Clinical challenges in diagnosing and managing adult hypertension

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ABSTRACT

Although there is still no consensus on how to diagnose hypertension, opinion is moving toward incorporating out-of-office blood pressure measurements into the process. The SPRINT trial poses potential opportunities and challenges. Simplified antihypertensive drug regimens incorporating single pill combinations are very effective.

KEY POINTS

- Diagnosing hypertension continues to require a sufficient number of well-performed office blood pressure measurements for most patients.
- First-tier drug choices are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (but not both together), calcium channel blockers, and thiazide-type diuretics. Add-ons to achieve blood pressure targets should come from first-tier classes not used initially.
- Simple implementation principles can achieve high control rates across a fractured healthcare delivery landscape. Equitable care can reduce racial disparities in hypertension control.

Hypertension is a primary care specialty. Most of the 70,000,000 adult Americans with hypertension are cared for by primary care providers. Medications are readily available that achieve high control rates when used in combination. Primary care providers are uniquely positioned to lead team-oriented approaches to improve medication adherence and provide equitable care that addresses racial disparity in hypertension control.

This review focuses on some of the challenges that primary care providers face, including diagnosis of hypertension, medication options, controversy regarding the goal systolic blood pressure in the elderly, and population care strategies in our fractured healthcare system.

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USING OUT-OF-OFFICE AND AUTOMATED MEASUREMENTS FOR DIAGNOSIS

A systematic review performed for the US Preventive Services Task Force concluded that the evidence supports ambulatory monitoring to confirm blood pressure in the office in all but the most severe cases of office-based blood pressure elevation in order to avoid misdiagnosis and overtreatment.[1] Elevated ambulatory pressure is the best predictor of cardiovascular events in prospective cohort studies.[1] A new hypertension diagnostic algorithm for Canada[2] is similar to an earlier American Heart Association algorithm[3] in recommending diagnostic confirmation by out-of-office measures including home blood pressure, ambulatory pressure, or automated office blood pressures. With automated blood pressure measurement, the clinician or medical assistant initiates preprogrammed oscillometric devices to take sequential blood pressure measurements after the assistant leaves the examining room. Thresholds for the diagnosis of hypertension are[1,2]:

- Office measurements: ≥140/90 mm Hg
- Automated office measurements (mean): ≥135/85 mm Hg
- Home blood pressure measurements: ≥135/85 mm Hg
- Ambulatory monitoring (mean of daytime readings): ≥135/85 mm Hg
- Ambulatory monitoring (mean 24-hour reading): ≥130/80 mm Hg.

However, evidence supporting the use of ambulatory monitoring, home measurements, and automated office measurements has significant limitations. There

is no evidence from prospective randomized controlled trials that withholding treatment on the basis of these measurements when office blood pressures are elevated leads to cardiovascular outcomes equivalent to normotensive outcomes. Also, the Centers for Medicare and Medicaid Services do not reimburse for ambulatory blood pressure monitoring, which would lead to inconsistent implementation and more disparity in healthcare. Moreover, when ambulatory monitoring is used to diagnose hypertension, how to determine response to treatment has not been defined.

Table 1 summarizes recommendations for the use of out-of-office measurements to diagnose hypertension.[1–4]

System-wide efforts can reduce the need for out-of-office confirmation; these include improving competence in measuring office blood pressure through peer validator spot-checking in the normal workflow, performance feedback reporting of repeat measurements when the first is elevated, and extensive use of walk-in measurements to reduce the white-coat effect.[5,6] Two well-performed office measurements performed on each of two or three visits over at least a month will continue to be the diagnostic standard for most patients. Small errors in technique introduce inaccuracies in blood pressure readings, which, if falsely high, can lead to unnecessary treatment or, conversely, if falsely low can lead to inadequate treatment. **Table 2** lists several common measurement errors that need to be consistently avoided.[7–9]

Table 1. Diagnosis of hypertension

Seventh Joint National Committee (2003)[4]
Mean of two or more properly measured seated blood pressure readings of each of two or more office visits

US Preventive Services Task Force (proposed 2015)[1]
Ambulatory blood pressure monitoring to confirm high blood pressure, except when immediate therapy is necessary (grade A recommendation)

American Heart Association (2008)[3]
- Home blood pressure measurements if office blood pressure is ≥140/90 mm Hg
- Ambulatory monitoring if home blood pressure is 126–134/77–84 mm Hg

Canadian (2015)[2]
If office blood pressure is 140–179/90–109 mm Hg:
- Ambulatory monitor (preferred)
- Home blood pressure
- Office blood pressure on visits 2–5 (only if ambulatory monitoring and home blood pressure are unavailable)

