

# Hypertension Management in 2002: Where Have We Been? Where Might We Be Going?

Lennart Hansson

The term “blood pressure” was coined almost 300 years ago by the man who first measured it, the Reverend Stephen Hales of England. However, our understanding of the pathogenesis and consequences of hypertension, as well as the available treatments for it, have remained greatly limited and inadequate until only the past 30 years.

Starting in 1977, reports from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC) have provided regular updates on developments in hypertension management, and have set guidelines for the diagnosis and treatment of hypertension. More than 20 years ago, the JNC stratified blood pressure (BP) levels into categories of mild, moderate, and severe (later renamed stages 1, 2, and 3, respectively). A stepped-care approach to hypertension therapy was originally recommended. With each revised JNC report, there was a reduction in target BP and a growing recognition of the

importance of high-normal BP and isolated systolic hypertension. The sixth and most current report of the Joint National Committee, JNC VI, emphasizes treatment of comorbidities of hypertension, sets a lower BP goal (<130/85 mm Hg) for high-risk patients—eg, those with diabetes or renal disease—than for those with uncomplicated hypertension (<140/90 mm Hg), and places a greater emphasis on disease prevention.

For the future, the current trend toward lower BP goals suggests that more effective and better tolerated antihypertensive therapies will be needed. Multiple antihypertensive agents used concomitantly will likely be needed to control elevated levels of BP in the majority of hypertensive patients. Am J Hypertens 2002;15:101S-107S © 2002 American Journal of Hypertension, Ltd.

**Key Words:** Hypertension, history, treatment guidelines, olmesartan medoxomil.

**F**or centuries, our understanding of the pathogenesis and treatment of hypertension paralleled the gradual, occult progression of the disease itself. The early observation that hardness of the pulse varies in individuals eventually led to the concept of blood pressure (BP) and to increasingly refined methods of measuring it. More than 100 years ago, the relationship between BP and cardiovascular (CV) morbidity and mortality became widely appreciated; yet, for many decades thereafter, the paucity of effective antihypertensive treatments was such that physicians could do little more than measure BP and monitor its rise.

In the past 30 years, however, there have been significant concurrent advances in research on the pathophysiologic mechanisms and associated morbidity and mortality risks of hypertension; the development of new antihypertensive therapies; the establishment of guidelines for hypertension management; and the recognition of high BP as a major public health problem. Hypertension is now understood to be an important but eminently treatable disease. However, rates of BP control remain poor world-

wide, suggesting that new antihypertensive therapies and strategies for using them are needed.

The current recommendations for hypertension treatment indicate that to be successful, antihypertensive therapy must have both high efficacy and tolerability, with beneficial effects in reducing the risks of target organ damage. The greatest questions and challenges for the future lie in how to optimize and combine the many, varied antihypertensive therapies now available to reach these goals. This effort will entail the use of new agents in the context of increasingly aggressive strategies for hypertension management.

## Milestones in the History of Hypertension Management

Blood pressure was first measured by the Reverend Stephen Hales of England, who coined the term “blood pressure.”<sup>1</sup> In the early 1700s, Hales measured BP invasively in dogs and in horses by inserting a long glass tube vertically into an incision made in the carotid artery and observing the height of blood in the tube.<sup>1</sup> About 100

Received July 8, 2002. First decision July 9, 2002. Accepted July 9, 2002.

From Uppsala University, Uppsala, Sweden.

Address correspondence and reprint requests to Dr. Lennart Hansson, Division of Clinical Hypertension Research, Department of Public Health, P.O. Box 609, Uppsala, Sweden; e-mail: Lennart.Hansson@pubcare.uu.se

years later, in 1828, the first manometer, a U-shaped device filled with mercury, was invented in France for laboratory measurement of BP in animals.

