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HYPERTENSION GUIDELINES

# Similarities and Differences among Recent Hypertension Guidelines

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## ABSTRACT

Hypertension treatment guidelines are intended to provide recommendations to practitioners on key issues such as diagnostic criteria and blood pressure treatment targets, the optimal use of lifestyle changes as well as drug therapy, and the management of co-existing cardiovascular risk factors. Unfortunately, despite several major clinical outcomes trials in hypertension, there is still insufficient evidence to allow firm recommendations in important areas. A major uncertainty with potentially large implications for stroke and cardiovascular event rates is the systolic blood pressure target in people aged 60 years or more: should it be 150 mm Hg or 140 mm Hg? This commentary addresses this and other controversial issues and differences of opinion across the several authoritative guidelines published in the last few years.


**Keywords:** Antihypertensive therapy, Diagnosis of hypertension, Hypertension treatment guidelines.

**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.

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## Why have Hypertension Guidelines?

It has been known for several decades that high blood pressure is an important risk factor for cardiovascular events; strokes, myocardial infarctions and heart failure in particular, and is also a major contributor to chronic kidney disease. It was first demonstrated in the late 1960s by pivotal trials of the United States veterans administration that the reduction of blood pressure in patients with hypertension decreased the rates of fatal and non-fatal cardiovascular events.[1]

Based on these observations, dealing with hypertension appeared to be straightforward: an increase in blood pressure above a particular threshold increased cardiovascular risk and compelled the start of treatment with antihypertensive treatment. But, the critical question then emerged: what, exactly, is the level of blood pressure that justifies the start of treatment? This was followed by a second critical question: when treatment is started, what should be the blood pressure target? And, finally, what are the best drugs to accomplish this goal?

These pertinent questions became the subject of early guidelines, in particular those published by the United States Joint National Committee (JNC) on the detection, evaluation and treatment of high blood pressure, known quickly as the 'JNC reports'. Over the years, there have been changes in the way these reports have responded to these basic questions.

First of all, we have continued to get a more insightful picture of hypertension epidemiology.[2] Then, as more hypertension outcomes trials were conducted, there was growing information about the clinical effects of treatment regimens achieving differing levels of blood pressure. Over the time span from the 1960s to the turn of this century, there was a continuing process of drug development that provided new agents with better tolerability and a wider range of therapeutic mechanisms.

The main goal of guidelines is to allow experts in a field to provide practical advice to practitioners on how best to manage their patients. The greatest value of guidelines is in those areas where knowledge or experience is incomplete, such that the advice and opinion of the experts becomes a valuable substitute when definitive evidence is not available. Unfortunately, the whole process of guidelines writing has tended to become rather confusing and complicated, particularly for hypertension. Despite a desire to be 'evidence-based', it has become clear that definitive information—truly strong and objective evidence is far from complete in this discipline. To this day, our recommendations for levels of blood pressure

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that can separate hypertension from 'normal' blood pressure are unclear, and treatment targets remain uncertain and even controversial. Indeed, the only area where there seems to be relatively good agreement is with the choice of drugs, where most contemporary guidelines have similar recommendations on how to construct effective and well-tolerated treatment regimens, validated by credible clinical trials evidence.

## How the Hypertension Guidelines have been Organized?

It is interesting to contrast the intentions of the major guidelines that have been published during the last 5 years. Let us consider briefly the scope and intended audiences of these publications:

### *The Guidelines of the European Society of Hypertension and the European Society of Cardiology*

These guidelines were intended to be a comprehensive source of information and support for hypertension specialists.[3] They are probably the most scholarly of any of the guidelines yet written, providing a thoughtful analysis of all aspects of hypertension: issues of total cardiovascular risk; evidence for concomitant risk factors and conditions; innovative diagnostic approaches for staging cardiovascular risk profiles; the role of ambulatory blood pressure monitoring; the varying approaches to therapy and how they can be best applied; detailed information about individual drug classes and how to deal with difficult to-treat patients, including some consideration of secondary hypertension. This impressive document clearly serves as a curriculum of well-considered and argued information for clinicians who plan on serving as informed experts in hypertension.

