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Current Opinion in Pharmacology

Hypertension update, JNC8 and beyond

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Hypertension is the most preventable major risk factor for cardiovascular morbidity and mortality. The etiology of elevated blood pressure is a complex process involving the interaction of genetics, demographics, comorbid disorders, and environmental influences. Effective hypertensive therapy has been shown to reduce cardiovascular morbidity and mortality. JNC reports have served as a valuable source of guidelines, and JNC 8 is the most recently updated guideline for the prevention, diagnosis, and treatment of hypertension. It includes modification of JNC 7 regarding the threshold for therapy, therapeutic goals, and medications or combinations of medications that differ in benefits for certain patient populations. However, JNC 8 generated a significant degree of controversy. This review will evaluate JNC 7 versus JNC 8 guidelines and discuss the most controversial aspects of JNC 8 through a therapeutic perspective. This review will also discuss the most recently available evidence that has an impact on the JNC 8 recommendations. Despite the nuance of clinical guidelines, blood pressure control rates remains suboptimal. We will explore potential reasons and solutions for this dilemma including pharmacogenomics, novel risk-stratification strategies, lifestyle interventions, and integrative care.

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Current Opinion in Pharmacology 2017, **33**:41–46

This review comes from a themed issue on **Cardiovascular and renal**

Edited by **David A Taylor**, **Robert J Theobald**, **Abdel A Abdel-Rahman** and **Ethan J Anderson**

http://dx.doi.org/10.1016/j.coph.2017.03.004

Perspective

The historical perspective of the pathophysiologic state we know as hypertension, its consequences to the population and its treatment have been well reviewed [1–3]. In the medical world of 1930, elevated blood pressure was thought to be a natural consequence of the atherosclerotic process. This led to the term 'essential hypertension'. An infamous quote states, "There is some truth in the saying that the greatest danger to a man with high blood pressure lies in its discovery because some fool is certain to try to reduce it" [4]. Failure to recognize the paramount risk associated with hypertension significantly impeded the development of antihypertensive agents.

The development of the present day perspective of the therapy of hypertension

The modern era of antihypertensive therapy was ushered in by the introduction of thiazide diuretics (TD) [5]. The next major advancement was the introduction of beta-adrenergic receptor blockers (BB) [1–3]. The major drug classes and their sites of action are provided in Figure 1. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) published the first clinical guidelines (JNC 1) for the treatment of hypertension in 1977 [6]. JNC 1 was eight pages and described 24 drugs available for use. JNC 7, published in 2003, (briefly summarized in Table 1) was 108 pages and described over 120 available drugs [7]. This reflects the significant increase in knowledge of hypertension, therapeutic options, and impact of comorbidities. JNC 7 recommendations were associated with achievement of lower rates of uncontrolled hypertension than previous JNC reports. JNC 8 aims to further improve recommendations and address unanswered questions in JNC 7 as outlined below [8].