The sphygmograph was introduced in 1896 by the Frenchmen Jules Herrison and Etienne-Jules Marey to show and record the BP pulse wave.<sup>2</sup> The same year, Scipione Riva-Roca, from Genoa, Italy, published his two classic papers on what was in fact the first modern sphygmomanometer, very similar to the equipment we use today.<sup>3</sup> In 1905, the Russian physician Nicolai Korotkoff described his method of gauging BP indirectly by listening with a stethoscope placed over the brachial artery to the auscultatory sounds, which are named for him.<sup>4</sup> This technique served as a model for modern BP measurement.<sup>4</sup>

As BP measurement improved, a profile of the natural progression of hypertension began to emerge. The following 1872 excerpt from the writings of F. A. Mohamed<sup>5</sup> describes the state of knowledge of high BP about 150 years after Hales's experiments, including significant clues to a more advanced understanding of hypertension (*italics added*):

“These persons appear to pass on through life pretty much as others do and generally do not suffer from their high blood pressure except in their petty ailments upon which it imprints itself. . . *as age advances*, the enemy gains accession of strength. . . the individual has now *passed forty years*, perhaps *fifty years of age*, his lungs begin to degenerate, he has a cough in the wintertime, but *by his pulse* you will know him. . . alternatively, headache, vertigo, epistaxis, a passing paralysis, a more severe apoplectic seizure, and then the final blow.”

Although hints of the morbidity and mortality risks of hypertension were thus being observed in the late 19th century, treatment of the disease remained mired in uncertainty and few effective therapies existed, even into the middle of the next century. The following writings by Paul Dudley White in 1937<sup>6</sup> reflect the contemporary view of high BP as a troubling but poorly understood syndrome:

“The treatment of hypertension itself is a difficult and almost hopeless task in the present state of knowledge, and in fact for aught we know. . . the hypertension may be an important mechanism which should not be tampered with, even were it certain that we could control it.”

## The Modern Era of Hypertension Management

The Veterans Administration (VA) trial in the treatment of mild hypertension, begun in 1964, was a seminal study that can be said to mark the beginning of the modern era of hypertension management.<sup>7,8</sup> The findings of this trial were published in the *Journal of the American Medical Association* in 1967 and 1970, sparking an increasing

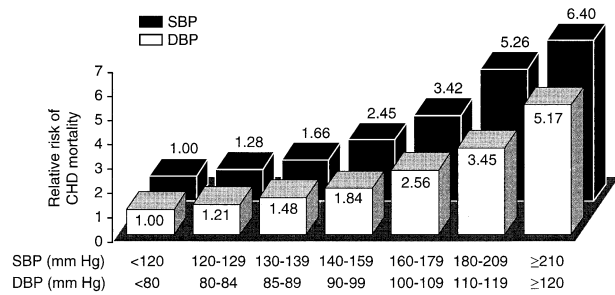
emphasis on the importance of controlling BP and on establishing guidelines for hypertension treatment.<sup>7-9</sup> The VA trial was the first prospective, randomized, double-blind study to demonstrate that treatment of mild hypertension, defined as a diastolic blood pressure (DBP) of 90 mm Hg to 114 mm Hg, significantly decreased morbidity and mortality.<sup>7,8</sup> These findings, along with a growing armamentarium of effective therapies for high BP, led to the development in 1972 of the National High Blood Pressure Education Program (NHBPEP) to promote public awareness of the importance of medical care for high BP, and to improve the treatment of hypertension in the general population.<sup>10</sup>

In coordination with the NHBPEP, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) was created to establish national clinical guidelines for the diagnosis and management of hypertension. The first of the Committee's reports, JNC I, was released in 1977.<sup>11</sup> Regular updates of the JNC reports have since been produced at 3- to 4-year intervals to keep pace with the rapid developments in hypertension management. The most recent of these reports, JNC VI, was released in 1997.<sup>12</sup> Throughout the same period, the World Health Organization and the International Society of Hypertension (WHO-ISH) issued recommendations for the management of hypertension, the most recent being their 1999 guidelines.<sup>13</sup>

In providing diagnosis and treatment guidelines, the JNC reports have served as consensus summaries and judgments of the latest advances in research on hypertension and the development of antihypertensive therapies. A number of studies have revised some long-standing concepts in the understanding of hypertension, and may point the way to novel trends and directions in antihypertensive therapy. The most important of these insights have been clearly reflected in the JNC reports, and new data are likely to influence future recommendations.

