# Chapter 1
# Changes in Guideline Trends and Applications in Practice: JNC 2013 and the Future

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The Joint National Committee Report on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has been in existence for more than three decades with the first report published in 1977. The purpose of this report is to provide an authoritative review and summary of available data from clinical trials that will educate and update healthcare providers on approaches to treatment and cardiovascular risk reduction of appropriate patients. It was initially due to be updated every 4–5 years as data became available that would further solidify or change practice patterns.

The nucleus of the JNC was within the Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health. However, it also had 45 other societies or groups that had input into the JNC report. The last of the true series of these reports was the JNC 7, published in 2003 [1]. Its main goal apart from updating the trial data was to simplify the classification of hypertension as well as the algorithm for initially treating patients with a focus of achieving the blood pressure (BP) goal [1]. As of June 2013, a publication by the NHLBI in circulation clearly states that there will be no further guidelines emanating from NHLBI. They will provide data evaluation but the joint efforts of the American Heart Association (AHA) and American College of Cardiology Foundation are to provide the actual guidelines sometime in 2014.

The JNC reports themselves have transformed over time. There were initially four stages of BP classification in the early JNC reports; these have evolved into two stages in more recent reports (Figs. 1.1 and 1.2). The early JNC reports did not focus on systolic BP (SBP) primarily because it was a younger population of patients and most of the studies were from the late 1960s and early 1970s [2, 3]. However, after the Systolic Hypertension in the Elderly Trial in 1991, there was a major shift in focus to systolic hypertension especially in those over age 50 [4],

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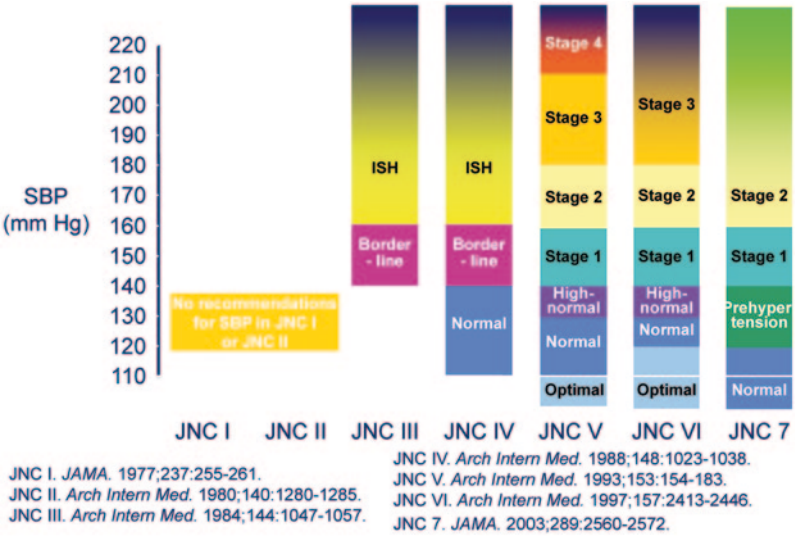


**Fig. 1.1** JNC overview of systolic BP. To simplify the classification of hypertension, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has reclassified stages 2 and 3 hypertension as outlined in JNC VI as "stage 2" hypertension. JNC 7 also introduces a new term, "prehypertension" to include individuals with BP measurements between 120 and 139 mmHg systolic BP among those requiring intervention. Background: Simplification of the classification of hypertension was one of the three main goals of the JNC 7 report. The other two goals were to include recently published clinical trials in the recommendations and to urgently provide updated hypertension guidelines. The inclusion of the new class "prehypertension" recognizes that the risk of vascular morbidity and mortality becomes evident at BP levels as low as 115/75 mmHg in adult patients

Fig. 1.1. The JNC 7 changed the BP classification to combine the previous stages yielding only two stages. This was based on the premise that there would be very little difference in treatment options if BP were 200 or 180 mmHg. Additionally, a new term, "prehypertension," was added. This term arose from focus groups of patients who were asked, "What term, if you were told by your doctor would stimulate you to ask him for treatment advice." From among the terms listed, the group, to the exclusion of terms such as borderline, high normal, and others, unanimously chose prehypertension. Prehypertension defined as an SBP reading of 120–139 mmHg now encompassed all the previous terms used for this group. It extended down to a systolic of 120 mmHg based on the most recent data published just before the JNC 7 was released indicating that risk starts at an SBP of 115 mmHg [5]. This extension below 130 mmHg as well as the premise for initial use of combination therapy was derived from Lewington et al. who showed cardiovascular mortality risk doubles with each rise in BP of 20/10 mmHg starting at 115/75 mmHg [5].