### *The United Kingdom National Institute for Health and Clinical Excellence*

These guidelines are quite different from those of ESH/ESC, because they are targeted primarily at the practicing community in Great Britain.[4] Unlike the ESH/ESC document, which was written by a large committee of acknowledged hypertension authorities, the NICE guidelines were written largely by experts in the evaluation of clinical evidence, with a focus on cost effectiveness. Of course, some true hypertension experts were included, but the process of developing recommendations was based on the evaluation of available diagnostic and treatment options in the context of the practical and economic realities of clinical practice. Ultimately, despite the comprehensive nature of the NICE commitment, the guidelines are best known for two major contributions: the recommendation that all patients suspected of new hypertension be subjected to ambulatory blood pressure monitoring (ABPM) or rigorous home blood pressure monitoring to confirm the diagnosis; and the recommendation of a drug treatment algorithm that prescriptively put forward a focused strategy for clinicians to follow in bringing their patients' blood pressures under control.

### *The American Society of Hypertension and the International Society of Hypertension Guidelines on Treatment of Hypertension in the Community*

These guidelines were published by a writing committee of 25 hypertension experts that included a strong global representation.[5] Although these guidelines, like the others discussed in this article, were based on the available evidence for diagnosing and treating hypertension, they were written with a rather different audience in mind. In essence, the ASH/ISH document was prepared to be a syllabus or curriculum for active clinical practitioners that could be applied across a broad spectrum of settings, ranging from relatively affluent communities all the way through to regions with limited resources. The document was written with the intention of providing an easy-to-read account of what a hands-on practitioner should know about hypertension, and to provide guidance on how best to make reasonable compromises when the full range of desirable resources is not available. Ultimately, the major recommendations of ASH/ISH regarding diagnostic criteria, treatment targets and optimal drug therapies were similar to those of ESH/ESC or NICE, but had a somewhat different readership in mind.

### *Panel Members appointed to the Eighth Joint National Committee (Panelists)*

The Joint National Committee (JNC), which have operated for several decades, have been sponsored and supported by the US government's national institutes of health, in particular the National Heart, Lung and Blood Institute (NHLBI). On this most recent occasion, however, the rules were somewhat different than in the past, with a strong and rigid focus on the report being 'evidence-based'. The committee worked for 5 full years until the time of their publication in 2014.[6] They addressed only three issues, albeit three highly relevant ones: At what levels of blood pressure should hypertension be diagnosed; what blood pressure levels should be the target of treatment; and what are the optimal drug strategies. There was no discussion in this most recent guideline, as compared with earlier JNC reports, of issues, such as risk factor evaluation, non-pharmacologic measures, secondary hypertension, or

treatment-resistant hypertension. The present article will discuss some of these recommendations, in particular the diagnostic and treatment blood pressure thresholds that were recommended. It will also be critical to understand how a highly funded 5-year project, involving several distinguished hypertension experts, was unable to reach a consensus on critical recommendations for clinical practice. Simply put, the diligent and dedicated exercise performed by the JNC panelists served to underscore a critical and troubling fact: even after many years of clinical trials, we still do not have sufficient authoritative evidence to address some of the most important questions in hypertension.

## A First Look at Similarities and Differences among Guidelines

It is interesting to take a preliminary look at some of the main features and recommendations of the various guidelines. These comparisons are summarized in Table 1. In this table, the main recommendation of the four sets of guidelines we have already discussed have been represented together with those of another group labeled as AHA/ACC/CDC, an ad hoc committee of the American Heart Association, the American College of Cardiology and the United States centers for disease control and prevention; that was asked to write a 'competing' guideline to counterbalance the recommendations of the JNC panelists.[7] More will be said later about this controversy.

We see that the definition of hypertension was similar among all the groups except for the JNC panelists, where it was not specified. Of importance are the recommendations governing the introduction of drug therapy in 'low risk' patients (those without diabetes or chronic kidney disease), where there are some sharp differences. The NICE guidelines, driven by their cost-saving mandate, specify a high blood pressure criterion (160/100 mm Hg) to justify treatment in patients who do not have a meaningful risk (defined as a >20% likelihood of a cardiovascular event during the next 10 years or current evidence for target organ damage). The JNC panelists, on the other hand, recommended 140/90 mm Hg as the threshold for people aged less than 60 but increased the threshold to 150/90 mm Hg for patients aged 60 or more. The other guidelines have stayed with the more traditional 140/90 mm Hg threshold.