## The Significance of Systolic BP

One of the most significant trends in hypertension management is the growing recognition of the importance of systolic BP (SBP) in the assessment of cardiovascular disease (CVD) risk.<sup>14</sup> Although much of the early research on the association between BP and coronary heart disease (CHD) was focused on DBP, more recent evidence shows that SBP is an even more powerful predictor of CVD mortality.<sup>15</sup> Among subjects screened for Multiple Risk Factor Intervention Trial (MRFIT), for example, a strong positive association was observed between both SBP and DBP levels and CHD mortality<sup>16</sup> (Fig. 1). The mean follow-up time in this study of 347,978 men without a prior myocardial infarction was 16 years; a total of 11,149 deaths were identified. Results indicated that the relative importance of SBP compared with DBP increased with advancing age. There was no evidence of any threshold

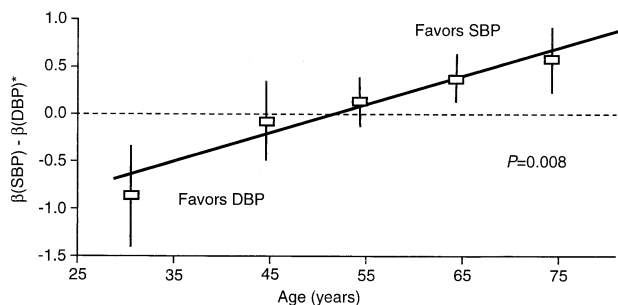


**FIG. 1.** Among 347,978 men with no history of previous myocardial infarction who were screened for the Multiple Risk Factor Intervention Trial (MRFIT), a strong positive association was observed between both systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels and the risk of coronary heart disease (CHD) mortality. (Reprinted with permission from Neaton JD, et al: Impact of systolic and diastolic blood pressure on cardiovascular mortality, in Laragh JH, Brenner BM (eds): Hypertension: Pathophysiology, Diagnosis and Management. Raven, New York, 1995.<sup>16</sup>)

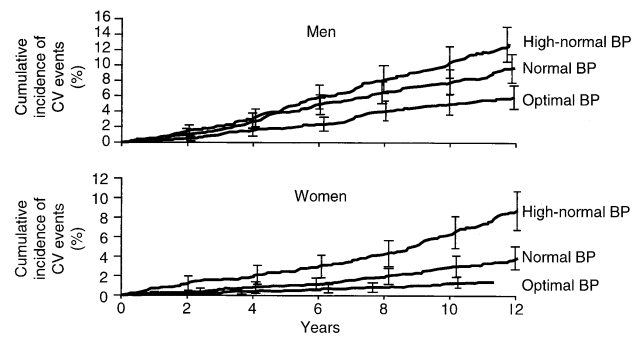
below which decreasing SBP and DBP were not associated with a lower risk of CHD death.

The MRFIT data also demonstrated a strong positive association between SBP and DBP levels and the risk of death from stroke (both hemorrhagic and nonhemorrhagic).<sup>16</sup> The BP and stroke risk gradient was steeper than that of BP and CHD, and was steeper for SBP than for DBP.

Interestingly, with increasing age, there is a gradual shift in the relative importance of DBP and SBP as predictors of CHD risk.<sup>17,18</sup> The relative role of DBP, SBP, and pulse pressure (PP) as predictors of CHD was evaluated in different age groups of 6539 Framingham Heart Study participants.<sup>17</sup> In this study, 3060 men and 3479 women between 20 and 79 years of age were observed to evaluate the relationship between BP indexes and CVD risk over a 20-year follow-up period. A Cox regression model, adjusted for age, sex, and CV risk factors, was used. Diastolic blood pressure was found to be the strongest predictor of CHD risk in the group of subjects



**FIG. 2.** With increasing age, there is a gradual shift in importance from diastolic blood pressure (DBP) to systolic blood pressure (SBP) as relative risk factors for coronary heart disease. \*Differences between SBP and DBP proportional hazard regression coefficients, ie,  $\beta(\text{SBP}) - \beta(\text{DBP})$ , were estimated for each age group. (Reprinted with permission from Franklin SS, et al: Does the relation of blood pressure to coronary heart risk change with aging? *Circulation* 2001;103:1245-1249, Lippincott Williams & Wilkins ©.<sup>17</sup>)