Given a history of rigorous review of each of the JNCs by acknowledged experts in the field and further review by more than 45 different groups, all involved in hypertension including the American Society of Hypertension, American Society of

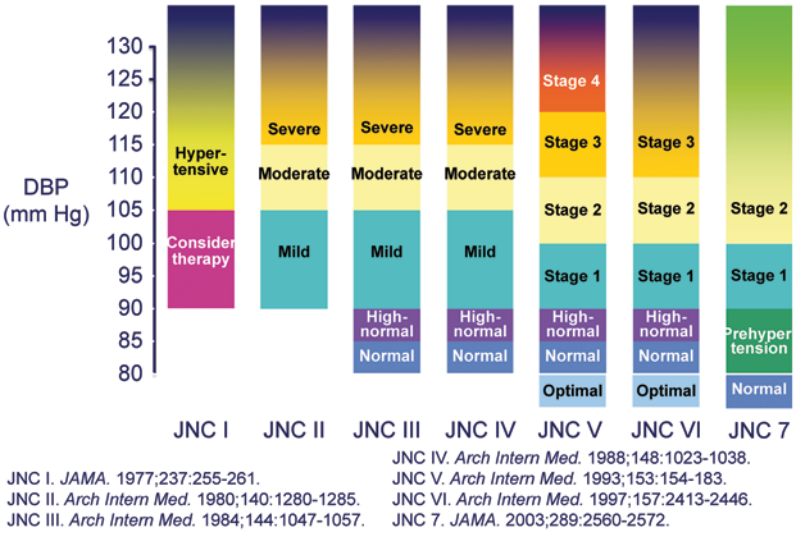


**Fig. 1.2** JNC overview of diastolic BP. To simplify the classification of hypertension, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has reclassified stages 2 and 3 hypertension as outlined in JNC VI as "stage 2" hypertension. JNC 7 also introduces a new term "prehypertension" to include individuals with BP measurements between 80 and 90 mmHg diastolic BP among those requiring intervention. Background: Simplification of the classification of hypertension was one of the three main goals of the JNC 7 report. The other two goals were to include recently published clinical trials in the recommendations and to urgently provide updated hypertension guidelines. The inclusion of the new class "prehypertension" recognizes that the risk of vascular morbidity and mortality becomes evident at BP levels as low as 115/75 mmHg in adult patients

Nephrology, and AHA, one has to ask why the process changed in 2007. This was the year, 2007, the next JNC committee was to assemble and develop what would have been JNC 8. The answer is twofold: one is a lack of funds to carry out the process as before and second there was a ground swell of concern initiated by the AHA report that of all their consensus reports only 9% had level 1 quality evidence with the majority of other guidelines being expert opinion [6]. This coupled with a political climate of concern regarding the influence of drug companies on the guidelines, based on little evidence, changed the entire process. The new process mirrors the National Institute for Health and Care Excellence (NICE) guidelines in the UK [7]. The evidence-based grading system used in JNC 8 is shown in Fig. 1.3 [8].

Upon reviewing the JNC guidelines, certain questions arise. First, were the previous JNC reports not evidence-based? Why the format change and what is it changing into? Should evidence-based medicine be the only way to practice or is it just the minimum standard that everyone should achieve? It is clear that not all aspects of hypertension have a good evidence base but clinicians are faced with patients daily that demand answers that are not always evidence-based but also require clinical judgment. This is true regardless of outcomes since the trials are only as


**Fig. 1.3** NHLBI evidence quality rating and recommendation strength JNC 2013

good as the inclusion criteria they employ to recruit patients. Hence, there are major limitations as well to evidence-based approaches.

