2014 Hypertension Guidelines: The Debate Continues

The recommendations from panel members appointed to the Eighth Joint National Committee (JNC 8) for hypertension management were published in *JAMA* on December 18, 2013. Unlike prior JNCs, the 2014 hypertension guidelines were based solely on a systematic review of randomized clinical trials (RCTs) by a multidisciplinary panel. In contrast, JNC 7 developed guidelines using a nonsystematic literature review by an expert committee, which included a range of study designs and recommendations based on a consensus of 46 professional, voluntary, and federal organizations.

This departure in methodology from earlier JNCs has caused much debate in the medical community. For instance, the latest guidelines relax blood pressure goals for many patients based on RCT results. This means that some patients who were not at goal according to JNC 7 are now considered at goal, and that some clinicians who may have prescribed treatment based on past JNC goals are no longer advised to do so. Clinicians are concerned that the 2014 guidelines issued by the JNC 8 panel members will reduce or delay treatment for those at high cardiovascular risk, particularly those with multiple comorbidities—patients typically not included in RCT populations.

**Hypertension guidelines focus: answer the highest-priority questions**

The JNC 8 panel member recommendations were based on the panel’s 3 highest-ranked questions related to high BP management:

1. In adults with hypertension, does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes?
2. In adults with hypertension, does treatment with antihypertensive pharmacological therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

The 5 key trials were the Hypertension Detection and Follow-up Program (HDFP), the Hypertension-Stroke Cooperative Study Group (HSCSG), the Medical Research Council (MRC), the Australian National Blood Pressure Study (ANBP), and the VA Cooperative Study.

**Featured Contributor**

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As a clinician, researcher, and nurse educator at the Johns Hopkins University School of Nursing, Dr. Dennison Himmelfarb is committed to improving cardiovascular care for high-risk, underserved populations.
Taking a systems approach, engaging patients at the highest level, and utilizing teams including nurses, doctors, and pharmacists, as well as patients as partners, will help to provide the highest level of hypertension care.
The 2014 guidelines panel was unified on many issues, but there were differences regarding certain aspects of the recommendations. A subgroup of panel members published a post-guideline article that outlined their concerns around the recommendations, including:

- Higher SBP goal reduces treatment intensity for a population at high cardiovascular disease (CVD) risk
- Evidence supporting increased SBP target in those 60 years or older was insufficient and inconsistent with the 2014 guidelines
- Higher SBP goal in those 60 years and older may reverse the decades-long decline in CVD, particularly stroke mortality
- Other guideline groups reviewing similar evidence recommended SBP of 140 mm Hg or higher, particularly in those 80 years or younger

Additionally, major organizations such as the International Society of Hypertension (ISH) and American Society of Hypertension (ASH) have been quick to point out the differences between the 2 sets of guidelines. ISH and ASH have also published their own guidelines in the *Journal of Clinical Hypertension.* Of note, there are 3 clinicians who coauthored both sets of guidelines, further raising some questions about the best way forward in managing different types of patients with uncontrolled hypertension.

### Quick RefGuide: JNC 8 Panel Guidelines vs 2014 ISH/ASH Guidelines Statement

<table>
<thead>
<tr>
<th>JNC 8 Panel Hypertension Guidelines</th>
<th>ISH/ASH Hypertension Guidelines</th>
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</thead>
<tbody>
<tr>
<td>Evidence-based literature and recommendations from randomized clinical trials. No observational studies, systematic reviews, or meta-analyses</td>
<td>Based on expert opinion, experience, and clinical studies</td>
</tr>
<tr>
<td>Process of evidence review/recommendations and panel inclusion discussed first</td>
<td>Various aspects of hypertension (epidemiology, causes, evaluation, definition, classification, special issues, and diagnosis) discussed first</td>
</tr>
<tr>
<td>No special populations section; addressed in specific recommendations (4-8)</td>
<td>Includes “Special Issues With Black Patients” as a separate section</td>
</tr>
<tr>
<td>Specific treatment recommendations (1-9) based on patient demographic and comorbidities</td>
<td>Additional information on specific drug classes includes adverse events, nonpharmacologic therapy, and treatment-resistant hypertension</td>
</tr>
<tr>
<td>Start-treatment threshold of ≥150/90 mm Hg for patients 60 years and older</td>
<td>Start-treatment threshold of ≥150/90 mm Hg for patients 80 years and older; ≥140/90 mm Hg for others</td>
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<tr>
<td>Nonblack patients should be initiated on thiazide-type diuretic, ACEI, ARB, or CCB</td>
<td>Nonblack patients &lt;60 years of age should be initiated on an ACEI or ARB; those &gt;60 years should be initiated on a CCB or thiazide-type diuretic</td>
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<tr>
<td>Treatment strategy option includes initiating therapy with 2 drugs at the same time, either as 2 separate pills or as a single-pill combination in certain patients</td>
<td>In all patients with stage 2 hypertension (≥160/100 mm Hg), 2 drugs should be started (CCB or thiazide-type diuretic + ACEI or ARB)</td>
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<tr>
<td>Initial drug dose should be increased or a second drug added if BP goal is not reached within 1 month; add on and titrate a third drug if combination does not result in reaching BP goal</td>
<td>Initial drug dose should be increased or a second drug added if BP goal is not reached approximately 2 to 3 weeks after initiation; most patients should be effectively treated within 6-8 weeks on a multidrug regimen</td>
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<tr>
<td>Hypertensive (nonblack) patients who have diabetes should be initiated on a thiazide-type diuretic, CCB, ACEI, or ARB</td>
<td>Hypertensive (nonblack) patients with diabetes should be initiated on an ARB or ACEI, with a CCB or thiazide-type diuretic added on if necessary</td>
</tr>
<tr>
<td>All patients with hypertension and chronic kidney disease may receive an ARB or ACEI initially or as add-on therapy</td>
<td>All patients with hypertension and chronic kidney disease may receive an ARB or ACEI initially or as add-on therapy; ACEI may be a better choice as initial therapy in black patients with CCB or thiazide-type diuretic as add-on therapy</td>
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</tbody>
</table>
Meet Nick*—tough-to-treat hypertension and type 2 diabetes

Nick is a fun-loving 71-year-old retired accountant who looks forward to meeting up with his buddies for their bowling match every week. He tries to pay attention to his diet and keep up with his medication but sometimes forgets. His wife puts his medications out for him in the morning before she goes to work.

