

Hypertension Treatment Guidelines: Is It Time for an Update?

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Several organizations have advocated an update of the US guidelines for the management of hypertension, which were published in 2003.¹ Is it time to update that report?

The Royal College of Physicians and the British Hypertension Society (BHS) have recently published new recommendations for pharmacologic management, which they believe should supersede all previous recommendations.² This report includes an extensive review of the literature and a detailed analysis of clinical trial data. I believe, however, that it is not a useful guide for practicing physicians. Ninety-five pages are devoted to reanalyses of previously available information, with an emphasis on comparative studies with β -blockers. The conclusion reached is that these agents should not be considered as initial or even second-step therapy in the management of hypertension except in special situations. A cost analysis with many problematic conclusions is also presented in the report.

The National Heart, Lung, and Blood Institute (NHLBI), which organized and published all of the previous reports of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNCs) in the United States, is not planning to undertake a specific update of hypertension management, at least within the immediate future. There appears to be more support in favor of a comprehensive report dealing with management of all cardiovascular (CV) risk factors in addition to hypertension.

DO WE NEED AN UPDATED GUIDELINE?

A major question is why we might need a new guideline. Are there new studies whose results

will change the way the practicing physician approaches the management of this disease? Do we have enough data on newer diagnostic modalities, newer approaches to nonpharmacologic therapy, or newer approaches to pharmacologic management that make it important to produce a new guideline at this time?

In the past, the JNC reports not only reviewed the pharmacologic management of hypertension but also updated information about other CV risk factors, diagnostic evaluation, and nonpharmacologic approaches to hypertension management. What would a new JNC report look like if data from 2003 to the present were to be added to the previous report?

THE DIAGNOSTIC EVALUATION: SHOULD IT BE UPDATED?

There have been numerous publications advocating the use of certain markers as routine in the evaluation of CV risk factors, not only in hypertensive patients but in all patients.

- High-sensitivity C-reactive protein, a marker of inflammation, has recently been advocated as a necessary component in any risk factor evaluation; higher levels appear to correlate with more risk. Yet there are no definitive data at present indicating that the results of a high-sensitivity C-reactive protein determination would improve the overall management of a patient more than information obtained from a history, physical examination, and routine evaluation of serum lipids, blood glucose levels, and blood pressure (BP).³ Efforts to reduce elevated lipid levels, if present, and elevated BPs to established goal levels would certainly not be changed.
- There are advocates of vascular and impedance studies and pulse tracings in the routine evaluation



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of hypertensive patients and reports suggesting that the results of these studies might improve management.⁴ Although evaluating vascular function represents an academic approach to management and scientifically has validity, there is no convincing evidence at present that having this information improves outcome.

- In the past few years, there have been additional studies on the significance of echocardiography in the hypertensive patient. It has been repeatedly shown that echocardiography is a sensitive indicator of left ventricular hypertrophy and important in diagnosing diastolic dysfunction. Most clinicians would agree, however, with current recommendations for treatment of all individuals with a persistent elevation of BP >140/90 mm Hg (or in patients with diabetes and renal disease, 130/80 mm Hg or higher). BP should be lowered whether or not an echocardiogram reveals left ventricular hypertrophy.
- The literature on ambulatory BP monitoring (ABPM) continues to grow. This procedure is useful in determining the 24-hour effects of BP-lowering agents and is now a requirement in many US Food and Drug Administration studies that are designed to prove the effectiveness of new antihypertensive drugs. There is some evidence that monitoring BPs with ABPM may prove useful in helping to guide therapy. Yet, at present, there is little definitive evidence that this is a necessary procedure in the routine evaluation of the hypertensive patient. There are advocates for the use of ABPM to monitor CV outcome in long-term studies, but again, no definitive data that this will help to achieve a reduction in CV events. The use of home BP monitoring, which provides an ongoing picture of BPs over a long period of time, may in fact prove to be more helpful in following patients than a single 24- or 48-hour recording, without the expense and difficulties of obtaining these readings.