**Table 1:** Comparison of hypertension guidelines (2011–2014)

| *Blood pressure in mm Hg* | *NICE 2011*[12] | *ESH/ESC 2013*[3] | *ASH/ISH 2014*[4] | *Go A et al AHA/ACC/CDC 2013*[5] | *2014 hypertension guidelines, US 'JNC 8*[6]*'* |
|---|---|---|---|---|---|
| Definition of hypertension | ≥140/90 and daytime ABPM (or home BP) ≥135/85 | ≥140/90 | ≥140/90 | ≥140/90 | Not addressed |
| Drug therapy in low-risk patients after non-pharmacologic treatment | ≥160/100 or daytime ABPM ≥150/95 | ≥140/90 | ≥140/90 | ≥140/90 | <60 y ≥140/90<br>≥60 y ≥150/90 |
| Beta-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 two drugs | Not mentioned | In patients with markedly elevated BP | ≥160/100 | ≥160/100 | ≥160/100 |
| Blood pressure targets | <140/90 | <140/90 | <140/90 | <140/90 | <60 y <140/90 |
| | ≥80 y <150/90 | Elderly <80 y SBP 140–150<br>SBP <140 in fit patients<br>Elderly ≥ 80 y<br>SBP 140–150 | ≥80 y <150/90 | Lower targets may be appropriate in some patients, including the elderly | >60 y <150/90 |
| Blood pressure targets in patients with diabetes mellitus | Not addressed | <140/85 | <140/90 | <140/90<br>Lower targets may be considered | <140/90 |

Lindholm LH, Carlberg B. HT News 2014, Opus 35

When it comes to drug therapy, there was a reasonably uniform approach among all the guidelines. The only meaningful difference is that most of them do not include beta blockers (unless there is a compelling indication) as first line treatment, instead relegate them to a later stage of hypertension treatment. Otherwise, there is a general agreement about drugs and a focus on what are now considered the standard 'three drug classes' that should be used in most patients: blockers of the renin angiotensin system (angiotensin receptor blockers or ACE inhibitors), calcium channel blockers, and thiazide diuretics. Only ESH/ESC still keeps beta blockers as first-line options.

When it comes to deciding which diuretic to recommend, there were some differences again. For instance, in addition to hydrochlorothiazide, several of the guidelines stressed the potential value of chlorthalidone and indapamide (NICE, ESH/ESC, ASH/ISH and the JNC panelists). Only the recently formed American consortium did not specify the potential value of these other agents.

For patients with high untreated blood pressures (>160/100 mm Hg), there was support for starting immediately with a two-drug regimen from ASH/ISH, the American consortium and the JNC panelists. The ESH/ESC supported the principle but did not specify a particular blood pressure to justify the immediate use of a two-drug combination. The NICE did not address this possibility, particularly as this guideline states that 160/100 mm Hg in many patients should be the routine starting point for drug therapy.

When it came to important questions of blood pressure targets during treatment, there was a general agreement that the definition of hypertension criteria (discussed above) should also represent the target of treatment values. Thus, 140/90 was universally recommended for people under the age of 60, though the JNC panelists preferred 150/90 mm Hg for people aged 60 or above, a recommendation that lead to intense debate (discussed more fully in the following section). However, for patients aged over 80, NICE, ESH/ESC, ASH/ISH and (by default) the JNC panelists, all recommended 150/90 mm Hg. Finally, for patients with diabetes or chronic kidney disease, for whom until just a few years ago a target of <130/80 mm Hg had been recommended, the target was now adjusted to <140/90 mm Hg by all the guidelines, except NICE. This actually was an important change, reflecting general agreement that there was, in fact, no credible evidence to support a more aggressive blood pressure treatment goal in these high risk patients.

## Treatment Targets: A Controversy emerges

As shown in Table 1, and discussed earlier, there are differences among the guidelines in the treatment target blood pressures that were recommended. In general, 140/90 mm Hg remained the single most common target. However, for patients over 80, there is a general agreement that 150/90 mm Hg is a reasonable goal of treatment.