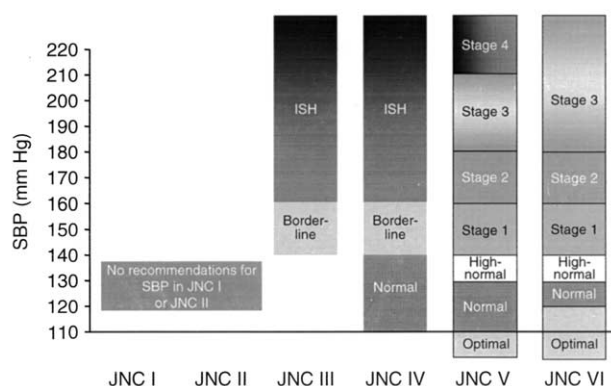
**FIG. 3.** In 6859 participants in the Framingham Heart Study who were initially free of hypertension and cardiovascular disease (CVD), high-normal blood pressure (BP) (systolic BP of 130 to 139 mm Hg and diastolic BP of 85 to 89 mm Hg) was associated with an increased risk of cardiovascular (CV) events. The 10-year cumulative incidence of CV events in subjects with high-normal BP at baseline was 4% in women and 8% in men. Optimal BP was considered to be <120/80 mm Hg; normal BP was 120 to 129/80 to 84 mm Hg. (Reprinted with permission from Vasan RS, et al: Impact of high normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291-1297. Copyright © 2001, Massachusetts Medical Society. All rights reserved.<sup>19</sup>)

younger than 50 years of age, suggesting that peripheral small vessel resistance is the major determinant of this parameter in younger adults<sup>17</sup> (Fig. 2). In the group of subjects who were 50 to 59 years of age, all three BP indexes predicted CHD risk to a similar degree, indicating that this age category is a transition period. In subjects aged 60 and older, DBP was inversely related to CHD risk, and SBP became a more important predictor (Fig. 2). Based on the divergent negative relationship of DBP and positive relationship of SBP to CHD, PP became the strongest relative risk factor for CHD. These results suggest that large artery stiffness is the major mechanism determining CHD risk in older adults.

Another follow-up study using data from the MRFIT population, which compared the relative predictive powers of DBP, SBP, and PP for CVD mortality in 342,815 men, found that SBP was an increasingly important predictor with advancing age in men aged 45 years and older, as compared with DBP.<sup>18</sup> These results support previous findings indicating that the approach to CVD risk assessment and hypertension treatment in older persons must consider high SBP paired with low DBP, not just concordantly high SBP and high DBP.<sup>18</sup>

### High-Normal BP as a Risk Factor

An additional focus of revised thinking in hypertension treatment is the association of high-normal BP with increased risk for CVD. This correlation was investigated in 6859 participants (3892 women and 2967 men) in the Framingham Heart Study who were initially free of hypertension and CVD.<sup>19</sup> Subjects were assigned to one of three groups according to their baseline BP level, based on risk stratification categories established by JNC VI<sup>12</sup> and on WHO-ISH guidelines,<sup>13</sup> as follows: optimal BP (<120/80



**FIG. 4.** From the first to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC; JNC I to VI), the changing classifications of systolic blood pressure (SBP) have reflected research data that increasingly have revealed the importance of this factor. The risk categories for SBP have moved from nonexistent, to crude and vague, to a clear and detailed six-category stratification.<sup>11,12,20–23</sup> ISH = isolated systolic hypertension.

mm Hg), normal BP (120 to 129/80 to 84 mm Hg), and high-normal BP (130 to 139/85 to 89 mm Hg).

In this study, a stepwise increase in the rate of CV events was observed to correlate with higher baseline BP across the three BP categories<sup>19</sup> (Fig. 3). In subjects aged 35 to 64 years with high-normal BP at baseline, the 10-year cumulative incidence of CVD was 4% for women and 8% for men; in subjects aged 65 to 90 years, it was 18% in women and 8% in men. Compared with optimal BP, high-normal BP was associated with a risk factor–adjusted hazards ratio of 2.5 in women and 1.6 in men. Thus, even slight elevations in BP above normal levels are associated with an increased risk of CVD.

## Guidelines for Risk Stratification and Treatment

The changing insights provided by research on hypertension are clearly reflected in the revised BP classifications set forth by succeeding JNC reports. Starting with JNC I in

1977, classification of DBP has evolved from a relatively crude two-category format, with the hypertension threshold set at 105 mm Hg, to a six-category risk stratification in JNC VI, with the hypertension threshold for DBP at 90 mm Hg.<sup>11,12,20–23</sup> An even more dramatic progression, however, is illustrated by the changing JNC classifications of SBP, which moved from no recommendations in JNC I to the current six-category risk stratification (Fig. 4).