JNC 7 created an algorithm for the treatment of hypertension [1]. This started with lifestyle modifications for all patients. If the BP was not at goal after this (defined as < 140/90 mmHg and < 130/80 mmHg for those with diabetes or kidney disease), then medical therapy would be needed. The choice of medical therapy depends on whether there are compelling indications for a specific drug, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or beta-blockers. In the absence of compelling indications, the severity of BP guided the decision as to initial mono- or single-pill combination therapy. In stage 1 hypertension, defined as SBP of 140–159 mmHg or diastolic BP (DBP) of 90–99 mmHg, thiazide-like diuretics were suggested as initial agents for most patients. In stage 2 hypertension, defined as SBP > 160/100 mmHg, a two-drug combination was recommended, usually a thiazide-type diuretic in addition to a blocker of the renin–angiotensin system (RAS) [1]. If BP remains uncontrolled despite these treatments, then the doses need to be increased or additional drugs added until the goal BP is achieved. If adding a third or fourth drug fails to achieve the BP goal, a board-certified hypertension specialist should be consulted.

The JNC 7 was helpful in that it gave compelling indications classes of drugs to be used for BP control based on the best available randomized placebo controlled trials [1]. It summarized data for BP management in a variety of concomitant conditions, such as heart failure post myocardial infarction (MI), chronic kidney disease, stroke, and diabetes. It also provided guidance on the delayed development or prevention of hypertension based on evidence from trials.

Given this background in 2008, the NHLBI developed new directions for cardiovascular prevention guideline development that would encompass all future guidelines. In effect, they are starting over with an evidence-based process performed by nonclinician epidemiologists/statisticians who would dispassionately review the data and then provide guidance for grading by the committee. The updated clinical recommendations on BP and cholesterol control and obesity used this process of systematic review of the literature based on selecting studies meeting specific criteria and then grading the evidence and providing recommendations.

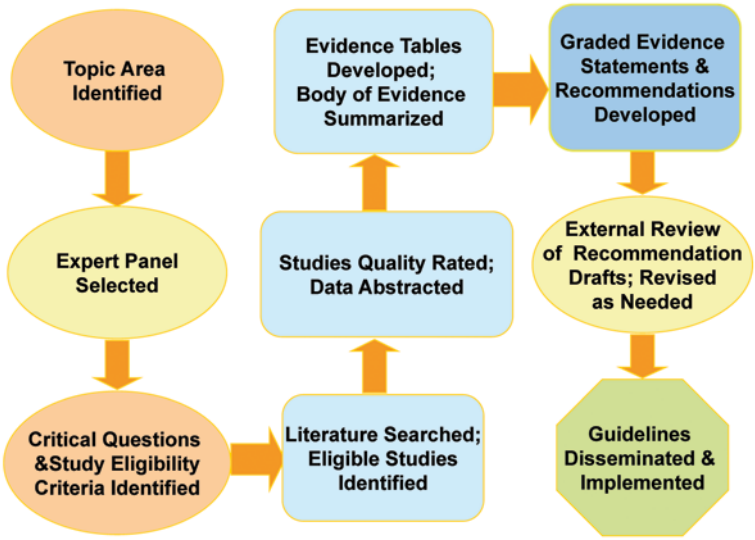


**Fig. 1.4** NHLBI systematic review and guideline development process. Here, we see the series of steps for the systematic reviews and guidelines development—from identification of the topic area to dissemination of the final guidelines

They recommend standardizing and coordinating approaches to develop consistent recommendations for lifestyle and risk assessment. After each of these guidelines is completed, which is now the case for all three guidelines as of March 2013, an integrative fourth guideline for clinicians is planned for release within the next 2 years.

The NHLBI recommends a series of steps, from identification of the topic area to the dissemination of the final guidelines, Fig. 1.4. Briefly, after a topic area is identified, an expert panel is selected which asks critical questions and studies eligibility criteria. The literature is then searched with eligible studies identified then selected based on their quality. Evidence tables are developed, the body of evidence summarized, and graded statements and recommendations are developed. These are subject to an external review including by government officials, i.e., Centers for Medicare and Medicaid services (CMS) and revisions are made. The guidelines are then disseminated and implemented.