The big issue, of course, is for patients aged between 60 and 80. This is actually a highly important group of patients, because they not only represent a very large fraction of the total hypertension population but also a group of patients who are at a particularly high risk of cardiovascular, stroke and renal outcomes. The unfortunate fact is that we do not have definitive evidence to guide decisions for these patients. Even so, the differing recommendations among the guidelines regarding this group have caused controversy and confusion. It is important to take a closer look.

## Evaluating Evidence to guide Treatment Targets

It is remarkable that guidelines during the past 20 years have depended largely on clinical trials that were started in the 1980s. Perhaps, the best known of these is the systolic hypertension in the elderly program (SHEP) that was carried out in the United States, to learn whether treating people aged over 60 with isolated systolic hypertension (systolic BP > 160 mm Hg and diastolic BP < 90 mm Hg) provided an outcomes benefit. The main result of the study was that patients randomized to active treatment with the diuretic 'chlorthalidone', had a 36% reduction in stroke rate as compared to the patients receiving placebo.[8] This was a landmark study, which beyond the stroke benefit, reported that other cardiovascular endpoints were also reduced by active therapy. Why has SHEP been so often used by guideline committees as part of their recommendations? For a start, it is a placebo-controlled study, thus clearly establishing the benefit of active treatment. It also had a clearly defined age criterion, namely 60 years or older.

The problem with using SHEP, however, was that it was not designed primarily to answer any question other than the obvious one: Is the treatment beneficial in patients aged 60 or more with isolated systolic hypertension? An ideal study intended to provide evidence to support clinical recommendations for blood pressure thresholds should meet certain criteria. First, the study protocol should prespecify not only what the entry blood pressure criteria should be, but also what the trial's target of treatment should be. Second, the trial should specify what other characteristics its patients must have, in particular concomitant clinical conditions and other characteristics that would be of value in interpreting the results of the trial. The SHEP study, although defining its patients clearly, did not establish a treatment target for many of its patients, but simply specified

certain reductions in blood pressure according to each patient's starting value. Furthermore, it did not compare the outcomes benefits of prespecified differing blood pressure treatment targets.

The stroke benefit in SHEP was associated with achieved systolic blood pressures of 155 mm Hg in the placebo group and 143 mm Hg in the actively-treated group. It was this 12 mm Hg delta in blood pressure that appeared to explain the 36% reduction in stroke. How can these numbers be used as a basis for guidelines recommendations? Until recently, most guidelines took the view that it would be wise to treat patients over 60 to a level close to that observed in SHEP (143 mm Hg), presumably so as to keep things simple—a target value of 140 mm Hg.

The JNC 8 panel in 2014 reinterpreted the previous recommendations and claimed that since the achieved systolic blood pressure in the placebo group was >150 mm Hg, and the actively treated group <150 mm Hg, 150 mm Hg (rather than 140 mm Hg) should be the new threshold for treatment. Critics were not slow to point out that 150 mm Hg, if anything, was actually closer to the achieved placebo blood pressure than to the actively treated blood pressure, and so appeared to be compromising the principal benefits promised by SHEP. Just as easily, the JNC panelists could have chosen 145 mm Hg using the same type of reasoning; and if they did not like using a value intermediate between deciles, will not 140 mm Hg be closer to the level associated with the better outcomes? There were other issues as well. The trial was done in patients with isolated hypertension, who in fact were very hard to find and recruit for the SHEP trial. In fact, for every patient enrolled in the study, it was necessary to screen and evaluate 100 of them! So, it seemed rather strange that the JNC panelists, considering only a particular type of hypertension and apparently a difficult one to recruit into a trial, would seek to generalize their recommendation to all people aged 60 or older (it should be noted, however, that the JNC panelists did not apply their 150 mm Hg recommendation to patients with diabetes or chronic kidney disease, where 140 mm Hg was still recommended).

Another study, similar in many respects to SHEP, was the systolic hypertension in Europe trial (Syst-Eur). In fact, the results of the Europe trial were very similar to SHEP, showing that older people with isolated systolic hypertension, when treated with a calcium channel blocker compared with placebo, had clear outcomes benefits.[9] The major difference from SHEP was that the end of study blood pressures in Syst-Eur were 160 mm Hg for placebo and 150 mm Hg for active treatment, thus not clearly establishing a threshold of <150 mm Hg. However, without splitting hairs, Syst-Eur and SHEP basically showed the same thing, that treating older people with isolated systolic hypertension is a highly desirable undertaking.

