; 95% confidence interval (CI), 0.57–0.94; p = 0.013].5 In turn, no major difference in HR for the primary outcome was found between CTD and HCTZ participants who had no history of MI and stroke [HR 1.12; 95% CI, 1.00–1.26; p = 0.054].5 As all the patients were taking HCTZ for an unknown period before randomization, shifting to CTD for a mere median duration of 2.4 years was not sufficient to make a difference in the low-risk population. However, in the high-risk population, such short exposure to CTD did achieve clinically meaningful differences between the two drugs. This seems to indicate that the unequal exposure to the two thiazides before randomization was a critical issue.

CONCLUSION

In the study of Ishani et al.,1 the following appear to be the study limitations:

• There was unequal exposure to the two thiazides.
• Lack of established dose equivalency in the two thiazides.
• Absence of commonly used dose of 12.5 mg HCTZ in older hypertensives.
• Open-label nature of the study.

Thus, the authors’ conclusion that “participants who received CTD did not have a lower occurrence of major adverse cardiovascular (CV) events (MACE) than patients who received HCTZ” is questionable. This illustrates the design limitations of conclusions drawn on pragmatic studies in comparison to randomized controlled trial (RCTs). Hence RCTs remain the gold standard for comparison of time-tested drugs.

REFERENCES


© The Author(s). 2023 Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.