

Special Focus Issue on Hypertension Guidelines

Recently Published Hypertension Guidelines of the JNC 8 Panelists, the American Society of Hypertension/International Society of Hypertension and Other Major Organizations: Introduction to a Focus Issue of *The Journal of Clinical Hypertension*

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This issue of *The Journal of Clinical Hypertension* focuses on recent hypertension guidelines and how they might affect the clinical practice of hypertension. The original stimulus for this special issue of the Journal was the anticipated arrival of the JNC 8 report about 2 years ago, but due to the longer-than-expected time to produce that document it appeared recently as one of 4 sets of guidelines on hypertension published within the past few months.¹⁻⁴

Appropriately, most of the commentaries in this issue about JNC 8 and the other guidelines represent opinions by experts in the field who themselves have been contributors to hypertension guidelines, either in the United States or elsewhere.

ARE THERE MAJOR DIFFERENCES AMONG THE GUIDELINES?

A key difference among the guideline statements is in their target audiences. The primary intention of JNC 8 was to put forward strict evidence-based recommendations focusing on thresholds for defining and treating hypertension and the selection of antihypertensive drug classes. Likewise, the recent guidelines of the European Society of Hypertension and the European Society of Cardiology, although broader in scope, provided recommendations that were based on available evidence.³

The recent joint guidelines of ASH/ISH, although utilizing the same major sources of evidence as the JNC 8 and European publications, also considered a wider range of research articles that could support a more complete and practical guidance for practitioners in the community.²

However, beyond these different structures, the comparisons in Table I show some interesting and important differences among the guidelines, some related to the definitions of hypertension and others to the choices of therapeutic agents.¹⁻⁵ These differences will be

discussed in the commentaries that follow in this issue of the *Journal*.

In considering the JNC statement¹ it should be noted that it includes 9 recommendations regarding BP thresholds and drug selections. Two of these were classified as “strong recommendations”: recommendation 1, which specified 150/90 mm Hg as the diagnostic criterion for hypertension in people aged 60 or older and <150/90 mm Hg as their target for treatment; and recommendation 2, which specified a diastolic BP of 90 mm Hg as a diagnostic criterion and treatment target in people aged between 30 and 59 years. In addition, there were two recommendations classified as “moderate” and one as “weak,” and there were 4 classified as “expert opinions.”

Ironically, it is recommendation 1, one of the only two “strong recommendations,” that has led to the major controversy to arise from the work of the JNC panelists. Quite apart from the reaction of other experts to the new recommendation of 150/90 mm Hg (rather than 140/90 mm Hg recommended in previous JNC reports and by other guidelines) for people aged 60 or older, the lay press seemed to be intrigued that the rules for treatment had now been “relaxed” for a large part of the hypertension population. This response was unfortunate because it could be misinterpreted by patients and even some practitioners as a justification for easing off on hypertension treatment, which was not what the JNC authors intended.

But the question remains: What is the appropriate threshold for defining and treating hypertension in people aged 60 or older? This is a vital issue because the major proportion of people with hypertension are in this age group and are at high levels of cardiovascular risk.

AN INTRIGUING CONTROVERSY

The recommendation by the JNC 8 panelists (see later for why this designation is used rather than simply “JNC 8”) that a threshold of 150/90 mm Hg be used to define hypertension and serve as the treatment target for people aged 60 or older was based largely on 3 major placebo-controlled clinical trials.⁶⁻⁸ These were all conducted in hypertensive patients with isolated systolic hypertension (systolic BPs of ≥ 160 mm Hg with normal

