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EDITORIAL

What impacts do the new ESH 2023 guidelines have on the management of hypertension in Japan?

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Introduction

The European Society of Hypertension (ESH) has just released new guidelines that are global, standardized and evidence-based, and were authored by a task force of 59 experts from Europe who represent the areas of internal medicine, cardiology, nephrology, endocrinology, general medicine, geriatrics, pharmacology and epidemiology [1]. The 'class of recommendation' (CoR) and 'level of evidence' (LoE) for all recommendations in the new guidelines were reviewed by an Evidence Grading Committee, and the number of references cited was about three times greater than in the previous version of the ESH guidelines [2].

These new guidelines come in the context of inadequate blood pressure (BP) control rates worldwide, with significant regional differences and disparities [3]. In Japan, it is estimated that approximately 43 million people have hypertension, but the BP control rate is only 25% [4]. This suggests that the most important challenge that guidelines should focus on is to reduce the rate of uncontrolled hypertension, with the goal of achieving "zero" cardiovascular events. To help achieve the goal, we propose two approaches to promote the guideline utilization. Firstly, providing a simplified version of guidelines with concise messages is important to facilitate their adoption among general practitioners who manage individuals with hypertension within a short consultation time. Secondly, taking a personalized approach based on each individual's profile is important for comprehensive management and to achieve personalized BP control. By comprehensively implementing personalized approaches alongside standardized methods to control BP in each individual, there should be a significant improvement in the rate of BP control in populations worldwide.

Key points and areas of focus for the ESH 2023 hypertension guidelines are summarized in Table 1.

Out-of-office BP monitoring

Recommendations on the use of home and ambulatory BP monitoring have been upgraded in the ESH 2023 guidelines, without any changes in the each corresponding BP value [1]. While there are no randomized controlled trials (RCTs) that demonstrate the priority of home BP- or ambulatory BP-based management of hypertension over office BP-based management, accumulated evidence suggests that home and ambulatory BP measurements provide stronger risk prediction regarding target organ damage and cardiovascular events compared with office BP [1, 4–7]. In addition, the importance of detecting and treating nocturnal hypertension (BP ≥ 120/70 mmHg) is stressed in the new guidelines [1]. There is a recommendation to assess nighttime BP because this is a better prediction of risk than BP (CoR I, LoE B) [1], and because nocturnal hypertension and the non-dipping and riser (reverse dipping) patterns of nighttime BP are associated with increased cardiovascular risk [8–14] and elevated nighttime BP may be reduced by

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Table 1 Key points from the 2023 European Society of Hypertension guidelines

- This is the global standard evidence-based guidelines, and has a strong focus on the use of a personalized approach to hypertension management
- Use of home and ambulatory BP monitoring is highly recommended, and there is a focus on nocturnal hypertension
- Practical approaches to reduce rates of uncontrolled hypertension are provided; including the use of single-pill combinations (including a triple combination containing a CCB, a RASi and a diuretic at their maximum recommended dosages), and the addition of a beta blocker
- There is a Class II recommendation for the use of renal denervation in individuals with uncontrolled hypertension
- Practical management of hypertension in a broad range of individuals is covered, from children to the very elderly (age >80 years), pregnant women, and high-risk people with comorbidities such as HF, AF, diabetes, CKD, etc.
- New topics such as COVID-19 and onco-hypertension are included
- Follow-up strategies to improve the quality of BP control by improving adherence and reducing clinical inertia, facilitated by telehealth and a multidisciplinary collaborative approach, are more precisely documented

AF atrial fibrillation, *BP* blood pressure, *CCB* calcium channel blocker, *CKD* chronic kidney disease, *RASi* renin-angiotensin system inhibitor

antihypertensive treatment (CoR II, LoE C). The Treatment in Morning versus Evening (TIME) study is an open-label and blinded-endpoint RCT that compared morning versus bedtime dosing of antihypertensive drug therapy in individuals with hypertension [15]. The results showed that there was no difference in cardiovascular prognosis between the two dosing groups, resulting in the following guideline statement: "in the general hypertensive population morning dosing or bedtime dosing results in similar outcome (CoR I, LoE B)" [1]. Therefore, routine bedtime dosing is not recommended. Instead, a pragmatic personalized approach of bedtime dosing for treated individuals with hypertension who have uncontrolled morning or nocturnal hypertension seems more appropriate in clinical practice.