Recommendations of the JNC VI⁵ and JNC 7¹ were based on evidence. The reports concluded that these diagnostic modalities, eg, echocardiograms, ABPM, and vascular studies, may be necessary in some situations but not as part of a routine evaluation. There is not enough evidence at present to change these recommendations. Perhaps, therefore, we do not need new guidelines for the routine diagnostic evaluation of the hypertensive patient.

NONPHARMACOLOGIC THERAPY: DO WE NEED AN UPDATE?

Nonpharmacologic management continues to be an important component in hypertension or CV

risk factor management. The increase in obesity, the metabolic syndrome, and diabetes are major concerns, especially as the population ages. It is clear that the recommendations of the JNC and all international guidelines to keep weight as close to optimal as possible (losing weight if obese), to limit sodium intake to about 100 mmol/d (which may represent a marked decrease in usual sodium intake), to limit alcohol intake (only 1–2 drinks a day; 10 ounces of wine or 24 ounces of beer) and to encourage exercise (walking briskly 4 or 5 times a week for 30–45 minutes) are still valid and should be advocated by every physician who treats hypertensive patients or indeed any individual with CV risk factors. There have been additional studies within the past few years dealing with different methods and systems to improve patient adherence to lifestyle changes and to increase physician awareness of their importance.

Refinements of the Dietary Approaches to Stop Hypertension (DASH) diet, a diet rich in fruits and vegetables and low-fat dairy products, have been reemphasized, indicating that a very-low-sodium intake will reduce BP even more than a moderate-sodium diet.⁶ This diet is a model for what might be accomplished, but it should be remembered that all foods in this study were provided to the participants in the trial. Most people are unable to reduce sodium to the degree advocated by the DASH investigators.

Thus, although refinements in the implementation of lifestyle modifications and patient/physician adherence might be stressed in a new report, the basic message has not changed. These approaches are useful, should be encouraged, and will reduce BPs to goal in some patients, but pharmacologic therapy is most often a necessary addition to non-pharmacologic interventions.

PHARMACOLOGIC INTERVENTIONS: DO THESE RECOMMENDATIONS NEED TO BE UPDATED?

Several long-term trials have been published since the JNC 7 report in 2003.^{7,8} Specific studies that have been highlighted in the British recommendations are:

- The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,⁷ which compared an angiotensin-II receptor blocker (ARB)-based treatment program to a calcium channel blocker (CCB)-based regimen. While there was no difference in overall outcome results, myocardial infarctions were fewer in patients treated with a CCB-based program. These results may not have

been expected, since previous studies had reported that the use of a CCB resulted in more myocardial infarctions and heart failure than treatment programs based on a blocker of the renin-angiotensin system. A finding in the VALUE trial was that BPs, especially during the first 3–6 months, were lower with CCB-based treatment. This finding was not surprising since the population in VALUE was elderly and it has been known for years that these patients respond more readily to CCBs than to angiotensin-converting enzyme (ACE) inhibitors or ARBs. The VALUE trial again raised the question whether it was the BP difference within the first few months or the specific treatment regimen that made the difference in myocardial infarction outcome. This debate has been ongoing since publication of the United Kingdom Prospective Diabetes Study (UKPDS 39)⁹ in type 2 diabetes, which reported no difference in outcome between a β -blocker and an ACE inhibitor-based program but significantly fewer CV events in patients whose BPs were lowered 10/5 mm Hg more than a group of less vigorously treated individuals.

- The Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA),⁸ a multicenter randomized controlled trial, which (like the VALUE study) was not blinded, reported that “contemporary therapy,” specifically a CCB titrated upward with an ACE inhibitor added, was superior to “older therapy,” specifically a β -blocker, atenolol, titrated upward with a diuretic added if necessary. Although the primary outcome of both fatal and nonfatal coronary heart disease did not differ between the 2 groups in this trial, there was a difference in favor of the CCB-based regimen in total CV mortality and morbidity. The conclusions of the investigators were that contemporary therapy was superior to older therapy and that the results were generalizable, despite the fact that the population studied was elderly, more than three quarters were men, and more than 90% were white.

