

Ten Years and Counting: *The Journal of Clinical Hypertension*

Marvin Moser, MD
Editor in Chief

It is hard to believe that this is the 10th year of publication of *The Journal of Clinical Hypertension* (*JCH*). When *JCH* was initially conceived, it was intended to serve as an update for a large number of practicing physicians at a time when the distribution of several peer-reviewed journals in the field of hypertension was limited to nephrologists, cardiologists, and physicians specifically interested in hypertension. Since 1999, *JCH* has grown from a bimonthly, nonindexed publication to a peer-reviewed, monthly, indexed journal. It has progressed from a time when many of the articles were initially solicited to the present, when a majority of the papers represent original research with some invited commentaries or editorials.

The success of *JCH* is largely due to the hard work of the editorial board, which includes experts from the United States and many other countries. Without their assistance, *JCH* could not have succeeded in becoming a major source of information for the practicing physician in the field of hypertension and cardiovascular disease. Special thanks must go to the section editors, to individuals who have written editorials, and to those who have conscientiously and consistently provided up-to-date reviews and columns in the *JCH*. Dr Pickering, Associate Editor in Chief, and Drs Townsend, Cohen, Basile, Bloch, Handler, Giles, Phillips, Vidt, Papademetriou, Prisant, Sica, Kerwin, Black, Cushman, and Sowers have been especially helpful in providing interesting, thoughtful, and controversial columns and commentaries. Finally, we must recognize the staff of Le Jacq and the American Society of Hypertension and the numerous reviewers who, behind the scenes, have evaluated and critiqued submissions to *JCH*. Their work is time-

consuming and has been invaluable to the journal's success. At this 10-year anniversary, it is appropriate to thank them. (A list of the reviewers is noted at the end of the editorial.) It is interesting to note that many of the topics discussed in recent years were actually highlighted in the initial publications of the *JCH* in July 1999 and throughout 2000 and 2001. Discussions of the prognostic indications of ambulatory monitoring,¹ control of blood pressure (BP) in older persons,² improvements in lifestyle management,^{3,4} adherence to therapy and physician inertia,⁵ evaluation of diagnostic procedures,⁶ and substance abuse as a cause of resistant hypertension⁷ were all addressed. The journal has continued to focus in recent years on treatment in octogenarians,^{8,9} isolated systolic hypertension,¹⁰ hypertension and diabetes,¹¹ controversies about specific approaches to management,¹² BP as a biomarker for cardiovascular disease, and definitions of optimal or normal BP.¹³ In 2005, the journal was designated the official journal of the American Society of Hypertension. It has been an exciting and rewarding journey.

It is especially interesting to reflect and comment on some of the developments in the treatment of hypertension that have evolved over the past 10 years and have been highlighted in the *JCH*.

LIFESTYLE MANAGEMENT OF HYPERTENSION

Editorials and articles in the journal continue to highlight the importance of lifestyle management and whether this has been implemented in treatment programs.¹⁴ It is apparent that most hypertensive patients are now being given advice about the benefits of exercise, moderation of alcohol intake, sodium restriction, and weight loss in



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controlling BP. Two recent papers in *JCH* reported that >50% to 60% of hypertensive patients have been implementing at least 2 or 3 of these lifestyle modifications.^{15,16} Recommendations have not been modified significantly over the past 8 to 10 years, but increasing emphasis has been placed on obesity management and use of the Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruit, vegetables, and low-fat products.