Table 2. Common measurement errors that cause falsely high systolic readings[7-9]

Error	False elevation in systolic pressure (mm Hg)
Cuff too small	5–10
Unsupported arm	5–10
Patient talking	10
Patient actively listening	5
Back unsupported	5–10
Feet not on floor	5–10
Legs crossed	5–10
Full bladder	10
Forearm blood pressure	5–10

ANTIHYPERTENSIVE DRUG TREATMENT STRATEGIES

The Eighth Joint National Committee (JNC 8)[10] issued a strictly evidence-based guideline based on adequate randomized controlled trials comparing representative drugs of different antihypertensive classes with respect to hard cardiovascular outcomes to arrive at well-supported recommendations (**Table 3**). The three groups of agents with the greatest evidence to support their use are:

- Thiazide-type diuretics
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers
- Calcium channel blockers.

Beta-blockers did not make the first tier because the beta-blocker atenolol was found to be inferior to the angiotensin receptor blocker losartan in terms of the rate of the primary end point (death, myocardial infarction, or stroke) in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial,[11] and we lack hard end point evidence to support other beta-blockers. However, patients with coronary artery disease or heart failure have a compelling drug-specific indication for a beta-blocker outside of blood pressure reduction.

There is an important race-based difference in the initial antihypertensive drug treatment options based on the findings of the prespecified subgroup of more than 10,000 black patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[12] The thiazide-type diuretic chlorthalidone was more effective than the ACE inhibitor lisinopril in improving the rates of adverse cardiovascular and cerebro-

Table 3. Hypertension treatment strategies: JNC 8 recommendations[10]

Select one of the following drug classes Thiazide-type diuretic Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) Calcium channel blocker					
Select one of the following two-drug treatment strategies Start one drug, titrate to maximum dose, and then add a second drug from another class Start one drug and then add a second drug from another class before achieving maximum dose of the initial drug Begin with two drugs from different classes at the same time, either as two separate pills or as a single-drug combination					
Add a drug from a third class Maximize doses to achieve blood pressure control					
Consider race and comorbidities in initial drug selection					
General population		**With diabetes**		**With chronic kidney disease**	
Nonblack	**Black**	**Nonblack**	**Black**	**Nonblack**	**Black**
ACE inhibitor, ARB, calcium channel blocker, or thiazide-type diuretic	Calcium channel blocker or thiazide-type diuretic	ACE inhibitor, ARB, calcium channel blocker, or thiazide-type diuretic	Calcium channel blocker or thiazide-type diuretic	ACE inhibitor or ARB	ACE inhibitor or ARB

vascular outcomes, including stroke and heart failure, and the calcium channel blocker amlodipine was more effective than lisinopril in improving the rate of stroke. There have been no randomized controlled trials or prespecified subgroups in randomized controlled trials evaluating angiotensin receptor blockers in black patients. Therefore, thiazide-type diuretics and calcium channel blockers are the preferred initial options for reducing cardiovascular outcomes in the general black population. ACE inhibitors and angiotensin receptor blockers are preferred across all races for patients with chronic kidney disease to improve renal outcomes.[10] However, a strategy using initial combination therapy with an ACE inhibitor or an angiotensin receptor blocker together with a thiazide diuretic or calcium channel blocker does satisfy the evidence, improving both cardiovascular and renal outcomes in black patients with and without chronic kidney disease.

JNC 8 recommended thiazide-type diuretics as a class rather than specifically recommending chlorthalidone because confirmatory trials used thiazide-type diuretics other than chlorthalidone, such as hydrochlorothiazide. For example, whereas the ALLHAT trial found that chlorthalidone 12.5 or 25 mg was superior to the calcium channel blocker amlodipine in terms of reducing the incidence of heart failure, the International Nifedipine Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) similarly found that hydrochlorothiazide titrated up to 50 mg was superior to the calcium channel blocker nifedipine in reducing the incidence of heart failure.[13]

Dose as well as drug is important. Inadequately dosed hydrochlorothiazide (12.5–25 mg/day) in the Second Australian National Blood Pressure (ANBP2) and the Avoiding Cardiovascular Events through Combination Therapy in Patients with Systolic Hypertension (ACCOMPLISH) trials[14,15] did not fare as well as comparator agents. The hydrochlorothiazide dosage in these trials was decided on the basis of usual prescribing practices rather than strict examination of prior comparators. Common rationales for prescribing lower doses of diuretics are fear of renal failure in the elderly or drug-induced incident diabetes. However, analyses of ALLHAT patients did not reveal increased renal failure or worsened outcomes due to drug-related diabetes.[16,17] A supplement to the JNC 8 report, available online, provides a rationale for the target hydrochlorothiazide dose of 50 mg.[18]

