Indian Heart Journal 69 (2017) 417

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Research Letter

Pathophysiological mechanisms should be taken into account and guide the treatment of essential arterial hypertension

In the review on diuretics use in primary hypertension published in the Indian Heart Journal, Professor Mishra, concluded that low-dose thiazide diuretics are safe but lack of the mortality benefit data shown by high-dose, while indapamide (INDAP) and low-dose chlorthalidone (CTDN) have fewer side-effects but continue to provide mortality benefit.[1]

The anti-hypertensive effect of diuretics is mainly based on blood volume reduction determined by enhanced renal sodium and water excretion. However, as a consequence of these effects, diuretics cause a reactive increase in sympathetic and RAAS activity, resulting in opposed vasoconstriction and reduced sodium loss and enhancing metabolic side effects.[2]

Thiazide diuretics have been the mainstay of antihypertensive treatment for almost 40 years and have also been confirmed as a first line choice in the last European Society of Cardiology (ESC) hypertension guidelines[3] and JNC 8.[4] However, even if the evidence about clinical outcomes benefits seems stronger for thiazide-like diuretics, the latest ESC guidelines underline that a real recommendation cannot be given in favor of a specific drug from the available data, especially when considering the lack of randomized head-to-head comparisons.[3]

In the present review it is underlined how CTDN was found superior in preventing cardiovascular complications in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[5] The real value of the ALLHAT study has been widely debated, receiving several criticisms.[6] Among the others, it should be noted that diuretic therapy was withdrawn in several patients at the time of enrollment and many of them had a history of previous myocardial infarction or hypertensive cardiomyopathy: withdrawal of diuretics in such patients could have increased the risk of developing heart failure.

Moreover, hydrochlorothiazide (HCTZ) has often been compared with CTDN, but relatively little is known about HCTZ versus INDAP. It must be underlined that there are only a few trials directly comparing HCTZ with INDAP and all the available trials lack of cardiovascular events as outcomes.[7] However, a systematic analysis of the recent literature did not show a superiority of INDAP over HCTZ in terms of metabolic and/or electrolytes adverse effects.[7]

All in all, when feasible and economically affordable, we believe that treating hypertension by directly counterbalancing its main pathogenetic mechanisms, rather than just reducing blood volume, still remains the most intelligent therapeutic approach.[8] In case the “deflating balloon” approach is sought, repeated phlebotomies, a low-cost and minimally invasive technique, can effectively reduce blood pressure with a mechanism that is independent of insulin resistance.[9] Routine phlebotomies in these patients may reduce health care costs related to the epidemic metabolic syndrome and, eventually, also contribute to increase the rate of blood donations.[10]

References

1. Mishra S. Diuretics in primary hypertension—reloaded. *Indian Heart J*. 2016;68:720–723.
2. Grassi G, Seravalle G, Dell'Oro R, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. *J Hypertens*. 2003;21:1761–1769.
3. Mancia G, Fagard R, Narkiewica K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219.
4. James PA, Oparil S, Carter BL, et al. Evidence-based guideline for the management of high BP in adults. *JAMA*. 2014;311:507–520.
5. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trail (ALLHAT). *JAMA*. 2002;288:2981.
6. Weber MA. The ALLHAT report: a case of information and misinformation. *J Clin Hypertens*. 2013;5:9–13.
7. Roush GC, Ernst ME, Kostis JB. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone- antihypertensive and metabolic effects. *Hypertension*. 2015;65:1041–1046.
8. Maranta F, Spoladore R, Fragasso G. Pathophysiological mechanisms and correlates of therapeutic pharmacological interventions in essential arterial hypertension. *Adv Exp Med Biol*. 2016;(November (19)) [Epub ahead of print] PMID: 27864806.
9. Houschyar KS, Lüdtke R, Dobos GJ, et al. Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. *BMC Med*. 2012;10(May (30)):5410.1186/1741-7015-10-54.
10. Manco M, Fernandez-Real JM. Back to past leeches: repeated phlebotomies and cardiovascular risk. *BMC Med*. 2012;10(May (30)):5310.1186/1741-7015-10-53.

Roberto Spoladore
Francesco Maranta
Gabriele Fragasso*
Heart Failure Clinic, Istituto Scientifico San Raffaele, Via Olgettina 60, 20132 Milano, Italy

* Corresponding author.
E-mail address: gabriele.fragasso@hsr.it (G. Fragasso).

Available online 12 January 2017

http://dx.doi.org/10.1016/j.ihj.2017.01.002
0019-4832/© 2017 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).