THE ELDERLY

Poor BP control in the hypertensive elderly population, which remains the single most common cause of so-called difficult-to-treat or resistant hypertension, has been repeatedly stressed. Commentaries, editorials, and expert panel discussions have described results of treatment in this segment of the population. New evidence from clinical trials, including data from the Hypertension in the Very Elderly Trial (HYVET) indicates that not only are strokes and congestive heart failure decreased by lowering BP but myocardial infarctions and mortality are also reduced in elderly patients, even those older than 80 years.¹⁷ These data reinforce the concept that the elderly, whatever age, should receive treatment and BP should be lowered to as close to 140/90 mm Hg as can be accomplished, consistent with as little interference with the enjoyment of life as possible. Although this may not be possible in all cases of isolated systolic hypertension, numerous articles in the journal over the years have stressed that even a reduction in systolic BP of 10 to 15 mm Hg is beneficial; this is the average level of decrease in BP in most of the treatment trials in the elderly. No definitive data have emerged to suggest an adverse affect on cardiovascular outcome if BP is lowered carefully in this age group. Some data suggest that lowering diastolic BP to <55 or 60 mm Hg may decrease benefit, but these levels are infrequently achieved.

THE SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE

Since publication of *JCH* in 1999, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) was published in 2003, extending guidelines that were originally published in 1977 by the National Heart, Lung, and Blood Institute.^{18,19} These reports continue to serve as roadmaps for the treatment of hypertension worldwide. The new guidelines simplified

the classification of hypertension. Categories were defined as (1) normal or optimal BP, <120/80 mm Hg; (2) prehypertension, 120–139/80–89 mm Hg; (3) stage 1 hypertension, 140–160/90–100 mm Hg; and (4) stage 2 hypertension, >160/100 mm Hg. The committee noted that treatment was not significantly different with BP values >160 mm Hg or >180 mm Hg systolic or 100 to 110 mm Hg diastolic. Therefore, the category of stage 3 (systolic BP >180 mm Hg) noted in the 1997 report was dropped. In all cases, the goal of therapy is similar; obviously, the higher the BP the greater the effort to lower it and prevent CV disease.

The new prehypertension designation, now used instead of the category “high-normal,” evolved from the fact that epidemiologic data have shown an almost linear increase in risk as BP rose from levels of 115/75 mm Hg.²⁰ There has been some criticism of the prehypertension designation both in the United States and Europe. Traditionally, the level of 140/90 mm Hg has served as a criterion to define hypertension; levels lower than that were considered normal or high-normal. The number 140/90 mm Hg is arbitrary, but it is a level above which the risk of cardiovascular events increases more rapidly with each 10-mm Hg increase than, for example, from 120 to 130 mm Hg. This is a useful definition so that health care providers can communicate with one another and agree on specific levels of treatment.

The JNC 7 committee believed that it was important to do away with the designation of high-normal and replace it with prehypertension. The term prehypertension may have a more ominous connotation, but the new definition might serve to alert more physicians to more vigorously advocate a change in lifestyles and alert more patients to the possible risk of having BP that is not optimal. The committee concluded that the risk of using this designation was overshadowed by the potential benefit of earlier intervention. The question of the use of specific medication in addition to lifestyle changes in this group of patients was left unsettled. Expert panel discussions in *JCH* have debated this issue and concluded that although there is some risk of “labeling” millions of patients, the potential benefits may outweigh the risk.²¹

PREHYPERTENSION: TO TREAT OR NOT TO TREAT WITH MEDICATION?

In 1978, a meeting was held in New York City to discuss whether “to treat or not to treat” what was then defined as mild hypertension (140–160/90–104 mm Hg).²² Abundant data since that time have

demonstrated that treatment of these patients with medication as well as lifestyle changes is justified.²³ Now the question is not whether to treat patients with BP >140/90 mm Hg but whether to treat high-normal BP, or prehypertension, with medication if patients do not respond to sodium restriction, weight loss, etc.

The Trial of Preventing Hypertension (TROPHY) study in 2006 attempted to determine whether treatment with an angiotensin II receptor blocker (ARB) compared with placebo in patient groups already on lifestyle management might prevent the progression of prehypertension to hypertension as currently defined (BP >140/90 mm Hg).²⁴ Results indicated that BP was reduced in the specific treatment group and new-onset hypertension (BP >140/90 mm Hg) was less than in the placebo group. The study results remain controversial because of the methods of defining the onset of hypertension, although a recent publication may have clarified some of these issues. Obviously, confirmation of these data and their clinical importance is necessary. The JNC expert panelists reviewed the TROPHY results and were unable to agree that medication was indicated in patients with prehypertensive BP levels without other cardiovascular risk factors. They believed, however, that in those patients who had other risk factors (ie, diabetes, coronary heart or renal disease), specific medication was indicated.