ACE inhibitors and angiotensin receptor blockers should not be prescribed together to control hypertension in the general population, due to increased risk of acute renal failure.[19] However, a nonprogressive decrease in creatinine clearance of up to 30% at the beginning of ACE inhibitor or angiotensin receptor blocker therapy in patients who have chronic kidney disease can be viewed as a good sign, indicating that intraglomerular pressure has been reduced and the kidneys are better protected against structural damage.[20]

Intensifying therapy

While the first-tier antihypertensive drug classes have been identified by randomized controlled trials, most patients require drug intensification. In the absence of randomized controlled trials examining second-step options, the JNC 8 recommended adding a drug from another of the first-tier treatment classes, based on expert opinion. The preferred medication intensification strategies are:

- Maximizing the first medication before adding a second, as was done in the randomized controlled trials
- Adding a second medication before reaching the maximum dose of the first, recognizing dose plateau relationships
- Starting with two medication classes separately or as a fixed-dose combination, a strategy that enhances hypertension control in large populations.

At the conclusion of the process, three drug classes are maximized as needed to achieve the goal blood pressure (**Table 3**).

CONTROVERSY REGARDING GOAL SYSTOLIC PRESSURE IN THE ELDERLY

JNC 8 set a systolic blood pressure target of less than 150 mm Hg in patients 60 years and older without diabetes or chronic kidney disease. This target was based on results of the Systolic Hypertension in the Elderly Program (SHEP)[21] and the Systolic Hypertension in Europe (Syst-Eur) trial.[22] In SHEP,[21] the goal systolic pressure was individually tailored on the basis of the systolic pressure at study entry, and mean of the trial participants' goal systolic pressure was less than 148 mm Hg, compared with less than 150 mm Hg in Syst-Eur.[22] Participants in these two trials were representative of a broad spectrum of cardiovascular risk. In SHEP, 14% of the patients were black, compared with 12.6% in the US population, and both studies included patients with a history of myocardial infarction and stroke. In SHEP, 61% of the patients had a baseline electrocardiographic abnormality, and 30% of patients in Syst-Eur had a prior "cardiovascular complication." In these randomized controlled trials, stroke, the primary end point, was reduced by 32% and 31% respectively, and major cardiovascular events were reduced by 32% and 31%, respectively.[21,22]

The JNC 8 panel followed a process mandated by the National Heart, Lung, and Blood Institute that excluded "as-treated" or "achieved" blood pressure trials such as the Felodipine Event Reduction study (FEVER)[23] because of bias due to selection of patients of inherently low cardiovascular risk who were associated with lower achieved systolic pressures. Cochrane methodologists independently arrived at the same conclusion.[24] In fact, in the landmark African American Study of Kidney Disease and Hypertension (AASK), a post hoc analysis according to the blood pressure achieved indicated improved renal outcomes associated with lower achieved blood pressures—the opposite conclusion of the intention-to-treat blood pressure analysis.[25] Alternative viewpoints and guidelines recommending the older goal of less than 140/90 mm Hg for elderly patients rely on observational and post hoc data, which were excluded by the National Heart, Lung, and Blood Institute process.[26]

As this article is prepared for publication, a press release from the NHLBI announced that the Safety and Monitoring Committee of the Systolic Blood Pressure Intervention trial (SPRINT) stopped the study early because of fewer cardiovascular complications and lower mortality in the more intensely treated group.[27] SPRINT randomized more than 9300 patients age 50 years and older with at least one additional cardiovascular disease risk factor to an intensive treatment arm targeting goal systolic pressure less than 120 mm Hg vs a standard treatment arm targeting goal systolic pressure less than 140 mm Hg. Approximately 25% of patients were age 75 years and older. Preliminary data indicate reduction of the primary composite outcome of fatal and nonfatal cardiovascular disease events by 30% and a 25% reduction in overall mortality that was homogeneous across major prespecified subgroups including those above and below age 75 years. The intensive treatment protocol was based upon combination therapy with a thiazide-type diuretic and/or an ACE inhibitor or angiotensin receptor blocker (but not both) and/or a calcium channel blocker.[28]