Recent real-world data from Japan have highlighted the inadequate control of nighttime and morning BP in treated individuals with hypertension, even when multiple agents are used. The Home-Activity ICT-based Japan Ambulatory Blood Pressure Monitoring Prospective (HI-JAMP) study is a general-practitioner-based, nationwide, multicenter, prospective study that started in 2017 and is continuing follow-up until March 31, 2026 [16]. This study is using an "all-in-one" BP monitoring that can measure office, home, and ambulatory BP. Of the 2731 medicated participants with hypertension, nearly half (46.5%) did not have well controlled nighttime ambulatory BP (≥120/70 mmHg), and over half (54.4%) had poor morning home BP control (≥135/85 mmHg), and this included participants being treated with three or more antihypertensive drugs [16]. These rates of uncontrolled BP were higher than those for office BP (≥140/90 mmHg; 33.2%) and daytime ambulatory BP (31.2%).

The 2014 Japanese Society of Hypertension (JSH) guidelines were the first to emphasize the importance of home BP-guided management of hypertension, stating that "when the diagnosis and management of hypertension is different between office BP and home BP, home BP is prioritized" [4]. With recent advancements in digital technology, it may be better to shift from home BP-guided management of hypertension to a home BP-centered approach for hypertension management [17]. Targeting the control of morning home BP seems like an appropriate first step in majority of individuals with hypertension. This could be facilitated by the use of ambulatory BP monitoring (ABPM) or use of a validated nocturnal home BP monitoring (HBPM) device (wrist-type [18] or upper-arm type) in high-risk individuals with hypertension [11] and/or those with a high nocturnal hypertension prediction score [19]. This seems especially important in Asian countries because masked hypertension is common in this region, and there is a high prevalence of nocturnal/morning hypertension [20, 21]. Considering these differences between Asia and other regions, the Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network has published a list of the seven action approaches that are likely to be effective in Asia [22] and for morning hypertension management [23].

Improving hypertension control

The new European guidelines provide practical approaches to address current high rates of uncontrolled hypertension [1]. This includes the recommendation to use single-pill combinations, including a triple combination containing a calcium channel blockers (CCB), a renin angiotensin system inhibitor (RASi) and a diuretic at their maximum recommended dosages [1]. In Japan, other potential options include the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan, and the new highly-selective, long-acting non-steroidal mineralocorticoid (MR) receptor blocker, esaxerenone. Both agents have potent BP-lowering effects for office readings and over the 24-h period, including nighttime and morning [24–28].

Renal denervation

The ESH 2023 guidelines include a Class II recommendation for the use of renal denervation (RDN) in individuals with uncontrolled hypertension [1]. RDN effectively reduces 24-h BP, including nighttime and morning BP

measurements, which are regarded as blind spots in the pharmacological management of hypertension [29, 30]. Although a recent Japanese RCT comparing ultrasound RDN with a sham procedure did not find any significant differences in reductions in 24-h SBP (the primary endpoint) between the RDN and control groups [31], a post-hoc analysis suggested that greater than expected BP reductions in the control group in this study may have been due, at least in part, to changes in drug adherence [32].

RDN may be an especially useful option for Asian individuals with hypertension, who are susceptible to experiencing nocturnal and morning hypertension [33]. The ongoing sham-controlled RADIANCE-HTN DUO RCT (https://jrct.niph.go.jp/en-latest-detail/jRCT2032220027) is evaluating the effectiveness of ultrasound RDN in individuals with uncontrolled hypertension despite treatment with two antihypertensive drugs. Japan is currently preparing for the introduction of RDN into clinical practice.