The only new study to cast further light on these issues was the hypertension in the very elderly trial (HYVET). This trial was conducted in patients aged 80 or older, and compared treatment with an ACE inhibitor plus a thiazide with placebo.[10] Unlike SHEP and Syst-Eur, HYVET did specify a treatment target of <150 mm Hg. They accomplished this goal with active treatment (average of 143 mm Hg) while demonstrating a significant reduction in mortality and other outcomes. In some ways, HYVET was easier to interpret than the previous trials since the prespecified <150 mm Hg target compelled guidelines to recommend that this goal be applied to patients aged 80 or more.

## Why All the Fuss?

After so many years of guidelines recommending <140/90 mm Hg, the switch by the JNC panelists was surprising given that their decision was based on the same basic evidence used by the other guidelines and by previous JNC reports. Not only that, but also it raised some concerns. In their public announcements and press releases, some authors of the JNC report claimed that by raising the threshold from 140 to 150 mm Hg, there would now be many patients aged over 60 for whom it would no longer be necessary to offer active hypertension care, thus providing a large reduction in the costs of professional services, clinical testing and drug use.

The big concern, however acknowledged within the new JNC report, was that we simply do not have any prospective randomized trials designed to compare outcomes with the 150 mm Hg and the 140 mm Hg targets. It is well established through several clinical trials in hypertension that stroke is particularly dependent on systolic blood pressure, across the wide range from 180 mm Hg all the way down to under 120 mm Hg.[1,11] So for stroke events alone, it could be estimated that the threshold target of 140 mm Hg *vs* 150 mm Hg should result in a 25 to 30% lower stroke rate, a potentially compelling difference in a cohort of people aged 60 or more; in whom stroke is a common result of hypertension. Would not prudence dictate, critics might argue, that we should stay with 140 mm Hg until we know with certainty that it is safe to relax the treatment standards to 150 mm Hg?

It is interesting that the critics of the JNC panelists were not all external. An authoritative group among the JNC authors felt so strongly that the 150 mm Hg recommendation was harmful that they published their own minority report arguing that 140 mm Hg be retained for people aged over 60.[12] It was also noteworthy that the NHLBI, the

government sponsors of the JNC 8 effort, dissolved the committee before their report could officially be published, so that what would have been the JNC 8 report was now published as an independent article by authors referring to themselves as 'panelists appointed to the JNC 8 committee'.[16]

## Is There Evidence for using the 140 mm Hg Threshold?

In addressing this question, there is at least one positive start: even the JNC panelists have acknowledged, in their report, that there are no safety concerns with using the <140 mm Hg systolic blood pressure target.[6] There are analyses from hypertension outcomes trials that provide some reasonable support for the 140 mm Hg threshold, though just as with the criticisms of SHEP as a basis for guidelines recommendations, none of these studies can be used as authoritative evidence to support diagnostic or treatment target thresholds. Despite that, it is interesting to look at these analyses since they may add confidence that achieving a systolic blood pressure of < 140 mm Hg might be associated with better clinical outcomes than with higher targets.

Findings from the valsartan antihypertensive long-term use evaluation (VALUE) trial are shown in Figure 1.[13] This was a trial that originally compared two classes of therapy—the angiotensin receptor blocker, valsartan; and the calcium channel blocker, amlodipine, for their efficacy in preventing major outcomes. The analysis in the Figure 1, however, pooled the two treatment arms into a single cohort and compared outcomes depending on whether or not a systolic blood pressure < 140 mm Hg was achieved. For virtually all major outcomes, including mortality, stroke and heart failure, there were clear benefits in achieving this blood pressure target. It should, however,