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diastolic BPs <90 or 95 mm Hg): the SHEP⁶ and Syst-Eur⁷ trials were performed in patients aged at least 60, and HYVET⁸ in patients aged at least 80. Syst-Eur did

not report its on-treatment BPs, but in both SHEP and HYVET active treatment reduced systolic BPs to <150 mm Hg and was associated with significantly lower event rates than with the systolic BPs of >150 mm Hg observed with placebo. Similar data, however, were not directly available to allow evaluation of the more traditional 140 mm Hg systolic threshold recommended by the previous JNC 7 report⁹ and by other contemporary guidelines.²⁻⁵ Unfortunately, studies originally designed specifically to test 140 mm Hg were underpowered and inconclusive,^{10,11} although (as discussed later) analyses of data from other clinical trials in patients 60 years or older appeared to demonstrate that patients who achieved the systolic BPs <140 mm Hg specified by the trial protocols had significant outcomes benefits compared with patients who failed to reach this target.¹²⁻¹⁴

THE MINORITY OPINION

As the JNC panelists report in their article, they were unable to achieve consensus as a committee on their 150 mm Hg recommendation and acknowledged that some of their members strongly believed that 140 mm Hg would have been a better choice. Indeed, the dissenting members of the panel felt so strongly on this

List of Abbreviations	
ACC	American College of Cardiology
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension
AHA	American Heart Association
ASH	American Society of Hypertension
CDC	Centers for Disease Control
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HYVET	Hypertension in the Very Elderly Trial
INVEST	International Verapamil SR Trandolapril Study
ISH	International Society of Hypertension
JNC	Joint National Committee
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
SHEP	Systolic Hypertension in the Elderly Program
Syst-Eur	Systolic Hypertension in Europe Trial
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation

TABLE I. Comparison of Hypertension Guidelines 2011–2014

	NICE 2011 ⁵	ESH/ESC 2013 ³	ASH/ISH 2014 ²	AHA/ACC/CDC 2013 ⁴	2014 Hypertension Guidelines, US JNC 8 ¹
Definition of hypertension	≥140/90 and daytime ambulatory BP (or home BP) ≥135/85	≥140/90	≥140/90	≥140/90	Not addressed
Drug therapy in low-risk patients after nonpharmacologic treatment	≥160/100 or daytime ambulatory BP ≥150/95	≥140/90	≥140/90	≥140/90	<60 y ≥140/90 ≥60 y ≥150/90
β-Blockers as first-line drug	No (Step 4)	Yes	No (Step 4)	No (Step 3)	No (Step 4)
Diuretic	Chlorthalidone, indapamide	Thiazides, chlorthalidone, indapamide	Thiazides, chlorthalidone, indapamide	Thiazides	Thiazides, chlorthalidone, indapamide
Initiate drug therapy with 2 drugs	Not mentioned	In patients with markedly elevated BP	≥160/100	≥160/100	≥160/100
BP targets	<140/90 ≥80 y <150/90	<140/90 Elderly patients <80 y: systolic BP <140 in “fit” systolic BP <150 in “fragile” elderly ≥80 y: systolic BP 140–150	<140/90 ≥80 y <150/90 Young adults: Consider <130/80 if tolerated	<140/90 Lower targets may be appropriate in some patients, including the elderly	<60 y <140/90 ≥60 y <150/90
BP targets in patients with diabetes mellitus or chronic kidney disease	Not addressed	<140/85	<140/90	<140/90 Lower targets may be considered	<140/90

Abbreviations are listed in Table I. Blood pressure (BP) values are expressed in mm Hg. Adapted from Lindholm LH, Carlberg B. Hypertension News 2014, Opus 35 (International Society of Hypertension).

issue that they subsequently published an article of their own to express their minority opinion.¹⁵