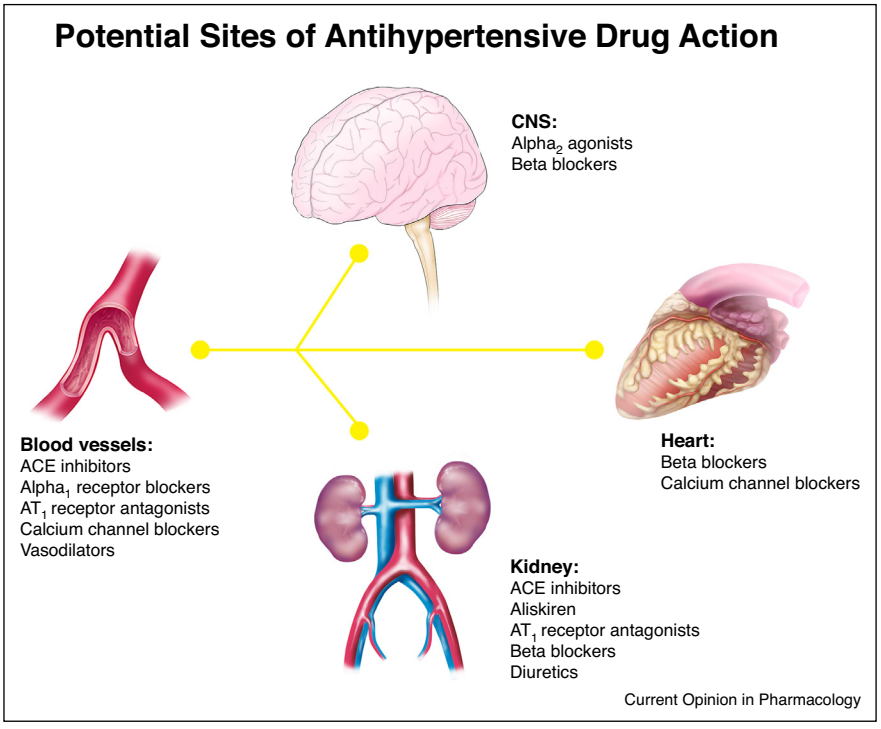
JNC8 addressed the following questions

- Does therapy initiation at a specific threshold improve health outcomes?
- Does treatment to a specific goal range lead to improved health outcomes?
- Do various antihypertensives differ in benefits, harms, and specific health outcomes?

The resultant JNC 8 guidelines were based on analysis of several randomized control trials that addressed these questions and are summarized in Table 2 [see Ref. [9•] for a brief review]. Several changes were made to the JNC 7 recommendations including:

- Treatment in patients with diabetes or chronic kidney disease should begin at 140/90 mmHg (JNC 7 recommended treatment at 130/80 mmHg) making treatment recommendations for individuals <60 years more straightforward by setting a single treatment level regardless of comorbidities.

Figure 1



An illustration of the physiologic effectors of blood pressure and the sites at which antihypertensive drugs can act.

- Recommended initial therapy comes from one of four drug classes. TD, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (AT1 blocker). BB are no longer recommended as first-line agents.
- In the black population with uncomplicated hypertension or hypertension with diabetes, CCB or TD are recommended as first-line treatments. In nonblack or black hypertensives with chronic kidney disease, an ACE-I or AT1-blocker should be the initial treatment.
- In patients >60 years, treatment begins at >150/90 mmHg.

JNC 8 controversies

The most controversial recommendation was to change the threshold of treatment initiation for patients >60 years from 140/90 to 150/90 mmHg. JNC 8 cites a 2009 Cochrane Review [10] that demonstrated a risk-benefit actuarial analysis and concluded that there was insufficient evidence to support initiation of therapy <150/90 mmHg in elderly patients. However, five members of JNC 8 voted against this recommendation and published a separate opinion [11] in which, they provided evidence that when compared to 150/90 mmHg, initiation

Table 1

Summary of JNC7 recommendations

Definition	SBP, mmHg	DBP, mmHg	Treatment
Normal	<120	and <80	None
Prehypertensive	120–139	or 80–89	[a]None, unless compelling conditions
Stage 1 Hypertension	140–159	or 90–99	[b]TD, BB, CCB, ACE-I, AT1 blocker
Stage2 Hypertension	>160	or >100	[b]Two drug combination of TD, BB, CCB, ACE-I, AT1 blocker

TD = thiazide diuretic; BB = beta-blocker; CCB = calcium channel blocker; ACE-I = angiotensin converting enzyme inhibitor; AT1 blocker = angiotensin 1 receptor blocker.
Adapted from Ref. [7].
[a] Compelling conditions = heart failure, post MI, diabetes, coronary artery disease, chronic kidney disease, high stroke potential. These are co-existing conditions that alter the therapeutic choice and promote individualized patient care.
[b] The presence of compelling conditions could alter therapy.