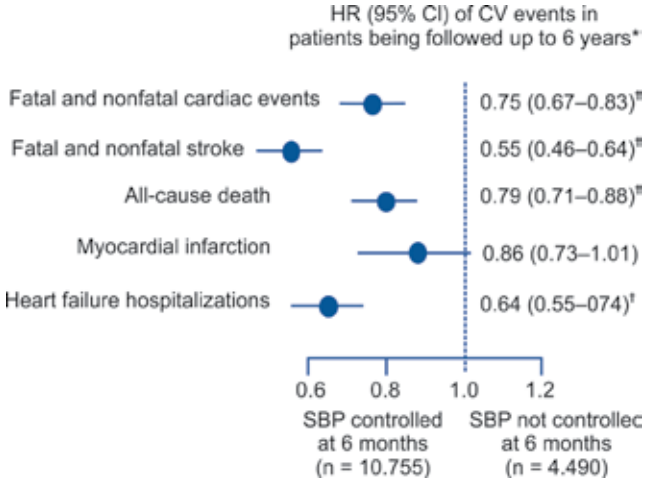


**Fig. 1:** A pooled analysis of data from the VALUE trial comparing outcomes in high-risk hypertensive patients who reached the trials systolic BP treatment target of <140 mm Hg with those who did not achieve this target[13] [*Pooled analysis of patients enrolled in the VALUE trial; blood pressure control defined as SBP < 140 mm Hg; †Statistically significant difference ($p < 0.05$) *vs* SBP not controlled at 6 months; BP: Blood pressure; CI: Confidence interval; CV: Cardiovascular; HR: Hazard ratio; SBP: Systolic blood pressure]

be immediately acknowledged that analyses based on achieved blood pressures within a single cohort can be prone to bias, because it is quite possible that patients with more healthy vasculatures, who in any case might have a better cardiovascular prognosis, are the ones most likely to exhibit a greater fall in blood pressure. Even so, when the results of an analysis are as powerful as shown in Figure 1, it can be argued that these findings are at least suggestive, even if not definitive.

A similar analysis, performed with data pooled from the ACCOMPLISH (avoiding cardiovascular events through combination therapy in patients living with systolic hypertension) trial, is shown in Figure 2. Like VALUE, this trial was focused on patients with average

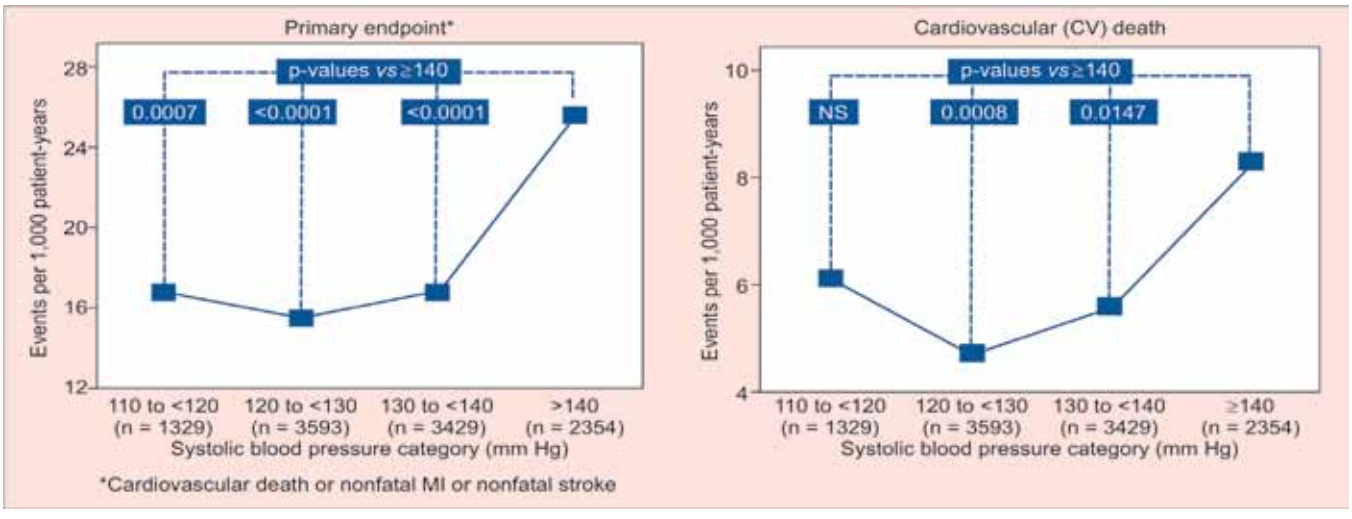


**Fig. 2:** A pooled analysis of data from the ACCOMPLISH trial showing event rates for the composite endpoint of cardiovascular death or nonfatal stroke or myocardial infarction and, for the single endpoint of cardiovascular death, according to deciles of achieved systolic BP. Further details are given in the text[14]

ages in their 60s and 70s, and was originally designed to compare different therapeutic strategies. The findings shown in the Figure 2 indicate that achieving a blood pressure below 140 mm Hg has clear benefits for the composite primary endpoint of cardiovascular death, nonfatal myocardial infarctions or strokes.[14] Similarly, the single outcome of cardiovascular death is also reduced, although there is a suggestion that patients achieving an excessive treatment response (<120 mm Hg) may no longer have an advantage, as far as this outcome is concerned.