Even so, as pointed out by the members of the minority group, the decision to express their opinions separately did not in any way reflect on their strong commitment to the JNC evidence-based process. In fact, the JNC 8 panel achieved consensus on all recommendations except recommendation 1, and even arising from recommendation 1 the panel members were unanimous in defining the evidence gaps that should be resolved. The minority group argued that the more rigorous threshold of 140 mm Hg might be safer than 150 mm Hg in patients aged 60 or older because until the uncertainty regarding the merits of 140 mm Hg vs 150 mm Hg is resolved it would not be prudent to recommend a less stringent BP target in patients at high cardiovascular risk. In addition, they made an argument based on the actual achieved BPs in the pivotal SHEP⁶ and HYVET⁸ trials. They noted that the cardiovascular and mortality benefits in these trials were observed at treated systolic BPs of 143 mm Hg and 144 mm Hg, so that a recommendation specifying a threshold of 145 mm Hg rather than 150 mm Hg would be more consistent with the evidence. And if, for simplicity's sake, a decile threshold were to be proposed, wouldn't 140 mm Hg be closer than 150 mm Hg to the hard evidence produced by these trials? In fact, considering this argument by the minority group, and bearing in mind the achieved systolic BPs in SHEP of 143 mm Hg with active treatment and 155 mm Hg with placebo, it could be argued that the JNC 8 panelists' threshold of 150 mm Hg might actually be "giving back" a good part of the stroke and cardiovascular benefits achieved by active treatment.

In support of the JNC minority view, it can be noted that most contemporary clinical trials in hypertension have specified 140/90 mm Hg as their target; and when analyses have been performed to evaluate the effectiveness of this target they have demonstrated that patients treated to below this threshold have significantly fewer fatal and nonfatal cardiovascular events than those whose BPs have remained above 140 mm Hg. Such trials include VALUE,¹² INVEST,¹³ and ACCOMPLISH.¹⁴

In considering how evidence is interpreted and used, there is a further perplexing question to be considered about the JNC 8 panelists' recommendation 1 for 150 mm Hg in patients aged 60 or older. In their own words, this recommendation was directed at "The *general population* aged 60 years or older." The reason for the term *general* was to indicate that certain high-risk groups, specifically those with diabetes or chronic kidney disease, were excluded because the JNC 8 panelists recommended that their target be 140/90 mm Hg rather than the 150/90 mm Hg for all other hypertensive patients older than 60 years. Fair enough. But, putting aside these special groups, the three studies that the panelists depended on for their "general population" recommendation (SHEP,⁶ Syst-Eur,⁷ and

HYVET⁸) were all conducted in patients with the very specific condition of isolated systolic hypertension who were carefully selected and recruited from among the far larger number of patients aged 60 or older with "general" hypertension. Thus, it is a point of curiosity that the 150 mm Hg threshold was recommended by the panelists for "the general population" when, in fact, the "general population" was excluded from the trials on which the recommendation relies. This inconsistency highlights the major extrapolations that guideline writers are compelled to make when the available evidence is not fully relevant to the matter at hand.

THE JNC PANELISTS WERE ACCOMMODATING

In reaching their principal recommendation, the JNC 8 panelists recognized that the decision for 150 mm Hg, compared with 140 mm Hg, was not clear-cut. Careful reading of their report reveals a thoughtful awareness of this issue, which, to their credit, they have acknowledged in the following ways:

- They provide a "corollary" recommendation that stems immediately from their 150 mm Hg declaration for people aged 60 or older, and states: "...based on expert opinion, treatment for hypertension does not need to be adjusted if treatment results in systolic BP lower than 140 mm Hg and is not associated with adverse effects on health or quality of life." Clearly, this statement is intended to represent a modifying influence on the original recommendation 1.
- The rationale for the panelists to include the modifying "corollary" was the fact that not only were systolic levels below 140 mm Hg well tolerated by patients in the SHEP⁶ and HYVET⁸ studies, but that in other trials that had prospectively explored the potential benefit of achieving systolic BPs below 140 mm Hg^{10,11} the findings were so inconclusive that the possibility of clinically important benefits of achieving this lower target could not be excluded.
- The panelists were unusually candid in acknowledging (as discussed earlier) their lack of unanimity in reaching the recommendation for the 150 mm Hg threshold in people 60 or older. In general, guideline statements emerge from a so-called "consensus" of their authors, so this departure by the JNC 8 group reflects a willingness to acknowledge that their recommendation cannot be regarded as prescriptive.
- Perhaps the most important comment in the panelists' paper is their recognition that critical evidence for reaching definitive guidelines is simply not available, leading to the statement: "[JNC 8] agreed that more research is needed to identify optimal goals of systolic BP for patients with high BP." In essence, the panelists are formally acknowledging the fact, recognized by other guidelines writers as well,^{2,3,9} that despite many years of hypertension research we still lack the critical clinical trials

evidence needed to definitively establish BP threshold recommendations for clinical practice.