TREATMENT TRIALS

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

In 2003, the JNC 7 evaluated all of the clinical trials, including the largest randomized blinded controlled trial in hypertension, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),²⁵ and concluded that most hypertensive patients should initially receive a diuretic. ALLHAT, which was highlighted in several editorials and papers in *JCH*,^{26,27} concluded that there were no specific advantages to a treatment regimen based on an angiotensin-converting enzyme (ACE) inhibitor or a calcium channel blocker (CCB) compared with a diuretic-based regimen. Primary end points (ie, coronary heart disease events) did not differ in the 3 treatment groups, but patients in the diuretic-based treatment group experienced fewer episodes of heart failure (which were well-documented and carefully reviewed by the investigators) than did those in the CCB-based treatment group and fewer strokes and heart failure events than in the ACE inhibitor-based group.

Results of this trial still evoke controversy. A major debate about ALLHAT and other trial data have centered on the question, “Is it BP lowering or something specific about particular drugs that makes the difference in outcome?”²⁸ In ALLHAT, BP was lowered to a greater extent (as expected) in black patients in the diuretic-based compared with the ACE inhibitor-based treatment group. This may have accounted for the improved outcome, especially with regard to stroke. The ALLHAT investigators, however, did not believe that the BP difference accounted for all of this difference in outcome.

ALLHAT has been criticized because a study drug could not be used as a second-step drug after initial therapy. For example, a diuretic or a CCB could not be given as a second-step drug with the ACE inhibitor, although this might be a logical choice. On the other hand, a β -blocker, which was not one of the specific drugs being evaluated, could be used as a second-step with the diuretic—a logical choice. Those who have argued over the years against the use of these 2 medications (diuretics with or without a β -blocker) should note that there was no difference in coronary heart disease outcome, but that there were fewer episodes of heart failure and stroke in older or younger patients or in those with diabetes or the metabolic syndrome with these agents when compared with other medications. It should also be reemphasized that ALLHAT was one of the few trials that was blinded.

The Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm and Valsartan Antihypertensive Long-Term Use Evaluation Trials

In another study reported in 2005, the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA), which compared a regimen based on a CCB (with an ACE inhibitor added) to a β -blocker-based treatment program (with a diuretic added), the primary outcome (coronary heart disease events) did not differ, but there was a benefit in favor of the CCB regimen in overall cardiovascular events.²⁹ The conclusion of this trial was that “contemporary” therapy was superior to “old” therapy, but was the difference in outcome secondary to the specific drugs or BP differences? BP values were lower with the CCB (as expected in an elderly population) compared with a β -blocker within the first few months. This study also demonstrated that central arterial BP levels as measured by radial tonometry were lower than peripheral BP values with the CCB/ACE inhibitor treatment than with β -blocker/diuretic treatment. Did this difference account for the benefit?

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial in 1998 also indicated that early control of BP improves outcome. BP in patients receiving a CCB were lower than those receiving an ARB during the first few months of the trial, and overall outcome was better.³⁰ Both of these trials have been repeatedly discussed and critiqued in the journal. Would the results have been different if BP had been reduced to a similar degree?