In yet another major trial known as International Verapamil SR Trandolapril Study (INVEST), investigators compared outcomes in patients achieving a systolic blood pressure <150 mm Hg (but not <140 mm Hg) with those who did achieve a systolic blood pressure <140 mm Hg.[15] As shown in Table 2, there was a significant benefit for achieving the lower threshold for cardiovascular death, stroke and total death. Again, basing analyses on comparing achieved blood pressures within a cohort is not an optimal way to create evidence, nevertheless the clear results shown in this study are difficult to ignore. The value of this analysis is that it provides a direct comparison of the JNC panelists' <150 mm Hg threshold with the more widely recommended <140 mm Hg threshold, and thus contributes usefully to the debate.

## When to Initiate Treatment?

The information shown in Table 1 that compares recommendations among the different guidelines does not make it completely clear that there are, in fact, some interesting differences. It is noteworthy that the JNC panelists, like in the earlier JNC reports, simply put forward a blood pressure value as a basis for starting treatment. There are no qualifiers to this recommendation; it is based on blood pressure alone.

**Table 2:** Post hoc analysis of invest trial achieved treatments: SBP <140 *vs* <150 mm Hg (*Courtesy*: Derived from Bangalore S, et al. JACC 2014;64:784-793)

| | *<140 mm Hg* | *140–<150 mm Hg* | *RR (95% CI)* | *p-value* |
|---|---|---|---|---|
| Cardiovascular death | 12.2 | 15.9 | 0.74 (0.63, 0.86) | <0.0001 |
| Total MI | 12.1 | 14.6 | 0.77 (0.59, 1.01) | 0.0603 |
| Total stroke | 4.5 | 9.2 | 0.45 (0.31, 0.66) | <0.0001 |
| Heart failure | 7.2 | 6.2 | 1.07 (0.72, 1.60) | 0.7401 |
| Total death | 29.6 | 34.9 | 0.79 (0.66, 0.93) | 0.0056 |

Values are events/1000 patient-years

In contrast, the ESH/ESC guidelines not only have a recommended blood pressure for initiation of hypertension treatment, but also in addition require an analysis of overall cardiovascular risk; such that there can be patients whose blood pressures exceed 140/90 mm Hg but do not qualify for drug therapy. Of course, lifestyle modifications are recommended for these patients, but active therapy can still be delayed if overall risk is not high.

A very similar approach has been adopted by the NICE guidelines. In fact, for patients with blood pressures between 140 and 160 mm Hg in the office, these guidelines recommend drug therapy only if there is evidence for target organ damage or if the calculated 10 year risk of a cardiovascular event is >20%. It should be recalled, as discussed earlier, that there is a strong cost-saving component to the NICE recommendations, but it is still might be reasonable to assume that there need not be any urgency about starting treatment in patients with stage 1 hypertension.

The ASH/ISH guidelines followed a similar thought process as the NICE guidelines, albeit less specifically. It should be remembered that the ASH/ISH guidelines were targeted at primary care providers across a range of communities, including regions of the world with limited healthcare resources. It was suggested, as a matter of policy and not as an issue of evidence, that when resources are limited they should be focused primarily on patients with stage 2 hypertension or where there is clear evidence of adverse cardiovascular changes associated with hypertension.

## Choosing Therapeutic Agents

In most respects, the major guideline reports have agreed on the drug approaches to hypertension therapy. In essence, the three major types of agents: blockers of the renin angiotensin system, calcium channel blockers and thiazide diuretics represent the agents preferred for single-agent or combination-agent regimens. The JNC panelists, the ASH/ISH guidelines and the NICE guidelines recognized that blockers of the renin angiotensin system are generally not used as first line treatment in patients of African ancestry, but often are the best first choice in patients of other ethnicities. The ASH/ISH and NICE guidelines, in particular, tended to prefer calcium channel blockers over thiazides as first line treatment when ACE inhibitors or angiotensin receptor blockers are not selected.