Hypertension treatment guidelines need to be based upon the results of high value randomized clinical trials and the federally funded NHLBI sponsored SHEP, ALLHAT, Action to Control Cardiovascular Risk in Diabetes (ACCORD),[29] and SPRINT trials are noteworthy. Because the results of SPRINT are preliminary, updated recommendations need to await a peer reviewed publication. Important questions include the magnitude of the absolute risk reductions in SPRINT, and the apparent disparity between the ACCORD and SPRINT outcomes. ACCORD was similar in design to SPRINT, examining the same primary composite outcome and comparing goal systolic pressure less than 120 mm Hg to goal systolic pressure less than 140 mm Hg in patients with diabetes defined as glycated hemoglobin at least 7.5%. The principle finding was that there was no difference in benefit, but there was a significant increase in adverse events driven by hypotension.[29]

Table 4. Implementation principles

Create a hypertension registry
Give performance feedback monthly, unblinded at team leader level; teams include medical office building physician leaders, clinical department and care management leaders, nursing and clinical pharmacist leaders, hypertension champions, and the appropriate administrative and quality improvement directors
Allow blood pressure visits with medical and clinical assistants, walk-in or scheduled, with follow-up according to protocol
Use an evidence-based hypertension treatment algorithm that is simple, inclusive, and based on single-pill combination therapy
Implement continuous quality improvement on blood pressure measurement competency using peer validators
Provide equitable care, with treatment booster interventions and improved trust building for black patients

Additionally, rather than dialing in blood pressures for patients, the effect of antihypertensive treatment of large populations is to move mean population pressure and the bell shaped curve of blood pressure distribution. For example, in the southern California Kaiser Permanente hypertension population age 60 years and over, a hypertension control rate of almost 90% achieving goal blood pressure less than 140/90 mm Hg has moved the mean systolic pressure to 127 mm Hg. Almost 10% of treated patients have a last systolic pressure less than 110 mm Hg, and safety net features have been introduced to downtitrate medications for these individuals. Achieving 90% control with goal systolic pressure less than 120 mm Hg would be proportionally forecasted to move the population mean systolic pressure to 107 mm Hg, with systolic pressures in the 80s and 90s for sizable numbers of patients. Potential SPRINT implementation would require strong anticipatory safety net features. How many antihypertensive medications should be used to drive systolic pressure less than 120 mm Hg in more resistant patients? Certainly SPRINT raises important strategic population care issues.

POPULATION CARE STRATEGIES IN A FRACTURED HEALTHCARE DELIVERY SYSTEM

High rates of hypertension control have been achieved in large, very well-integrated healthcare systems even before widespread adoption of the electronic health record,[5,30,31] and the essential implementation principles can be adapted to large and small health plans (**Table 4**).

A hypertension registry is necessary to generate regular performance feedback reports, and performance feedback provides factual information to drive improvement via competition and sharing of best practices. Those experienced in registry building can share their experience.[5,31] Creating a hypertension registry may be as simple as identifying all patients who have an International Classification of Diseases 9 (ICD 9) code of 401.9 (essential hypertension) twice within a rolling 12-month period.

Antihypertensive drug treatment protocols should be simple, inclusive, and evidence-based. Although there are thousands of individual drug permutations of the JNC 8 treatment algorithm, ease of implementation should always be the tie-breaker. Most often, a treatment algorithm based on single-pill combination therapy will fulfill those requirements.

For example, one could start with one-half of a combination pill containing lisinopril 20 mg and hydrochlorothiazide 25 mg and then, at intervals of 2 to 4 weeks, titrate this dosage up to a full pill and then to two pills (ie, lisinopril 40 mg plus hydrochlorothiazide 50 mg) before adding amlodipine in sequentially higher doses to achieve goal blood pressure. This algorithm is inclusive for black patients, patients with stage 1, 2, or 3 chronic kidney disease, and patients with diabetes. There is good physiologic support for combination drugs, and goal blood pressure is achieved more rapidly than with sequential monotherapy.[32,33] The ACCOMPLISH trial, which showed an ACE inhibitor-calcium channel blocker combination to be superior to an ACE inhibitor plus a thiazide diuretic, was not considered definitive in either the JNC 8 or European guideline reports.[5,34] Implementation success supports protocol-driven algorithmic care,[35] which can be practiced by physician providers, nurse practitioners, and clinical pharmacists within their scope of practice.

Given the large number of hypertensive patients, the multiple medication titration encounters necessary to attain high control rates, and the limited numbers of providers who can prescribe medication, medi-

cal and clinical assistants play a key role. The protocol-driven no-copayment walk-in or scheduled blood pressure check is an essential component of hypertension care.[5,31]

These principles focus on simplicity and inclusiveness and can drive high hypertension control rates nationally across a wide spectrum of healthcare plan capabilities. Health plans practicing equitable care, assigning priority and additional resources to black patients with hypertension, can close the racial performance gap.[36]

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