*Hypothetical patient.

Why is Nick’s hypertension tough to treat?

Nick has type 2 diabetes and is overweight—2 comorbidities that make BP goal more difficult to achieve. His SBP continues to be high despite 3 months of BENICAR HCT® 40/25 mg. Additionally, 2014 JNC 8 panel guidelines recommend that Nick’s BP goal be <140/90 mm Hg. He needs a different option to gain additional BP reduction. Considering he is somewhat forgetful with his medication regimen and has the added burden of his diabetes medications, it may be worth considering switching Nick’s therapy to EDARBYCLOR (azilsartan medoxomil/chlorthalidone) to help get him to his goal BP.

How EDARBYCLOR (azilsartan medoxomil and chlorthalidone) may help

- EDARBYCLOR is the only ARB fixed-dose combination with chlorthalidone for the treatment of hypertension to lower blood pressure
- Meets JNC 8 panel recommendation criteria as a combination therapy option using an ARB and thiazide-type diuretic

Significantly more patients with moderate-to-severe hypertension reached target BP with EDARBYCLOR 40/25 mg vs BENICAR HCT® 40/25 mg

Achievement of target SBP/DBP

<140/90 mm Hg at week 12

81.4% EDARBYCLOR 40/25 mg

74.6% BENICAR HCT 40/25 mg

*Target BP attainment was a secondary goal in the study.

EDARBYCLOR is an angiotensin II receptor blocker (ARB) and a thiazide-like diuretic combination product indicated for the treatment of hypertension to lower blood pressure.

WARNING: FETAL TOXICITY

See full Prescribing Information for complete boxed warning.

- When pregnancy is detected, discontinue EDARBYCLOR as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

For further information, please see Important Safety Information and the accompanying full Prescribing Information.
Important Safety Information for EDARBYCLOR

- EDARBYCLOR is contraindicated in patients with anuria.
- Do not coadminister aliskiren with EDARBYCLOR in patients with diabetes.
- Fetal Toxicity: Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, discontinue EDARBYCLOR as soon as possible. Thiazides cross the placental barrier and appear in cord blood and may be associated with adverse reactions, including fetal or neonatal jaundice and thrombocytopenia.

In patients with an activated renin-angiotensin-aldosterone system (RAAS), such as volume- and/or salt-depleted patients, EDARBYCLOR can cause excessive hypotension. Correct volume or salt depletion prior to administration of EDARBYCLOR.

- Monitor for worsening renal function in patients with renal impairment. In patients whose renal function may depend on the activity of the renin-angiotensin system, treatment with ACE inhibitors and ARBs has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death. In patients with renal artery stenosis, EDARBYCLOR may cause renal failure. In patients with renal disease, chlorthalidone may precipitate azotemia. Consider withholding or discontinuing EDARBYCLOR if progressive renal impairment becomes evident. Avoid use of aliskiren with EDARBYCLOR in patients with renal impairment (GFR <60 mL/min).

- Hypokalemia is a dose-dependent adverse reaction that may develop with chlorthalidone. Coadministration of digitalis may exacerbate the adverse effects of hypokalemia. EDARBYCLOR attenuates chlorthalidone-associated hypokalemia.

- Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone or other thiazide diuretics.

- Adverse Reactions (AEs):
  - AEs that occurred at an incidence of ≥2% of EDARBYCLOR-treated patients and greater than azilsartan medoxomil or chlorthalidone were dizziness (8.9%) and fatigue (2.0%).

- Incidence of consecutive elevations of creatinine (≥50% from baseline and >ULN) was 2% and were typically transient, or nonprogressive and reversible, and associated with large blood pressure reductions.
**Important Safety Information for EDARBYCLOR (cont)**

- **Drug Interactions:**
  - Renal clearance of lithium is reduced by diuretics, such as chlorthalidone, increasing the risk of lithium toxicity.
  - Monitor renal function periodically in patients receiving EDARBYCLOR and NSAIDs who are also elderly, volume-depleted (including those on diuretics), or who have compromised renal function, as deterioration of renal function, including possible acute renal failure, may result. These effects are usually reversible. NSAIDs may interfere with antihypertensive effect.
  - Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

**Indication and Usage**

EDARBYCLOR is an angiotensin II receptor blocker (ARB) and a thiazide-like diuretic combination product indicated for the treatment of hypertension to lower blood pressure. EDARBYCLOR may be used if a patient is not adequately controlled on monotherapy or as initial therapy if multiple drugs are needed to help achieve blood pressure goals. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. There are no controlled trials demonstrating risk reduction with EDARBYCLOR, but trials with chlorthalidone and at least one pharmacologically similar drug to azilsartan medoxomil have demonstrated such benefits.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals.

EDARBYCLOR may be used with other antihypertensive agents.

**For further information, please see accompanying Prescribing Information for EDARBYCLOR.**

**References:**