Hypertension Research (2023) 46:2419–2420
https://doi.org/10.1038/s41440-023-01381-0

COMMENT

Impact of medication adherence on renal denervation trials in resistant hypertensive patients

Keiko Hosohata[1]

Keywords Blood pressure · Hypertension · Poor medication adherence · Post-hoc evaluation · Liquid chromatography/high-resolution mass spectrometry

Received: 9 June 2023 / Revised: 25 June 2023 / Accepted: 1 July 2023 / Published online: 2 August 2023

During the past decade, several devices targeting the autonomic nervous system have been developed as additional treatment options for patients with resistant hypertension (RH). Of these, renal denervation (RDN) is a promising nonpharmacological treatment for uncontrolled hypertension [1]. In the first-generation RDN trial (SYMPLICITY HTN-3), there was no significant difference in office systolic BP reduction at 6 months between radiofrequency-based RDN and a sham procedure in patients with severe RH [2]. Since then, new devices and techniques have been developed to improve the efficacy and safety of RDN procedures. The REQUIRE trial is the first trial in Asia to compare 24-h ambulatory systolic blood pressure (ASBP)-lowering effects of ultrasound renal denervation (uRDN) versus sham in RH patients [3]. The study findings were neutral for the primary endpoint, with similar reductions in 24-hour ambulatory SBP in the renal denervation and sham control groups.

In this issue of *Hypertens Res*, Kario et al. [4] report on their recent findings based on post-hoc analysis, in which they objectively evaluated adherence at the baseline and 3 months using available urine samples from the REQUIRE trial. The authors found that the rate of poor baseline adherence to prescribed BP-lowering drugs was very high (45%). In addition, there was a change in the adherence rate in sham-operated patients with poor baseline adherence. In this sham procedure group with poor baseline adherence, 36% of them showed improved adherence (change in 18.0%). This improvement of adherence in sham patients with poor baseline adherence led to marked ASBP reductions greater than -30 mmHg. Considering such large BP reductions after improvement of adherence in RH patients with poor baseline adherence in spite of sham-operation, it is possible that they might show "pseudoresistance", which distinguishes them from "true" RH patients. A frequently underestimated cause of pseudoresistant hypertension is partial adherence (ranging from 13 to 46%) or full non-adherence (ranging from 2 to 35%) to prescribed antihypertensive medication [5, 6]. It is difficult to separate true RH from "pseudoresistance" [7].

Medication adherence is defined as the extent to which patients take medications as prescribed by their health care providers. Reasons for poor adherence may be diverse. The five dimensions of adherence as reported in the 2003 WHO Report remain useful [8]: sociodemographic, healthcare system-related, therapy-related, condition-related, and/or patient-related factors, as factors leading to poor medication adherence (Fig. 1). Especially, increasingly complicated treatment regimens (e.g., number of pills, number of medications, and number of daily doses) may be a particular challenge for patients with uncontrolled hypertension. The methods available for evaluation of medication adherence can be classified into indirect and direct measurements. Each method has advantages and disadvantages, and no method is considered the gold standard [9]. Indirect methods include questionnaires, self-reports, patient diaries, performing pill counts, ascertaining rates of refilling prescriptions, and the use of medication event-monitoring systems. Direct methods include the response to directly observed therapy (DOT) and measurement of drug concentrations in blood or urine. Direct approaches are expensive and burdensome to medical staff. Almost all antihypertensive drugs or their

✉ Keiko Hosohata
hosohata@gly.oups.ac.jp

[1] Education and Research Center for Clinical Pharmacy, Faculty of Pharmacy, Osaka Medical and Pharmaceutical University, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan

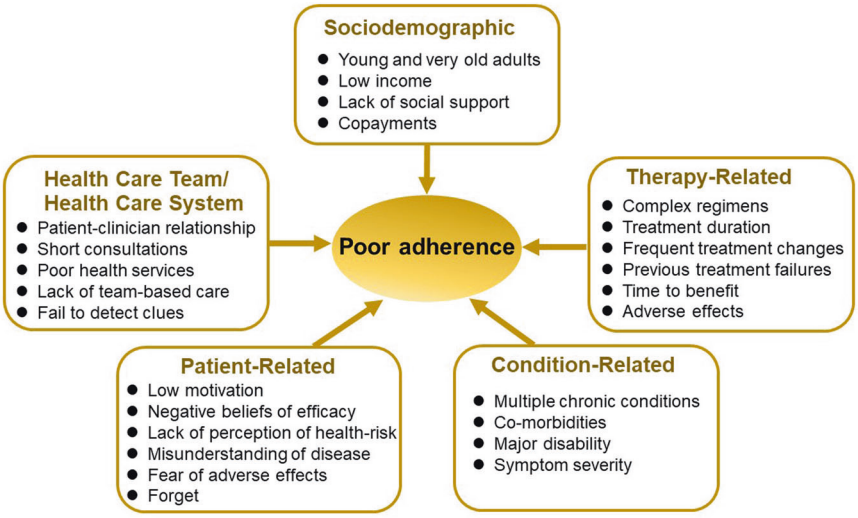

Fig. 1 Adherence is simultaneously influenced by several factors. The five dimensions of adherence as reported in the 2003 WHO Report remain useful [8]

metabolites can be detected in urine. The non-detection of a drug in a urine sample means that the drug has not been taken for a duration equivalent to several half-lives. In the present study, a direct approach was adopted and drug concentrations in urine were quantified using liquid chromatography/high-resolution mass spectrometry, which is a high-sensitivity method for the detection of chemicals. The authors evaluated adherence strictly in the present study.

This REQUIRE post-hoc analysis revealed that approximately 45% of Japanese RH patients showed poor medication adherence, and there were uncontrolled changes in medication adherence during the follow-up. In patients with good baseline adherence, the adherence rates did not change at 3 months regardless of the procedure of uRDN and sham. This good-adherence group showed significant BP-lowering effects of uRDN. Monitoring and maintaining medication adherence are important for future intervention studies in RH.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Lauder L, Azizi M, Kirtane AJ, Bohm M, Mahfoud F. Device-based therapies for arterial hypertension. Nat Rev Cardiol. 2020;17:614–28.
2. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N. Engl J Med. 2014;370:1393–401.
3. Kario K, Yokoi Y, Okamura K, Fujihara M, Ogoyama Y, Yamamoto E, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled require trial. Hypertens Res. 2022;45:221–31.
4. Kario K, Kai H, Nanto S, Yokoi H. Anti-hypertensive medication adherence in the require trial: Post-hoc exploratory evaluation. Hypertens Res. 2023;46:2044–47.
5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 esc/esh guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104.
6. Berra E, Azizi M, Capron A, Hoieggen A, Rabbia F, Kjeldsen SE, et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension. 2016;68:297–306.
7. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, et al. Resistant hypertension: Detection, evaluation, and management: a scientific statement from the american heart association. Hypertension. 2018;72:e53–e90.
8. World Health Organization. Adherence to long term therapies: Evidence for action. Geneva: World Health Organization; 2003.
9. Alcoba M, Cuevas MJ, Perez-Simon MR, Mostaza JL, Ortega L, Ortiz de Urbina J, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. J Acquir Immune Defic Syndr. 2003;33:253–8.