TREATMENT RECOMMENDATIONS: THE β -BLOCKER DEBATE

Several meta-analyses within the past 10 years have indicated that there is little difference in outcome with different medications if BP is lowered to a similar degree.³¹ However, based primarily on the results of ASCOT and 2 other trials, the Losartan Intervention for Endpoint Reduction in Hypertension Study³² and the Medical Research Council Trial of Treatment of Hypertension in Older Adults,³³ several European Guideline Committees and some experts concluded that the use of β -blockers did not reduce strokes to the same degree as other medications^{34,35} and should, therefore, not be used as first-, second-, or even third-step agents in management except in patients post-myocardial infarction or with angina, etc. The journal's expert panelists have noted, however, that the data used in the recent meta-analyses were mainly derived from trials in the elderly; it is well known that β -blockers are not as effective in lowering BP in this population as diuretics or CCBs. The European recommendations, therefore, may not apply to many younger individuals. In addition, most of the trials summarized, especially the Medical Research Council in the Elderly, were not blinded and there was a high dropout and cross-over rate; the β -blocker used was atenolol, given in relatively small doses once a day. The possibility exists that different results might have been noted if a truly once-a-day β -blocker in appropriate doses had been used and BP reduced to a degree equivalent to the other agents.³⁶ There are also no comparative outcome data with the vasodilating β -blockers, so the British recommendations do not apply to these medications.

At present, most experts believe that nonvasodilating β -blockers may not be as effective as other agents (ie, diuretics, renin-angiotensin-aldosterone inhibitors, or CCBs) in reducing cardiovascular events, especially strokes, and probably should not be used as preferred initial therapy in hypertensive patients who do not have evidence of coronary heart disease. This conclusion is one of the major

differences in treatment recommendations that have occurred in the past 5 years since publication of JNC 7. It should be noted, however, that the nonvasodilating β -blockers may be effective and useful medications in many patients, especially those with any evidence of ischemic heart disease.

INITIAL THERAPY

The JNC 7 report in 2003 recommended that unless there was a specific medical reason for the use of another agent, a diuretic was the drug of choice in most cases.¹⁹ ACE inhibitors, ARBs, CCBs, and β -blockers were suggested as alternative therapies, especially in specific situations. For example, data suggest that a renin-angiotensin-aldosterone inhibitor, usually in combination with a diuretic, is more effective in slowing down the progression of nephropathy, especially in diabetics, than regimens that do not include one of these agents. It has also been reported that recurrent strokes can be prevented in persons with known cerebrovascular disease with an ACE inhibitor and a diuretic, although monotherapy with the ACE inhibitor was not shown to be effective.³⁷ It is possible that the use of other combinations will produce the same results, but studies have not been done. ACE inhibitors, ARBs, diuretics, and β -blockers are specifically indicated in congestive heart failure and other conditions.

JNC 7 did not differ significantly from the previous 6 JNC reports, which had suggested a diuretic as one of the preferred first-step drugs. It did differ, however, in that β -blockers were not recommended along with diuretics as preferred initial therapy. This recommendation is consistent with results of the studies published subsequent to 2003.

JNC 8, which will probably be published at the end of 2008 or early 2009, will most likely reflect the different recommendations with regard to the use of nonvasodilating β -blockers.

THE CONTROVERSY ABOUT NEW-ONSET DIABETES

The occurrence of new-onset diabetes as a result of antihypertensive therapy has also been highlighted and discussed in the journal's original papers, expert panel discussions, and editorials.^{38,39} It is clear that this is more common in hypertensive compared with normotensive individuals regardless of treatment; with the increasing occurrence of obesity and what is now termed the metabolic syndrome in hypertensive patients, this is to be expected. Several studies have reported that the use of certain antihypertensive drugs, specifically diuretics and β -blockers, will result in more new-

onset diabetes than the use of other agents such as ACE inhibitors or ARBs.^{25,29,30} A retrospective analysis of a large database had in the past, however, indicated that the incidence of diabetes is not increased in patients treated with diuretics compared with other agents.⁴⁰ Other studies have indicated that the use of β -blockers results in more new-onset diabetes than any of the other agents.⁴¹

In ALLHAT, 11.6% of patients in the diuretic-based treatment group compared with 8.1% of patients in the ACE inhibitor-based and 9.8% of patients in the CCB-based group developed diabetes. When the study was carefully analyzed in patients with fasting glucose intolerance, diabetes, the metabolic syndrome, or obesity and the elderly, however, there was no difference in cardiovascular outcome among the 3 medications. Despite the increased occurrence of new-onset diabetes, defined as a blood sugar level of ≥ 126 mg/dL, coronary heart disease incidence was not greater in the diuretic group (ie, there was no adverse clinical outcome despite the apparent increase in insulin resistance). Patients in the diuretic-based treatment group still had fewer episodes of heart failure and stroke events; BP lowering and perhaps some other actions of the diuretic-based regimen appeared to counterbalance the increase in new-onset diabetes.

