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COMMENTARY

Updated Guidelines for Management of High Blood Pressure in Japan
The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014)

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In an article published in *Hypertension Research*, the writing committee of the Japanese Society of Hypertension (JSH) updated the Society's 2009 Guideline for Hypertension Management using principles of evidence-based medicine based in part on the 2011 Report of the Institute of Medicine (USA) *Clinical Practice Guidelines We Can Trust*.[1,2] As described in the JSH 2014 Report, the primary objective of the JSH 2014 is to standardize antihypertensive treatment in order to optimize prevention of diseases of the brain/heart/kidney in the Japanese population. The Report acknowledges the importance of primary care clinicians, as well as teams that include nurses, dieticians and pharmacists, in caring for hypertensive patients in Japan, and directs its recommendations toward all of these groups. Accordingly, members of organizations representing primary care providers, clinical pharmacologists, pharmacists, clinical nutritionists and patients were included in the guideline development and review process. JSH 2014 clearly states that its recommendations are not proscriptive and that therapeutic strategies should be tailored to the specific needs and comorbidities of each patient.

THE PROCESS OF GUIDELINE DEVELOPMENT

Preparation of JSH 2014 began at the 15 May 2012 meeting of the JSH Board of Directors. Dr Kazuaki Shimamoto was selected as Chairperson, and a committee was constituted to update the JSH 2009 guideline according to advances in scientific knowledge, bearing in mind recent modifications of the European and British guidelines. Committee members disclosed potential conflicts of interest, including relationships with industry and participation in studies that were evaluated in the Report. The Report was divided into 13 chapters, and for each chapter, a PubMed search was carried out covering the period January 2009—June 2013 using 'disease', 'target of blood pressure control' and 'selected antihypertensive drugs' as key words. Evidence obtained from published studies was classified into six levels, with systematic reviews and meta-analyses of randomized controlled trials (RCTs) assigned to the highest level, followed by individual RCTs; descriptive studies (case reports, case series) and expert opinion were assigned to the lowest evidence levels. JSH 2014 acknowledges that a major limitation of attempting to use RCT data as its primary evidence base is that most pertinent RCTs of antihypertensive treatment with important health outcomes were carried out in Europe or the United States. Patient characteristics and disease outcomes of hypertension are very different in these populations. For example, rates of fatal and non-fatal stroke are 3–4 times higher than the rates of myocardial infarction (MI) in Japan, whereas MI is more prevalent than stroke in the West. Conceivably, this and other genetic and environmental differences could complicate efforts to extrapolate data from published RCTs to Japanese patients, highlighting the need for more RCTs of blood pressure (BP) treatment to be carried out in Japan.

Treatment recommendations were then graded based on the level of evidence supporting them. Draft recommendations were opened to public comment on the JSH website, and input was solicited from representatives of the Patient Corporation on issues related to home BP measurement, telephone consultations, lifestyle modifications and guidelines for patients. Representatives of The Japan Pharmaceutical Association were asked to comment on cost issues, characteristics and adverse effects of antihypertensive drugs and health insurance coverage.

SCOPE OF THE JSH 2014 GUIDELINE

The JSH 2014 Report is encyclopedic, covering virtually every topic relevant to clinical hypertension and its complications, and is heavily referenced, including over 1100 citations. The introductory chapter deals with the epidemiology of hypertension and its major health outcomes in Japan, and includes descriptions of national level public health programs designed to reduce the BP and cardiovascular disease (CVD) risk of the population. This is followed by a chapter devoted to the measurement of BP in the clinic and home setting, which includes definitions of various forms of hypertension, including white coat, masked, morning and evening hypertension, as well as recommendations for use of home and 24-h ambulatory BP monitoring (ABPM) in hypertension management. Basic aspects of the diagnostic

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Table 1 Comparison of JSH 2014 Hypertension Guideline and 2014 U.S. Hypertension Guideline (JNC 8)