The usual two-drug combination envisaged by ASH/ISH and NICE would be a renin angiotensin system blocker plus a calcium channel blocker, with a thiazide being added as a third line agent, if necessary. The JNC panelists and the ESH/ESC guidelines, however, do not

specify the make-up of combinations based on these drug classes. It can be anticipated that the renin angiotensin blockers, plus either calcium channel blockers or thiazides, would be equally effective in reducing blood pressure in patients of any ethnicity or age.

Most of the guidelines recommend that beta blockers be reserved for fourth line or later use in managing hypertension, largely because outcomes evidence in hypertension for this class of drugs have not been as convincing as with other classes. However, the ESH/ESC guidelines were not convinced of this differentiation and so included beta blockers as first line therapy choices. It should also be noted that most of the guidelines mention the aldosterone antagonist, spironolactone, as a useful drug to consider for those patients who require fourth line or later therapy to achieve blood pressure control.

### General Recommendations for Hypertension Management

As discussed at the beginning of this article, the JNC panelists did not provide input into areas of hypertension care beyond blood pressure thresholds and the selection of drugs. The other guidelines tend to be more comprehensive in their approaches.

In general, there has been unanimous agreement that lifestyle modifications are highly desirable, in particular, weight loss, reduction of salt intake and increase of potassium intake, regular exercise and cessation of smoking. The ASH/ISH guidelines put a particular focus on salt intake, bearing in mind that many cultures in which strokes are a common cardiovascular outcome and often occur early in life, are characterized by high dietary intakes of salt. This clearly is a major issue that cannot be dealt with entirely at the individual practitioner and patient level, but will require the participation of government agencies and food manufacturers to gradually reduce the overall community intake of salt. It should be acknowledged that there is some controversy on the salt issue since not all people respond to high salt diets with increases in blood pressure. However, there has been a suggestion that patients of African origin, whether in Africa or elsewhere, may be particularly vulnerable in terms of blood pressure responses and stroke risk to excess salt ingestion. It should be emphasized, however, that many other patients, regardless of ethnicity, are also at risk. In addition, it can also be argued that most people around the world consume in excess of their daily requirements of sodium, so there does not appear to be harm in population-based strategies for gradually limiting dietary salt.

The ASH/ISH guidelines also discussed briefly, but with some practical recommendations, how to deal with treatment-resistant hypertension. This is a difficult problem, and requires a systematic evaluation of many aspects of lifestyle, treatment, and external factors. These guidelines also provide some simple but practical approaches for considering secondary hypertension, which can sometimes be the cause of treatment-resistant hypertension. One key issue, still to be resolved, is the use of ambulatory blood pressure monitoring (ABPM). Interestingly, the NICE guidelines now mandate the use of ABPM (or carefully performed home blood pressure monitoring) as an essential part of the initial diagnosis of hypertension. The ESH/ESC guidelines also gave considerable attention to ABPM, but did not mandate its use. Parenthetically, it should be noted that the ESH/ESC guidelines, since they were aimed at a sophisticated specialty audience, discussed a variety of diagnostic procedures designed to get a far more comprehensive evaluation of overall vascular involvement and damage that can result from hypertension. Ambulatory blood pressure monitoring was only mentioned briefly by the ASH/ISH guidelines. It is likely that the use of this technology will grow, but only as the resources to support this procedure become more widely available.

## SUMMARY

It is not an easy task to compare and contrast the recommendations of the available hypertension guidelines. Even the most simple of them are lengthy and detailed documents, and there are many details and nuances that must be considered in understanding their recommendations.

Despite some of the differences that have attracted attention, there is a universal belief that hypertension represents the single greatest treatable risk factor for death and serious disability throughout the world. Clearly, it is foolish to be distracted about debating which parts of which guidelines should be preferred and utilized. Instead, efforts to identify people with high blood pressure, advise them on appropriate lifestyle changes, and provide them with the most effective treatment available must be seen as an international imperative.

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