Hypertension update, JNC8 and beyond
Tara Shrut1, David W Rudy2 and Michael T Piascik3

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 remain 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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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.
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>
<thead>
<tr>
<th>Definition</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
<td>None</td>
</tr>
<tr>
<td>Prehypertensive</td>
<td>120–139</td>
<td>or 80–89</td>
<td>None, unless compelling conditions</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or 90–99</td>
<td>TD, BB, CCB, ACE-I, AT1 blocker</td>
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<tr>
<td>Stage2 Hypertension</td>
<td>&gt;160</td>
<td>or &gt;100</td>
<td>Two drug combination of TD, BB, CCB, ACE-I, AT1 blocker</td>
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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.
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

<table>
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<th>Table 2</th>
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<tr>
<td>Summary of JNC8 recommendations</td>
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<td>Hypertensive goals per cohort</td>
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<thead>
<tr>
<th>Age (years)</th>
<th>General population</th>
<th>With diabetes</th>
<th>With chronic kidney disease</th>
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<tbody>
<tr>
<td>≥60</td>
<td>&lt;18</td>
<td>&lt;18</td>
<td></td>
</tr>
<tr>
<td>Blood pressure goal (mm Hg)</td>
<td>&lt;150/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
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<tr>
<th>Initial antihypertensive drug to use</th>
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<tbody>
<tr>
<td>Race</td>
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<tr>
<td>Race</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Non Black</td>
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<tr>
<td>ACE-I</td>
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<tr>
<td>ARB</td>
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<tr>
<td>CCB</td>
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<tr>
<td>TD = thiazide diuretic; CCB = calcium channel blocker; ACE-I = angiotensin converting enzyme inhibitor; AT1 blocker = angiotensin 1?receptor blocker. Adapted from Ref. [9].</td>
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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 guide-
lines 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. Pharmacoge-
nomics, 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. How-
ever, numerous candidate gene and genome wide associ-
ation 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 beta1 - 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, respect-
ively [35,36∗]. GWAS have also specifically iden-
tified chromosomal regions with association to therapeu-
tic 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 amloidipine, bisoprolol, hydrochlorthia-
zide and losartan [43]. None of these SNPs were common
to more than one drug indicating that the genomic deter-
ninants 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 comor-
bidity. 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 cardio-
vacular 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 hyperten-
sion. 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 limita-
tions 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 dem-
strates how using these methods improved hypertensive
control from 44% to 90% [47∗]. Personalized pharmacoge-
nomics 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 pharma-
cists. 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.

References and recommended reading
Papers of particular interest, published within the period of review,
have been highlighted as:
• of special interest
•• of outstanding interest

This page appears to be a scientific article discussing topics related to hypertension, cardiovascular disease, and treatment strategies. The text is a dense collection of references and may not be easily readable without proper context or previous knowledge of the subject matter. The references and sections discussed include:


17. Ng Y-Y, Wang J-G: The J-curve phenomenon in hypertension. Pulse 2016, 4:49-50. This article discusses the emergence of the J-Curve Phenomenon in which a risk of reoccurring stroke may be related to low systolic blood pressures. The trials evaluated indicate inconclusive evidence and suggested comparing blood pressure targets of 130/80 mmHg and 140/90 mmHg.


This article demonstrated the association of Black Cardiologists and the Working Group on Women’s Cardiovascular Health strong rejection of JNC 8 guidelines, attributed in part to the guideline’s disproportionate affect on hypertensive African Americans over the age of 60.


This report demonstrates the most up-to-date cardiovascular statistics, including prevalence of heart disease and stroke in the United States. The report also emphasizes that the American Heart Association prioritizes promotion of healthy lifestyle behaviors for the prevention and treatment of cardiovascular disease.


This review analyzed 123 studies with 613,815 participants and demonstrated that relative risk reductions in cardiovascular disease occurs in proportion to goal blood pressure reductions, especially in patients who had complicated hypertension. Methods generalized Beta-Blockers as a monolithic class. Conclusions recommended intensive systolic blood pressure control to <130 mmHg.


This review demonstrated that Beta-Blockers (BB) for initial antihypertensive therapy led to decreased cardiovascular disease with little to no effect on improved mortality. These effects were less than that of other antihypertensive drugs. Study conclusions emphasized that data on BB was generalized to atenolol, had high risk of bias, and that future studies should evaluate BB subtypes in different patient populations.


This review demonstrated the differential effects of beta-blockade in comparison with diuretics, angiotension-converting enzymes, and angiotension receptor blockers.


This communication discusses the latest statistics on hypertension focusing treatment efficacy, morbidity and mortality and health care costs.


This study explored the potential of personalized antihypertensive therapy and emphasizes that funding organizations, such as the National Institutes of Health and the Food and Drug Administration, have recently devoted significant funding resources to these endeavors.


This review explores the pharmacogenetics of response to antihypertensive therapy, and while additional research and validation are necessary at this time, current findings are encouraging for future personalized medicine implementation.


This review analyzed 6 clinical trials with 1739 Caucasian adults and identified three novel genomic loci associated with antihypertensive response to hydrochlorothiazide (GJA1, HSD3B1, and FOXA1). Results were cross-validated in African American cohorts treated with hydrochlorothiazide.


This review summarizes the most recent findings on pharmacogenetics of the most commonly used antihypertensive drugs in clinical practice.


This report evaluated pharmacogenomics candidate genes in relation to the treatment of resistance hypertension. Results identify SNPs that may affect antihypertensive responses to mineralocorticoid receptor antagonists and amiloride for resistance hypertension, but concludes that further research is necessary to better understand clinical significance.


This study evaluated four antihypertensive therapies with genomic interactions, exposures, and outcomes among meta-analyses. Although strong pharmacogenomic data were presented, no significant findings relating SNPs to cardiovascular outcomes or blood pressure response were found via GWAS studies.


This article evaluated methods used in a successful antihypertensive therapy initiative. Components of the program included a registrar of hypertensive patients, use of internally reviewed evidence-based hypertension guidelines, evaluation of quality performance scores in participation, additional patient visits with a medical assistant, and used of single-pill combination medications to improve compliance. An illustration of the physiologic effectors of blood pressure and the sites at which antihypertensive drugs can act.