Topic	*JSH 2014 Hypertension Guideline*	*2014 U.S. Hypertension Guideline (JNC 8)*
Methodology	• Clinical questions developed by working groups of JSH members • Nonsystematic review of literature from January 2009–June 2013 done by expert committee, including a range of study designs • Recommendations based on consensus and limited RCT data	• Critical questions and review criteria defined by expert panel with input from methodology team • Initial systematic review by methodologists restricted to RCT evidence • Subsequent review of RCT evidence and recommendations by the panel according to a standardized protocol
Definitions	• Defined hypertension and subtypes (white coat, masked, morning, nighttime) based on clinic and home BPs, as well as ABPM	• Definitions of HTN and pre-HTN not addressed, but thresholds for pharmacologic treatment were defined
Treatment goals	• Separate treatment goals defined for general hypertension population and for those with comorbid conditions (diabetes, CKD with proteinuria)	• Similar treatment goals defined for all hypertensive populations, except when evidence review supports different goals for a particular sub-population
Lifestyle recommendations	• Recommended lifestyle modifications based on literature review and expert opinion	• Lifestyle modifications recommended by endorsing the evidence-based Recommendations of the Lifestyle Work Group
Drug therapy	• Recommended four classes (CCBs, ARBs, ACEIs and diuretics) to be considered as initial therapy for the general hypertensive population based on RCT evidence • Recommended particular medication classes for subgroups of hypertensive patients, for example, diabetes, CKD, children, pregnant women and others • Recommended that drugs should be started at low doses and administered once a day • Commented on drug combinations, including single-pill combinations, adherence and cost	• Recommended selection among four specific medication classes (ACE-I, ARB, CCB or diuretic) and doses based on RCT evidence • Recommended specific medication classes based on evidence review for racial, CKD and diabetic subgroups • Panel created a table of drugs and doses used in the outcome trials
Scope of topics	• Addressed multiple issues (BP measurement methods, patient evaluation, secondary hypertension and hypertension in special populations and special situations) based on literature review and expert opinion	• Evidence review of RCTs addressed a limited number of questions, those judged by the panel to be of highest priority
Review process prior to publication	• Reviewed by multiple parties, including members of JSH and 14 affiliated specialty and primary care societies and persons recommended by the Patient Corporation, according to AGREE II (Appraisal of Guidelines for Research Evaluation II)	• Reviewed by experts including those affiliated with professional and public organizations and federal agencies; no official sponsorship by any organization should be inferred

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; HTN, hypertension; JNC, Joint National Committee; JSH, Japanese Society of Hypertension; RCT, randomized controlled trial.
Adapted from James *et al.*[3]

evaluation of the patient with suspected hypertension, including the focused history, physical examination and laboratory testing, are also outlined in this chapter. The principles of antihypertensive treatment, including both lifestyle modification and pharmacologic therapy, as well as the detailed characteristics of the various antihypertensive drug classes, are discussed. In addition to the general population of adults with hypertension, the Report includes recommendations for evaluation and treatment of many subgroups of hypertensive persons, including children, pregnant women, the elderly, and those with secondary hypertension, target organ damage and comorbid conditions that complicate BP management, such as diabetes, chronic kidney disease (CKD), dementia, obesity, asthma/COPD, gout/hyperuricemia and liver diseases. Special conditions, including hypertensive emergencies and urgencies, as well as the perioperative evaluation and management of hypertensive persons, are also discussed in depth.

The broad scope of JSH 2014 is both a strength and a weakness. The lengthy and complex document provides useful and up-to-date information on the management of many subgroups of hypertensive persons with a large variety of comorbidities, both acute and chronic. However, the length of the report and its extremely detailed and scholarly discussions of topics in the literature, some of which remain controversial, limit its usefulness for the busy primary care provider. While JSH has made a commendable effort to make this guideline evidence-based, its broad scope dictates that it must provide guidance for management decisions in many clinical areas where there is little or no RCT evidence of benefit or harm of treatment. Evidence from RCTs represents the gold standard for determining efficacy and effectiveness of treatments, and caution must be used in interpreting guidance based on expert opinion and observational data, which may be subject to unintended bias.

COMPARISON WITH OTHER CURRENT HYPERTENSION GUIDELINES

Table 1 compares JSH 2014 and the 2014 U.S. Hypertension Guideline (JNC 8).[3] In contrast to the comprehensive JSH 2014 Guideline, the 2014 U.S. Hypertension Guideline focuses on the three critical questions in hypertension identified by committee members as most important:

1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?

Table 2 Guideline comparisons of goal BP and initial drug therapy for adults with hypertension