One study reported that persons with new-onset diabetes had the same prognosis as those with long-standing diabetes.⁴² This conclusion has been debated and challenged; expert panelists in *JCH* have concluded that while new-onset diabetes may not be a desirable occurrence, there is no reason at present that diuretics should not be used as one of the preferred initial treatments in the management of hypertension.³⁹

SOME OTHER CONTROVERSIAL ISSUES

Some other issues addressed in the journal over the years have included the following:

- 1 Should pulse pressure or systolic BP be used to estimate risk? The journal's expert panelists agree that at present the systolic BP should remain the major determinant of cardiovascular risk.⁴³
- 2 Patient and physician adherence to antihypertensive therapy. The journal's expert panelists agree that while cost of therapy, adverse effects, and lack of patient incentive account for some so-called resistant or difficult-to-treat hypertension, a great many cases of nonadherence result from physician inertia and the lack of appropriate use of antihypertensive medications.^{44,45}
- 3 How much should BP be lowered to achieve benefit? The journal's expert panelists agree that

evidence supports reducing BP to $<140/90$ mm Hg, although many trials that reported benefit had not achieved these levels. Although the American Heart Association, diabetes experts, and nephrologists recommend goal BP levels of $<130/80$ mm Hg for maximum benefit, the evidence for this is not consistent.⁴⁶ The journal's expert panelists, however, agree intuitively and based on the available data that this recommendation is probably appropriate.

COMBINATION THERAPY

This has become the buzzword in hypertension management over the past 5 to 7 years. The concept is not new. We were using combination therapy in the late 1950s and 1960s when SerApEs, a combination of a vasodilator, hydralazine; a central adrenergic blocking agent, reserpine; and a diuretic, hydrochlorothiazide, was the most commonly prescribed medication for managing hypertension.⁴⁷ Numerous papers have been published in *JCH* as well as elsewhere confirming that the addition of a diuretic to a β -blocker, a diuretic to an ACE inhibitor or to an ARB, or a CCB to an ACE inhibitor or an ARB will increase the number of patients in whom goal BP is achieved and will lower the BP more than monotherapy with any of these agents. These results are not surprising and confirm what has been known for many years. The use of different medications with different modes of actions is beneficial.⁴⁸ In 2003, the JNC expanded on recommendations in the 1997 report and suggested that combination therapy might be considered as initial therapy in patients with stage 2 hypertension (ie, BP $>160/100$ mm Hg) or even in patients with stage 1 hypertension if they had comorbidities such as diabetes or renal disease. *JCH* editorials and expert panels have uniformly agreed with this recommendation. There is little question that in the future, the use of combination therapy as initial treatment will increase.^{49,50} Some recent data suggest that an ACE inhibitor/CCB combination may be more effective in reducing cardiovascular events than are ACE inhibitor/diuretic combinations. Some study results have been questioned because the diuretic may not have been used in appropriate doses. There is no evidence at present to suggest reduced cardiovascular events with an ACE inhibitor/ARB combination when compared with ACE therapy alone.

NEWER DRUGS

In the past 10 years, there have been some new medications introduced for treatment of hypertension. Many of the medications, however, represent

combinations of previously available drugs such as a combination of ACE inhibitors and CCBs, CCBs and ARBs, and diuretics in combination with any of the above. Abundant data demonstrate conclusively that combinations are extremely effective. Long-term clinical trials, which in almost all cases do not involve monotherapy comparisons but compare multiple drug therapies, have verified this approach to treatment.