The ASCOT study has been criticized for many reasons, the least of which may have been that the outcome differences may have been determined by differences in BP during the first few months between the 2 drug groups rather than the result of the specific drugs used; the CCB lowered BP more than the β -blocker. During this period, atenolol was given once a day; it may not be effective with this dosage frequency. There is also nothing new, however, about the finding that a β -blocker is not as effective in lowering BP in the elderly as other agents, specifically CCBs and diuretics.¹⁰ The ASCOT trial used the wrong comparator

medication; based on previous studies, a diuretic should have been the initial drug used, with a β -blocker added. It is possible that contemporary therapy would not have proven superior to older therapy if BP had been reduced to the same degree during the titration phase.

The JNC VI report, which was published in 1998,⁵ recognized that a β -blocker was not as effective as a diuretic in the elderly. This report stated that in elderly patients (who were the individuals studied in the VALUE and ASCOT trials), β -blockers should not be the first drug of choice. Diuretics were recommended as initial therapy; it was suggested, however, that a diuretic with a β -blocker or other medications would be acceptable if a diuretic was not effective in reducing BP. This seemed to have been a reasonable recommendation.

The new recommendations of the Royal College of Physicians and the BHS that β -blockers should not be the initial drug of choice and might not even be the second-, third-, or fourth-step drugs of choice are partially based on the ASCOT trial findings plus a meta-analysis of a number of trials that included mostly elderly subjects.¹¹ These analyses indicate that the use of β -blockers may have an equivalent effect on myocardial infarctions but reduce stroke rates to a lesser degree in the elderly than other agents including diuretics, CCBs, ACE inhibitors, and ARBs. Other concerns about β -blockers that do not have vasodilating properties include the possible adverse effects of these agents on high-density lipoprotein and triglyceride levels, insulin resistance, and the occurrence of new-onset diabetes. The significance of these metabolic effects on long-term outcome is controversial. The reasoning behind the BHS guidelines appears to be that if BP can be lowered to goal with a CCB, diuretic, ACE inhibitor, or ARB without the possible metabolic effects of a β -blocker, this is a better approach even without definitive outcome data on the significance of these changes. This may appear to be a reasonable argument, but getting BP to goal levels will often require the use of a β -blocker with other medications. Even though it may not be the intent of the new guidelines, it is possible that they will have the effect of convincing doctors and the public alike that these medications should be avoided. This would be a mistake.

There are some conflicting data. Meta-analyses before the recent β -blocker review have indicated that the use of a diuretic and β -blocker results in the same outcome as the use of CCBs and ACE inhibitors.¹² The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

<p>Stage 1 hypertension (SBP 140–159 or DBP 90–99 mm Hg) Thiazide-type diuretics for most.* May consider ACEI, ARB, CCB, or (BB??)---or combination†</p>	<p>Stage 2 hypertension (SBP \geq160 or DBP \geq100 mm Hg) 2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, CCB, or [BB??])</p>
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Figure. Suggested updated algorithm for drug treatment of hypertension: initial drug choices in patients without specific or compelling indications. SBP indicates systolic blood pressure (BP); DBP, diastolic BP; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; and BB, β -blocker. *Diuretic or CCB preferred in patients older than 60 years. †Combination therapy may be appropriate initial therapy as an alternative to monotherapy in patients with diabetes or renal disease.

(ALLHAT)¹³ reported that a diuretic regimen with a β -blocker added if necessary was as (or in some subsets of patients, more) effective in improving CV outcome than a CCB- or ACE-based treatment program both in patients older and younger than 65 years and in diabetics and nondiabetics. In addition, a recent ALLHAT follow-up review of incident or new-onset diabetes with diuretic, CCB, or ACEI-based regimens reported no significant association of fasting glucose changes with these therapies and with coronary heart disease, stroke, CV disease, total mortality, and end-stage renal disease. ALLHAT concluded that there was no statistically significant difference in the risk of a CV disease outcome with hypertension treatment with amlodipine or lisinopril compared to treatment with chlorthalidone with a β -blocker added in about 30% of patients.¹⁴ The Swedish Trial in Old Patients With Hypertension-2 (STOP-2)¹⁵ in essentially the same population as ASCOT showed no difference in outcome between a diuretic/ β -blocker-based and a CCB/ACE inhibitor-based group. In this trial, however, BP lowering was the same in both groups of subjects. Perhaps ASCOT results may reflect BP differences, not medication differences. There are no trials at present demonstrating that β -blockers produce a less favorable outcome in younger patients.