Treatment recommendations from the JNC have also followed the development of new antihypertensive therapies. With 28 approved antihypertensive medications available when the first report was released, JNC I introduced the stepped-care approach to hypertension treatment. This strategy involved initial monotherapy followed by the substitution or addition of agents from different drug classes, with a maximum of three to four agents used until goal BP was reached.<sup>11</sup> The basic stepped-care approach has remained intact in the JNC reports, with recommendations for the use of specific drugs updated as new antihypertensive agents have become available.

The JNC VI report included some important updates in treatment guidelines that still present challenges. To place greater emphasis on prevention of hypertension, for example, the JNC changed its name to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>12</sup> When the report was released, there were 84 antihypertensive medications available, providing many therapeutic options but also raising questions regarding their application. Although the BP goal for patients with uncomplicated hypertension remained <140/90 mm Hg, as in JNC V<sup>23</sup>, lower BP goals for high-risk groups were established.

The JNC VI report further emphasized that the goal of prevention and treatment of hypertension is to reduce target organ morbidity and mortality.<sup>12</sup> In this vein, the report stratified hypertensive patients with diabetes or renal disease into the highest risk group and recommended immediate antihypertensive drug therapy for these populations. Blood pressure targets for hypertensive patients in high-risk groups were established in JNC VI as follows:

**Table 1.** WHO-ISH hypertension guidelines: stratification of cardiovascular risk<sup>13</sup>

Other Risk Factors and Disease History	BP (mm Hg)		
	Grade 1: Mild Hypertension (SBP 140–159 or DBP 90–99)	Grade 2: Moderate Hypertension (SBP 160–179 or DBP 100–109)	Grade 3: Severe Hypertension (SBP ≥ 180 or DBP ≥ 110)
I. No other risk factors	Low risk	Medium risk	High risk
II. 1-2 risk factors	Medium risk	Medium risk	Very high risk
III. 3 or more risk factors or TOD or diabetes	High risk	High risk	Very high risk
IV. Associated clinical conditions	Very high risk	Very high risk	Very high risk

WHO-ISH = World Health Organization–International Society of Hypertension; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; TOD = target organ damage.

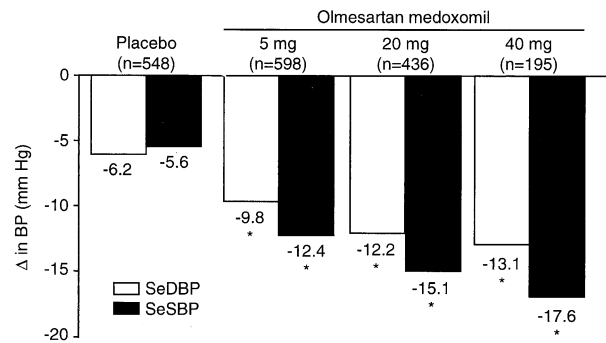
diabetes: <130/85 mm Hg; renal insufficiency and proteinuria  $\leq 1$  g/day: <130/85 mm Hg; and renal insufficiency and proteinuria >1 g/day: <125/75 mm Hg.

The recommendations regarding hypertension treatment in JNC VI are generally echoed in the WHO-ISH guidelines<sup>13</sup> (Table 1). The WHO-ISH guidelines stress that when determining hypertension treatment, factors other than BP level must be considered, including the presence of other CVD risk factors, concomitant disease (eg, diabetes), target organ damage (left ventricular hypertrophy, proteinuria and/or slight elevation of serum creatinine, radiologic evidence of atherosclerotic plaque, or retinopathy), and associated clinical conditions (for example, CVD or renal disease). As in JNC VI, the WHO-ISH guidelines stratify hypertensive patients with diabetes into a high-risk category, recommending immediate antihypertensive drug therapy with a BP target of <130/85 mm Hg based on these patients' markedly elevated risk for CVD events (20% to 30% over 10 years).<sup>13</sup>