Table 2

Summary of JNC8 recommendations

Hypertensive goals per cohort

	General population		With diabetes	With chronic kidney disease
Age (years)	≥60	18–59	≥18	≥18
Blood pressure goal (mm Hg)	<150/90	<140/90	<140/90	<140/90

Initial antihypertensive drug to use

	General population		With diabetes		With chronic kidney disease	
Race	Non Black	Black	Non Black	Black	Non Black	Black
	ACE-I ARB CCB TD	CCB TD	ACE-I ARB CCB TD	CCB TD	ACE-I ARB	ACE-I ARB

TD = thiazide diuretic; CCB = calcium channel blocker; ACE-I = angiotensin converting enzyme inhibitor; AT1 blocker = angiotensin 1?receptor blocker.
Adapted from Ref. [9•].

of therapy at 140/90 mmHg has more beneficial than adverse potential in the elderly [11,12]. In particular, a recent meta-analysis of four 'high-quality' trials in over 10,000 elderly hypertensives demonstrated that reduction of systolic blood pressure to <140 mmHg decreased cardiovascular mortality, stroke, myocardial infarction and heart failure [13••]. Similarly, the SHEP [14] and HYVET [15] trials demonstrated that reducing systolic blood pressure to <140 mmHg in the elderly provided substantial benefit without unnecessary risks. Furthermore, the landmark SPRINT trial, showed that the elderly often suffer from isolated systolic hypertension and that a 5-year mean systolic blood pressure control of 121.5 mmHg, compared to 134.6 mmHg, led to a 25% decrease in cardiovascular outcomes and 27% decrease in all-cause mortality [16••]. While aggressive blood pressure lowering in the elderly to <120 mmHg systolic could also lead to an increased risk of stroke through the J-Curve phenomenon [17•], this may be prevented through lower antihypertensive doses and avoidance of two-drug strategies during treatment initiation in elderly patients [18].

The Association of Black Cardiologists and the Working Group on Women's Cardiovascular Health criticized the threshold change in the elderly for having a disproportionately adverse effect on African Americans and women [19••]. In fact, African Americans have one of the highest rates of hypertension, have an increased risk of organ damage, more risk factors, and lower therapeutic control rates [19••]. However, no racial considerations were discussed in light of the threshold change. Overall, among all Americans with hypertension, half are >60 years [20•]. The JNC 8 change to a treatment threshold of 150/90 mmHg in this population would remove 5.8 million treatment-eligible elderly patients from intervention and active monitoring [21].

Another contentious issue of JNC 8 was the removal of BB as first-line for uncomplicated hypertension in all patient populations. JNC 8 cited this change after a series of meta-analyses demonstrated an increased the risk of stroke and decreased efficacy with BB in elderly patients [22,23]. However, a meta-analysis showed that in patients <60 years, BB decreased stroke and mortality risk [24••]. Additionally, many of the analyses that led to the change were carried out with atenolol, with the extrapolation that the stroke liability represents a BB class effect [24••,25•]. However, evidence suggests that BB should not be considered as a monolithic class [25•,26]. There is significant diversity in the pharmacologic actions of BB including receptor selectivity, degree of lipophilicity, degree of sympathomimetic activity and the extent of novel actions unrelated to beta-blockade [26–28,29•,30,31]. For example, both carvedilol and nebivolol have a number of unique actions (antioxidant effects, decreasing free radicals and vasodilating actions) unrelated to beta-blockade [26,29•,31]. While BB may not be appropriate to treat uncomplicated hypertension in patients >60 years, it may be extreme to eliminate them all together as first-line agents in younger patients. Indeed, recommendations from Canada [32] indicate BB can be effectively used first-line to treat uncomplicated hypertension in patients <60 years.

Beyond JNC 8-toward personalized medicine

Between JNC 1 and JNC 8, dramatic improvements were made in our knowledge of hypertension and effective treatment methods. 2016 AHA statistics support this statement, but despite these improvements, the

percentage of patients being adequately controlled is still around 50% [20•]. Of the American population with hypertension, approximately 80% are diagnosed and 70% are receiving treatment [20•,33•]. One reason for the uncontrolled and untreated rates is that JNC guidelines are algorithms designed to treat large populations of patients presenting with similar characteristics. We cannot predict with certainty if a given antihypertensive is the correct choice for a specific patient. Pharmacogenomics, the study of how the genomic make up of a patient affects drug response, offers a way to individualize therapy by selecting a drug most likely to be effective while at the same time reducing adverse effects [34••].