- The panelists also note that other guidelines have selected a systolic threshold of 150 mm Hg for patients aged 80 or older, rather than 60 or older as in their recommendation 1.^{2,5} They again point out the difficulty in making firm recommendations based on currently available data and explain this inconsistency among guidelines by stating: “This changing landscape is understandable given the lack of clear randomized clinical trial evidence in many clinical situations.”
- In the Conclusion of their publication, the JNC 8 panelists again offer to close the circle and indicate that it is not yet possible to truly favor one threshold over another. They make the comment: “It is important to note that this evidence-based guideline (JNC 8 panelists) has not re-defined high BP, and the panel believes that the 140/90 mm Hg definition from JNC 7 remains reasonable.”

The willingness of the panel to be so candid is quite remarkable for a guideline statement and speaks highly to the openness and integrity of its members.

A CONTENTIOUS PROCESS

Despite the well-intentioned efforts of the JNC 8 panelists to reach out to those who might have interpreted the available evidence differently, the means of disseminating the guideline itself became a public issue. It should be recalled that the whole process of JNC 8, as with all the previous JNC reports, was initiated by the NHLBI of the United States NIH. The JNC panelists were selected from a large group of potential candidates, and included a well-recognized group of knowledgeable and respected hypertension experts who worked in good faith for 5 years, following a set of very rigid criteria employed by the NHLBI to ensure high standards of evidence-based recommendations.

After the panelists finished their task, the JNC 8 report was sent by the NHLBI to outside reviewers for their critiques. After a large number of these reviewers responded with comments, the panel revised its document and re-submitted it to the NHLBI. The NHLBI then decided not to endorse the guidelines and announced that the agency would no longer be responsible for developing clinical practice guidelines, which would now become a joint responsibility of the AHA and the ACC.¹⁶ There was no official explanation given for why this particular decision was taken by the agency after so many years of diligent and productive work by the hypertension panel. Still, it has been noted by readers of the JNC article that an NHLBI person who was a member of the JNC 8 panel was not listed as an author of the main guideline paper¹ but was an author of the minority report.¹⁵ However, at this stage it serves no useful purpose to speculate as to whether the NHLBI has a position on the JNC 8 panelists’ recommenda-

tions, particularly as the agency is no longer planning to sponsor guidelines.

In keeping with its decision, the NHLBI handed over the report of the JNC 8 panelists (together with other cardiovascular-related reports produced by NHLBI-sponsored committees) to the collaboration of the AHA and the ACA that henceforth would be responsible for disseminating cardiovascular guidelines.¹⁶ The nonhypertension reports were then published under the AHA/ACC banner, but the JNC 8 panelists who had already gone through the exceptionally prolonged effort of producing their report felt that it would be unwise to further delay their publication and so made alternative arrangements.

This meant that the JNC 8 panelists were compelled put forward their recommendations as an independent group of authors, hence titling themselves not as “JNC 8” but rather as “The Panel Members Appointed to the Eighth Joint National Committee.” And, as a further clarification, they acknowledge in their report that, “...this guideline was not endorsed by any federal agency or professional society prior to publication...” But, even if the article by the JNC panelists is not an official statement, it still represents a set of carefully constructed and thoughtful ideas that deserve careful consideration. As well, the experience of these authors has taught us a great deal about confronting the dilemmas that arise when working with evidence that is frustratingly incomplete.