JNC 8 was initially supposed to address five key questions. Unfortunately, there was only enough time and money to address three questions. The three questions are: (a) Among adults, does treatment with antihypertensive pharmacological therapy to a specific BP goal lead to improvements in health outcomes? (*How low should you go?*) (b) Among adults with hypertension, does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes? (*When to initiate drug treatment?*) (c) In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes? (*How do we get there?*)

To address these questions, studies from randomized controlled trials done after 1966 with at least a 1-year follow-up and a minimum of 100 patients were included [8]. The review found 56 trials met the criteria for determining specific BP goals, 26 to determine when to initiate treatment, and 66 for determining the choice of treatment.

The question of what is the goal BP needed to improve health outcomes has already been answered by two already published guidelines. The American Diabetes Association notes < 140/80 mmHg for those with diabetes [9] and the Kidney Disease Improving Global Outcomes (KDIGO) and Kidney Dialysis Outcome Quality Improvement (KDOQI) guidelines note < 140/90 mmHg for those with chronic kidney disease [10]. The goal for the elderly of < 150/80 mmHg was proposed by the AHA as well [11]. Although after public review, the goal became < 140/90 mmHg, it remains acceptable if between 140 and 145 mmHg. The JNC 8 does not differ markedly from these results as members of JNC 8 also served on these committees including an author of this chapter.

Multiple post-hoc analyses and one prospective trial support the goal BP put forth for high-risk patients and those with diabetes. A post-hoc analysis of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) noted that the composite outcome of cardiovascular risk, MI, stroke, or hospitalization for congestive heart failure, achieved a nadir at an SBP of 130 mmHg [12]. Post-hoc analyses of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial also demonstrate similar benefits for SBP levels down to 130 mmHg but risk increased as levels went below this nadir [13]. Finally, post-hoc analysis of the diabetes cohort of the International Verapamil SR-Trandolapril Study (INVEST) trial ($N > 7000$) demonstrated that those with an SBP of 130–140 mmHg had fewer cardiovascular events than those > 140 mmHg [14]. However, in those with a BP < 130 mmHg, no additional benefit on mortality was noted. In all these trials, however, stroke risk continued to decline with decreasing SBP without a similar nadir. This suggests that there is an increased risk of cardiovascular events except stroke in patients with extensive vascular disease when the BP is decreased below a critical level [13–15].

The only randomized trial that evaluated BP goal in diabetes was the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. It was found that a BP target of < 120 versus < 140 mmHg did not reduce the rate of a composite cardiovascular outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes (primary outcome annual rate of 1.87 % versus 2.09 %, respectively, $P = 0.20$, confidence interval (CI) 0.73–1.06) [15].

There are three randomized control trials involving 2272 participants with advanced stage chronic kidney disease and proteinuria. All three of these trials randomized BP to either 125/75 mmHg or around 140/90 mmHg. These trials were the Modification of Diet in Renal Disease (MDRD) [16], African American Study of Kidney Disease, Hypertension (AASK) [17], and Ramipril Efficacy in Nephropathy (REIN-2) studies [18]. All of these trials failed to show any clear difference in kidney disease progression in spite of achieving clear separation for at least 3 years.

These trials were all in nondiabetic patients that had a 2–4-year follow-up. Despite its prevalence, however, there have been no randomized controlled trials for BP goals among those with diabetic nephropathy.

In addition to these trials, the Kidney Early Evaluation Program (KEEP) evaluated the association between achieved levels of SBP and DBP and progression to ESRD in more than 16,000 people over an average of 2.8 years [19]. In this study, the risk of ESRD was the same in those with SBP of 130–139 mmHg as compared to those with SBP less than 130 mmHg. However, it is the first study to document that a reduced DBP below 60 mmHg is associated with a higher risk of progression to ESRD [19]. The risk of progression was higher among persons with SBP of 140–149 mmHg, with the rate doubling in those with SBP > 150 mmHg. As for DBP, the study showed that the rates of ESRD were highest among patient with levels of 90 mmHg or higher.

The question of initial therapy for treating hypertension has become clear from a meta-analysis of all antihypertensive agents showing no advantage to any specific class [20]. Thus, from the data available, one could say for patients who are elderly, now referred to by the JNC 8 expert panel as "older adults," either a calcium antagonist or thiazide-like diuretic, i.e., chlorthalidone or indapamide are appropriate first-line agents, a statement that also holds in African-American patients [8]. Diabetes patients can start with a blocker of the RAS or a thiazide-like diuretic, a statement that also holds for people with kidney disease.