A complete discussion of the pharmacogenomics of hypertension is beyond the scope of this review. However, numerous candidate gene and genome wide association studies (GWAS) have been carried out examining the gene sequences associated with the blood pressure response to BB, TD, ACE-I, AT1- blockers and CCBs [35,36•]. The strongest data has been obtained with BB and TD [35,36•,37,38•,39]. For example, polymorphs in the gene encoding the $beta_1$ - adrenergic receptor (ADRB 1) and a protein involved with renal epithelial sodium transport (NEDD4L) have been shown to be associated with the antihypertensive response to BB and TD, respectively [35,36•]. GWAS have also specifically identified chromosomal regions with association to therapeutic and adverse responses to TD [37,38•,39]. These studies offer the possibility that BB and TD effectiveness may be genomically predicted in the future. However, associations have not been shown in all studies [35,36•,40,41•]. GWAS and candidate gene identification is still in the nascent state. Currently, we can only say a gene, a single nucleotide polymorph (SNP), or group of SNPs are associated with hypertension or the response to drugs [35,36•,40,41•,42•]. For example, a recent study identified at least 20 SNPs that were associated with the responses to amlodipine, bisoprolol, hydrochlorthiazide and losartan [43]. None of these SNPs were common to more than one drug indicating that the genomic determinants for blood pressure reduction are specific. Furthermore, none of the 80 gene loci mentioned were common to the genes associated with hypertension [41•,43]. A recently completed GWAS concluded that there are no common variant alleles that modify the effect of common antihypertensive drugs on the likelihood of myocardial infarction, stroke or sudden cardiac death [44••]. A critical question about this information is: What is 'actionable' in terms of hypertensive therapy? While provocative, the data are not yet sufficient to direct prescribing practices. It is hoped that GWAS will provide the foundation for precision medicine in the future.

Future directions

The JNC guidelines focus on blood pressure as the only variable. A small fraction of patients present with elevated blood pressure alone. Most present with multiple comorbidities. Elevated blood pressure and comorbidities could synergize to produce a greater risk than any one factor alone. Another approach could be modeled on the ACC/AHA guidelines for the reduction of atherosclerotic cardiovascular disease [45] in which a risk calculation based on multiple factors is made to determine and guide the intensity of statin therapy. The European Societies of Cardiology and Hypertension [46] have also suggested a risk stratification scheme for the treatment of hypertension. Patients are rated from low to very high risk based not only on the level of blood pressure, but also a number of other risk factors such as smoking, dyslipidemias, diabetes, chronic kidney disease, obesity, ischemic heart disease. The intensity of treatment is then guided not only by the blood pressure but also by the presence of additional risk factors. For example, a patient with a systolic blood pressure >140/90 mmHg would initially be treated with only lifestyle modifications. A patient with the same blood pressure but multiple additional risk factors would have drug therapy along with lifestyle modification.

This paradigm shift represents forms of integrative and personalized patient care. Today, we realize the limitations of drug therapy alone. Antihypertensive treatment must incorporate health education, nutrition, exercise, ease of compliance, and patient engagement in care. In order to encourage these practices, medical payment models should change from pay-per-service to population management value-based systems. One success story from Kaiser Permanente in Northern California demonstrates how using these methods improved hypertensive control from 44% to 90% [47•]. Personalized pharmacogenomics may also improve antihypertensive treatment in the future. This presents great opportunity for further advancement in the field. The primary care medical home offers an additional way for a patient-centered approach to blood pressure control. In this model the patient's health care needs are addressed by a team of health care professionals. The team could include a physician, nurse practitioners, physician assistants, nurses and pharmacists. The goal is to provide comprehensive, patient-centered coordinated care, accessibility to service with quality control and improved patient safety.

Conflict of interest statement

Nothing declared.

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