WHAT HAVE WE LEARNED ABOUT WRITING GUIDELINES?

The JNC 8 panelists were part of an innovative experiment to develop hypertension recommendations based on a systematic assessment of carefully selected clinical trial evidence. The panelists worked at this task with unflagging commitment, an effort that should be recognized with gratitude.

Like all good experiments, the JNC experience has identified issues that could be applied to future efforts. Most of the evidence used in the JNC 8 work was several years old and had been the basis of previous JNC reports. Although the panel’s work defined key evidence gaps and areas where new research is needed to better define BP thresholds, the panel’s very rigid selection rules for evidence meant that only a small fraction of the available clinical trials data in hypertension could be utilized. This strategy should be carefully reconsidered with the thought that a quality-driven expansion of the evidence base could reduce the dependency on wide extrapolations when making recommendations.

Another aspect of the guidelines tradition has been the practice of making recommendations based on the consensus of panel members. This outcome has been achieved in the past by cajoling any unpersuaded panel members into supporting decisions even when they harbor continuing doubts. The JNC 8 experience, however, has taught us that major differences of opinion can no longer be concealed in the modern era. Specif-

ically, the report of the JNC 8 panelists drew attention to the dissenting minority opinion on recommendation 1 (140/90 mm Hg vs 150/90 mm Hg).

How should such a disagreement affect a report that hopes to provide clear guidance to practitioners? Should a contrived consensus be enforced on the panelists, or should both sides of the argument be fully presented in the report so that readers can reach their own conclusions? In the case of the JNC 8 exercise—notwithstanding the separate publication of the minority position—it is important to emphasize the cohesiveness of the full panel of academic hypertension experts who worked with remarkable collegiality during 5 arduous years to create a set of recommendations that, with only one exception, were unanimously supported.

PRACTICAL IMPLICATIONS

Given the lack of definitive evidence it is impossible to conclude whether a systolic BP threshold of 140 mm Hg or of 150 mm Hg is most appropriate for people between 60 and 80 years of age. In a sense, both of these BP levels may be correct. The JNC panelists have done a service by trailblazing a rigorous approach to the evaluation of data. They have recommended the threshold of 150 mm Hg for people aged 60 or older, but clearly acknowledge the possible validity of 140 mm Hg. Importantly, they have repeatedly issued powerful calls for clinical trials to resolve this issue and provide the critical guidance needed for the care of a large part of the population.

On the other hand, while we await new information—and, frankly, it could be a wait of several years—the 140 mm Hg recommended by other contemporary guidelines^{2,5} for patients aged up to 80 might reflect a safer strategy. After all, as the minority report points out, unless it can be shown that achieving BPs below 140 mm Hg is unwarranted, we should not take the chance of exposing vulnerable patients aged between 60 and 80 years to higher BP levels that might increase their risk of major events.

So, taking into account the tempered approach of the JNC 8 panelists to their recommended 150 mm Hg threshold, including the conclusion to their report that, “. . . the panel believes that the 140/90 mm Hg definition from JNC 7 remains reasonable,” it would be understandable that experts who were part of the JNC 8 panel and supported its 150 mm Hg recommendation could, at the same time, agree that guidelines providing pragmatic advice to practitioners in the community² can appropriately continue to recommend 140/90 mm Hg for patients aged up to 80, at least until we have authoritative clinical trials that might teach us otherwise.

Finally, we all recognize that people do not undergo the aging process at the same rate and that chronologic age is not always an accurate guide to a patient's physiologic age. And so, while guidelines may provide

well-considered, evidence-based recommendations, they need not be applied rigidly. The selection of appropriate BP targets during hypertension therapy for patients at any age should also be influenced by the clinical responses of the patients to their treatment and the practitioner's judgment.

Conflicts of Interest: The author discloses no conflicts of interest, but indicates that he was an author of one of the guidelines (ASH/ISH) referenced in this commentary.

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