Other key features of the new guidelines

The new guidelines cover the management of hypertension across all age groups, from children to the very elderly (age >80 years), in pregnant women, and in high-risk individuals with comorbidities such as atrial fibrillation, diabetes, chronic kidney disease [1]. This means that they have broad application for the practical management of a wide range of individuals with hypertension. Topics such as COVID-19 and onco-hypertension are also included [1], both of which have also been addressed in detail in JSH documents [34–37].

Telehealth and digital strategies

Follow-up strategies to improve the quality of BP control, facilitated by telehealth and a multidisciplinary collaborative approach, are documented in more detail in the latest ESH hypertension guidelines [1]. Regular follow-up is recommended as a key component of hypertension management, to assess BP control, the need for changes to lifestyle and drug therapy, and to identify the progression of organ damage and cardiovascular risk factors [1]. The term 'clinical inertia', which was used in the 2019 JSH guidelines [4], is also now addressed in the European document [1]. In addition, patient empowerment and use of telemedicine and telehealth technologies is recommended to increase adherence to hypertensive treatment [1]. Digital therapeutics for hypertension, which facilitate the implementation of lifestyle modifications by frequent mutual communications with a virtual nurse, have potential in this setting, and have been shown to reduce office, home, and ambulatory BP in an open-label RCT [38, 39]. In Japan, digital therapeutics for hypertension was approved by regulatory authorities, and this approach can now be used with reimbursement in clinical practice [40].

Conclusion

The 2023 ESH guidelines include not only strictly scientific evidence from RCTs, but also place the evidence in context and advocate for a personalized approach to hypertension management. This takes into account the fact that individuals with hypertension are a highly heterogeneous group with different characteristics and comorbidities. As such, the new European hypertension guidelines will have a positive impact on the practical management of hypertension, and development of local guidelines, in Japan and around the globe.

Compliance with ethical standards

Conflict of interest KK reports Lecture fees from Viatris, Otsuka pharmaceuticals, Otsuka Medical Device, Daiichi Sankyo, Terumo, Novartis Pharma, Omron Healthcare, JIMRO, A&D, CureApp, Sanwa Kagaku Kenkyusho; Funded research or joint research expenses from Fukuda Denshi, Omron Healthcare; Scholarship donations from Otsuka Pharmaceuticals, Daiichi Sankyo, Sumitomo pharma, Boehringer Ingelheim Japan, Takeda pharmaceuticals, outside the submitted work. Nishiyama A reports grants for collaborative studies from Daiichi-Sankyo Co. Ltd., Boehringer Ingelheim Co. Ltd., Taisyo Pharm Co., Ltd, Bayer Co. Ltd.; speakers bureau from Daiichi-Sankyo Co. Ltd., Boehringer Ingelheim Co. Ltd., Novartis Co. Ltd, Taisyo Pharm Co., Ltd,, Mochida Pharm Co., Ltd., Tanabe-Mitsubishi Co, Ltd., AstraZeneca; receipt of drugs from Daiichi-Sankyo Co. Ltd., Boehringer Ingelheim Co. Ltd., Tanabe-Mitsubishi Co, Ltd., Taisyo Pharm Co., Ltd,, Bayer Co. Ltd. Ohya Y reports lecture fees from Novartis, Otsuka Pharmaceuticals, Daiichi Sankyo. Node K has received honoraria from AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe Pharma, MSD, Novartis Pharma, Novo Nordisk Pharma, Ono Pharmaceutical, Otsuka, Takeda Pharmaceutical; Research grant from Asahi Kasei, Astellas, Boehringer Ingelheim Japan, Fuji Yakuhin, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Novartis Pharma, Teijin Pharma; Scholarship from Bayer Yakuhin, Medtronic, Teijin Pharma. All other authors report no potential conflicts of interest in relation to this article.

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