Guideline	*Population*	*Goal BP, mm Hg*	*Initial drug treatment options*
JSH 2014[1]	General, including early-phase elderly (65–74 years)	<140/90	CCB, ARB, ACE-I or diuretic
	Late-phase elderly (75+y)	<150/90	CCB, ARB, ACE-I or diuretic at ½ standard dose
	DM	<130/80	ARB or ACE-I
	CKD no proteinuria	<140/90	ARB, ACE-I, CCB or diuretic
	Proteinuria	<130/80	ARB or ACE-I
2014 Hypertension Guideline (JNC 8)[3]	General ⩾60 years	<150/90	Nonblack: thiazide-type diuretic, ACE-I, ARB or CCB; Black: thiazide-type diuretic or CCB
	General <60 years	<140/90	Nonblack: thiazide-type diuretic, ACE-I, ARB or CCB; Black: thiazide-type diuretic or CCB
	DM	<140/90	Thiazide-type diuretic, ACE-I, ARB or CCB
	CKD	<140/90	ACE-I or ARB
2013 ESH/ESC[4]	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACE-I or ARB
	General elderly <80 years	<150/90	Diuretic, β-blocker, CCB, ACE-I or ARB
	General ⩾80 years	<150/90	Diuretic, β-blocker, CCB, ACE-I or ARB
	DM	<140/85	ACE-I or ARB
	CKD no proteinuria	<140/90	ACE-I or ARB
	Proteinuria	<130/90	ACE-I or ARB
CHEP 2013[5]	General <80 years	<140/90	Thiazide, β-blocker (age <60 years), ACE-I (nonblack) or ARB
	General ⩾80 years	<150/90	Thiazide, β-blocker (age <60 years), ACE-I (nonblack) or ARB
	DM	<130/80	ACE-I or ARB with additional CVD risk, ACE-I, ARB, thiazide or DHPCCB without additional CVD risk
	CKD	<140/90	ACE-I or ARB
ADA 2013[6]	DM	<140/80	ACE-I or ARB
KDIGO 2012[7]	CKD no proteinuria	⩽140/90	ACE-I or ARB
	Proteinuria	⩽130/80	ACE-I or ARB
NICE 2011[8]	General <80 years	<140/90	<55 years: ACE-I or ARB
	General ⩾80 years	<150/90	⩾55 years or Black: CCB
ISHIB 2010[10]	Black lower risk	<135/85	Diuretic or CCB
	TOD or CVD risk	<130/80	Diuretic or CCB

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; β-blocker, beta blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; DM, diabetes mellitus; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; JSH, Japanese Society of Hypertension; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence; TOD, target organ damage.
Adapted from James *et al.*[3]

2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

The JNC 8 committee did not attempt to redefine hypertension, but did define thresholds and goals for its pharmacologic treatment. To facilitate implementation by a broad spectrum of health-care providers, treatment goals were simplified. Similar treatment goals were defined for all hypertensive persons, except when evidence review supported different goals for a particular sub-population, that is, those over age 60 years without CKD or diabetes. Similarly, the same four medication classes, ACE-I, ARB, CCB or diuretic, were recommended for the general population of hypertensives, except when evidence review indicated a preference for a specific medication class, as in racial, CKD and diabetic subgroups.

Important issues covered in JSH 2014, but not included in the US Hypertension Guideline, relate to the use of combination therapy (including fixed-dose combinations) and the role of home BP measurement/monitoring and ABPM in achieving and maintaining BP control and preventing CVD outcomes. These important questions were identified by JNC 8 committee members but could not be addressed due to lack of resources.

Table 2 places JSH 2014 in the context of other currently used hypertension guidelines. JSH 2014 and some other guidelines recommend treatment to lower BP goals for patients with diabetes and CKD, particularly CKD with proteinuria, based on observational studies. Recent guidelines from the American Diabetes Association (ADA)[4] and JNC 8[3] have raised systolic BP goals for patients with diabetes to those recommended for the general hypertensive population based on evidence from RCTs. Consistent with JSH 2014, the Kidney Disease Improving Global Outcome (KDIGO)[5] and JNC 8[3] guidelines have raised systolic BP goals to <140 mm Hg for patients with CKD but without proteinuria. All guidelines recommend a systolic BP goal of <150 mm Hg for the elderly, but differ in the age cutoff for this recommendation. This is defined as 75 years in JSH 2014,[1] 60 years in JNC 8[3] and 80 years

in the guidelines of the Canadian Hypertension Education Program (CHEP),[6] the European Society of Hypertension/European Society of Cardiology (ESH/ESC)[7] and the National Institute for Health and Clinical Excellence (NICE) of the UK.[8] Of note, a minority of the JNC 8 panel disagreed with the recommendation to increase the target systolic BP from <140 to <150 mm Hg in persons aged 60 years or older without diabetes or CKD, based on expert opinion.[9] The minority group expressed concern that increasing the goal might cause harm by increasing the risk for CVD, including CVD mortality, in Americans older than 60 years. The lack of consistency in recommendations is understandable given the lack of clear RCT evidence in many clinical situations. This caveat is particularly applicable to JSH 2014, as few RCTs of sufficient size and duration to yield clear CVD outcomes enrolled large numbers of East Asian participants.

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