Initial combinations for most patients have little data other than the ACCOMPLISH which supports initial use of single-pill combination therapy, and given the JNC 8 is evidence-based, it supports such an approach although there is only one outcome trial and hence, it did not give it a strong recommendation. Preferred combinations with evidence include RAS blockers with thiazide, thiazide-like diuretics, or calcium blockers [8]. This is also consistent with American Society of Hypertension Consensus Report on combination therapy [21]. Beta-blockers are suggested only as an add-on therapy only if there is a compelling indication but not as first-line therapy. The choice of which combination to use should take into account compelling indications in particular patients. All guidelines have relinquished beta-blockers to fourth-line treatment of hypertension without cardiac disease except for the European guidelines [22].

Finally, if one reviews the baseline data of studies and clinical trials used to initiate BP-lowering therapy, it is clear that for most studies the BP is > 150 mmHg in almost all trials. Therefore, one could argue that since the goal for the general population is > 140/90 mmHg, BP-lowering therapy should be initiated until BP with lifestyle modifications should not be started until the level is > 140/90 mmHg on repeated occasions. In older adults, if the goal is < 150/90 mmHg, then, likewise, BP-lowering therapy should not be started until BP is > 150/90 mmHg. It remains to be seen if the JNC 8 will adhere to this goal based on the evidence [8].

The issue of BP goal in older adults has been contested by a subgroup of the JNC 8 expert panel. Although there was almost unanimous agreement on nearly all recommendations, a minority of the panel (the authors of this commentary) disagreed with the recommendation to increase the target SBP from 140 to 150 mmHg in

persons aged 60 years or older without diabetes mellitus or chronic kidney disease [23]. This subgroup argues that the 2014 guideline panel failed to identify evidence of differential benefits or harms of treatment using an SBP goal of 140 mmHg with an age threshold of 60 years. They noted that while there is little randomized controlled trial evidence of risk or benefit in treating persons younger than 60 years to <150 mmHg, there are randomized trials in older adults showing a benefit in post-hoc analyses for those who could achieve an SBP 140–145 mmHg [23]. This is consistent with the guidance offered by the AHA guidelines in 2011 [11].

There are a number of questions not addressed by JNC 8. These questions include: (a) Should ambulatory blood pressure monitoring (ABPM) be used for initial assessment of HTN? (b) What is the role of central arterial pressure in the context of goal BP? (c) Should home BP monitoring be mandated for all patients to optimize control? and (d) Update on resistant hypertension. These questions while important could not be answered due to time constraints and financial concerns. A large evidence base does support the use of these modalities and included in other guidelines [7, 24].

In conclusion, the JNC 8 should state that the BP goal for all patients should be <140/90 mmHg. If a patient's BP is >20/10 mmHg above the goal, control can be achieved with single-pill combinations of RAS blockers with calcium channel blockers or thiazide diuretics as initial medications. Finally, a publication in June 2013 clearly states that NHLBI will no longer be in the "guideline" business. They will serve as the data analysis center and oversee this process but have appealed to the AHA and the American College of Cardiology Foundation to have representatives come together and produce guidelines from the database that currently has been generated [21]. This is a major change and is unclear how future guidelines will be developed, but JNC as we knew it died after JNC 7.

In conclusion, the JNC 8 states that the BP goal for all patients should be <140/90 mmHg, except for older adults where the goal is <150/90 mmHg (JAMES). It appears the panel felt that the strength of the evidence to support a goal of <140/90 mmHg, however, was not strong enough to give it a grade of A or B, and hence, relinquished it to E-expert opinion. In fact, most of the current practice of medicine surrounding BP received a grade of expert opinion. If a patient's BP is >20/10 mmHg above the goal, control can be achieved with single-pill combinations of RAS blockers with calcium channel blockers or thiazide diuretics as initial medications.

The reader should be aware that if they do not like the grades given to some of these guidelines, the problem lies with the amount of evidence and not the panels' interpretation of the evidence. This is evidenced by the disagreement over the goal for older adults where post-hoc analyses were used to support an argument, which violates the premise of evidence based in the true sense. In keeping with the theme of evidence-based medicine, however, if evidence does not exist, common sense is not a substitute. Fortunately, it is a substitute in clinical medicine where good judgment often trumps a lack of evidence.

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