The recent introduction of a renin inhibitor or a nitric oxide-enhancing vasodilating β -blocker offer some different pharmacologic approaches to management.^{51,52} At present, however, there is little evidence that blocking the renin-angiotensin system at its rate-limiting step with a renin inhibitor is going to prove any more efficacious than blocking it at the converting enzyme or peripheral angiotensin II site. Renin inhibitors may be helpful in some cases in combination with other therapy, especially diuretics, in difficult-to-treat hypertension. Newer β -blockers may be useful with fewer adverse metabolic effects than nonvasodilating β -blockers, but no outcome data are available with any of the new agents. Aldosterone blockade with spironolactone or epleronone has also received a great deal of attention.⁵³ There is little doubt that these drugs, in combination with others, are valuable additions to the management of resistant or difficult-to-treat hypertension. Studies with an endothelin-blocking agent are also ongoing.⁵⁴ This, too, is an interesting approach to management, but available data at present do not suggest that it will be a major advance in treatment. An endothelin blocker may prove to be useful as an add-on in resistant or difficult-to-treat hypertension.

PROBLEMS WITH PUBLICATION AND MEDICAL EDUCATION

A major issue relating to the publication of scientific articles and medical education has been highlighted several times in editorials in *JCH*.^{55,56} Numerous 8-, 12-, or 16-week trials that are designed specifically for US Food and Drug Administration approval have been published in this journal as well as in others. It is now common for multiple articles to be released that deal with the same study. These papers describe subsets of black, white, old, and young diabetics and nondiabetics, etc. Much of these data could be included in 1 or 2 papers. Multiple papers describing results in subsets of patients may, however, be appropriate with long-term outcome studies. The journal has published some of these repetitive papers, but not all. In some, there is good science. There is also, however,

a good deal of promotional content. Editors have made a strong effort to edit promotional content but may not have always been successful.

Another problem that has been highlighted over the past years is that more and more articles are being written by science writers, hired by an agency or a pharmaceutical or instrument company. Physicians are invited to lend their name to the publication; in some but not all cases, their input may not be significant. These articles are often well written with an extensive bibliography. However, there always seems to be a beginning, a middle, and an end, with the end advocating a new procedure or new approach to treatment that may not be much better than other well-accepted approaches. This process is ongoing and may become more prevalent. Not all papers that are written by a science writer will be rejected, but attempts to edit superlatives and add some of what has been omitted will be ongoing so that information provided to the practicing physician remains as unbiased and complete as possible.

SUMMARY

The past 10 years have provided new data on outcome and generated controversy. The bottom line, however, is that BP lowering should still be the paramount objective of treatment regardless of how it is accomplished, with some exceptions.

Numerous antihypertensive drugs are available for use as monotherapy and in various combinations and have proved effective in reducing cardiovascular and cerebrovascular events. We have learned to use these agents more intelligently in more appropriate doses and combinations than years ago, with better efficacy and fewer adverse effects.

The debate will continue as to whether it is BP lowering alone or specific medications that make the difference¹²; there is a large economic component to this debate as well as the debate regarding initial diagnostic procedures.⁵¹ Many of the claims made for one or more medications are based on the fact that specific studies were done with them, and while other medications in the same drug class that have not been studied for specific indications cannot make a claim, they may be just as effective.

The Future

Can we look forward to a time when there will be a vaccine against renin-angiotensin system activity, when patients might get an injection once every 3 months to lower their BP? Can we look forward to a time when some of the more complicated approaches to treatment, such as stimulating

baroreceptors, may play a role in management or gene therapy is effective? Perhaps, but at present these approaches are not ready for use other than in selected research studies. We continue to be optimistic about the future of hypertension management. The treatment of hypertension is a major success story.⁵⁸ While we have not achieved the level of success that is possible, a great deal has been accomplished; stroke and stroke deaths, congestive heart failure, coronary heart disease, progression of renal disease, and progression of less severe to more severe hypertension have all been significantly reduced by treatment.⁵⁹

JCH will continue to publish the controversies, review and critique the newer studies as they become available, and publish clinical research that should be helpful to practitioners.

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