We must continue to question whether or not the debate about which agent should be first-, second-, or third-step is a useful one. We should instead continue to stress, as many investigators have, that lowering BP to goal regardless of the medications used should be the objective of treatment.¹⁶ There are exceptions in special circumstances, such as diabetic nephropathy, where an ACE inhibitor or ARB (with a diuretic) is indicated, or in patients with ischemic heart disease, where a β -blocker is indicated.

So do we need an update of the pharmacologic treatment algorithm?

The JNC 7 report suggested thiazide diuretics in most patients as initial therapy and the possible use of other drugs. The treatment algorithm should probably be modified to indicate that preferred alternative medications should be a CCB, an ACE inhibitor, or an ARB, rather than list all of the drug classes including β -blockers, with the following caveat: in patients with evidence of coronary heart disease, angina, post-bypass surgery or post-myocardial infarction, β -blockers are still clearly indicated (Figure). Data have shown a definite reduction in myocardial infarction with β -blockers.¹⁷ Previous European and international committees had consistently suggested that any one of a series of drugs might be used as initial therapy— β -blockers, ACE inhibitors, CCBs, ARBs, or diuretics.¹⁸ They had not suggested specific medications in different age groups before the present recommendations. An updated guideline should recommend the use of a diuretic or a CCB as preferred initial therapy in older patients.

Recommendations should be modified periodically to reflect newer data, but should not overemphasize results from clinical trials where protocols might not have been ideal. Based on the recent trial data and updated meta-analyses, recommendations regarding the use of β -blockers should be changed, but it should be recognized that these are still useful medications, especially in combination with a diuretic or other agents.¹⁹ How would therapy and guidelines have been affected if we had reacted to warnings that CCBs increased gastrointestinal hemorrhages or risk of cancer,²⁰ that suicide rates were high with CCBs,²¹ that diuretics increased heart attack risk²² or increased end-stage renal disease,²³ or that hypertensive women taking CCBs had 64% more myocardial infarctions than those taking diuretics,²⁴ and that ACE inhibitors should

not be used in patients with renal disease? There were investigators who predicted dire consequences from the use of these medications. Fortunately, their warnings, which were often based on retrospective cohort studies or speculation, were largely ignored. Should we do what has been suggested by the British press to 2 million people in England who are taking β -blockers? The advice following the release of the latest BHS recommendations was "Restrict the use of β -blockers in favor of other therapy." While there may be some reason to advise that these are not the best drugs of choice in the elderly (a finding that is not new and was recognized by the JNC in the United States more than 8 years ago), there is little merit to a campaign to convince physicians and the public alike that these medications should not be used. The ongoing arguments about preferred initial therapy are also not productive since a majority of patients will require 2 or more medications to achieve goal BPs.

IF THERE IS A NEW GUIDELINE, WHAT SHOULD IT LOOK LIKE?

A new guideline: (1) would add little to the recommendations for the routine diagnostic workup of the patient; (2) could add some information with regard to the implementation of lifestyle interventions; and (3) should modify recommendations for initial and subsequent pharmacologic therapy, especially in the elderly patient. In addition, it should provide some additional guidelines for the management of the resistant or difficult-to-control hypertensive patient, especially with regard to the use of multiple medications and the use of agents that block aldosterone.²⁵ It might emphasize further efforts to control other risk factors and reemphasize the necessity of reducing BP to goal levels of 140/90 mm Hg (or as close to 120/80 mm Hg as possible without adverse effects). At present, there is not enough evidence regarding the use of newer renin-blocking agents or medications that affect nitric oxide activity to add them to the treatment algorithm.

CONCLUSIONS

Practicing physicians should be kept up-to-date on the latest results from treatment trials and these should be incorporated in guideline recommendations, but what kind of an update is indicated? The report should be user friendly; recommendations could be formulated relatively quickly with specific helpful summaries for the practicing physician in a 3- to 4-page update. I do not believe at this time that a major revision of the JNC report is indicated.

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