## Challenges in BP Control

Despite greater clarification of the goals of antihypertensive therapy and substantial evidence that controlling BP in hypertensive patients significantly lowers the risk of CV morbidity and mortality, BP control rates remain suboptimal. Only about 27% of hypertensive patients in the United States have their BP controlled to the nationally recommended goal level of <140/90 mm Hg, and control rates are even worse in other countries around the world.<sup>12,24</sup> In nations where the goal BP level of <140/90 mm Hg is generally accepted, control rates are estimated at 6% (England), 22% (Canada), and 24% (France).<sup>25–27</sup> In countries where a less aggressive target BP of <160/95 mm Hg is more common, control rates range from about 9% (India) to 22.5% (Germany).<sup>28</sup>

The poor rate of BP control worldwide is a multifactorial problem. A leading factor is the efficacy of the antihypertensive agent prescribed as first-line therapy. Use of an agent with inadequate BP-lowering efficacy for initial monotherapy prolongs the process of achieving the goal BP and can cause patient frustration with the regimen. Another major reason for poor BP control in patients being treated for hypertension is a lack of patient compliance.<sup>29,30</sup> Important reasons for noncompliance include the adverse events (AEs) associated with antihypertensive drugs and complex or inconvenient dosing schedules.<sup>31</sup> Adverse events tend to increase with increasing dosage of most antihypertensive agents. Blood pressure control rates are also adversely affected by the failure of physicians to treat intensively enough to achieve the recommended target BP,<sup>30,32</sup> due at least in part to concern that up-titration of medication may lead to AEs and reduced compliance.<sup>33</sup> This complex of factors contributing to poor BP control rates clearly suggests that an antihypertensive agent should not only be effective but should also have an



**FIG. 5.** In an integrated analysis of seven randomized controlled studies, the angiotensin II receptor blocker olmesartan medoxomil produced a mean change in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) that was significantly greater than that of placebo, in all dosage groups ( $P < .001$ ). The degree of blood pressure (BP) reduction from baseline was dose dependent (modified from Neutel JM: Clinical studies of CS-866, the newest angiotensin II receptor antagonist. *Am J Cardiol* 2001; 87(Suppl):37C–43C, Copyright 2001, with permission from Excerpta Medica Inc.<sup>34</sup>; unpublished data, Sankyo Pharma Inc., 2002). \* $P < .001$ .

excellent safety and tolerability profile, as well as a simple, convenient dosing schedule.

## An Advance in Antihypertensive Therapy

Olmesartan medoxomil, the newest angiotensin II receptor blocker (ARB) to be approved for the management of hypertension, appears to be a promising new drug. With once-daily dosing, olmesartan medoxomil provides potent BP-lowering efficacy (see<sup>34</sup>; unpublished data, Sankyo Pharma, Inc., 2002). In comparison trials, olmesartan medoxomil has been shown to have BP-lowering efficacy similar to that of drugs of other antihypertensive classes, as well as superior efficacy compared with that of several other leading ARBs.<sup>35,36</sup>

The safety and efficacy of olmesartan medoxomil was assessed in an integrated analysis of seven randomized, double-blind, placebo-controlled, parallel-group studies. Data from the efficacy analysis ( $n = 2145$ ) showed that the mean change from baseline in both seated DBP and SBP was significantly greater than for placebo at all dose levels ( $P < 0.001$ ) (see<sup>34</sup>; unpublished data, Sankyo Pharma, Inc., 2002). The degree of BP reduction from baseline was dose dependent (Fig. 5).

Data from the safety analysis ( $n = 2540$ ) indicated that most of the AEs experienced by study subjects were mild in severity and were not attributed by the investigator to the treatment.<sup>34</sup> The AE profile of olmesartan medoxomil was generally similar to that of placebo. The only type of AE that was reported at least 1% more frequently by subjects treated with olmesartan medoxomil than by subjects in the placebo group was dizziness (2.8% v 0.9%, respectively). Most reported episodes of dizziness were mild. Serious adverse events (SAEs) were infrequent.

Only 0.8% of olmesartan medoxomil–treated subjects experienced an SAE, v 0.7% of those who received placebo, and no relationship between any SAEs and olmesartan medoxomil was identified. Importantly, no association between olmesartan medoxomil dose and the incidence of AEs was observed.

Olmesartan medoxomil thus represents the newest, most promising addition to the ARB class. Importantly, recent research indicates that antihypertensive therapy with an ARB may provide significant protection against CV morbidity and mortality, independent of BP reduction.<sup>37</sup> In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the ARB losartan was associated with a lower incidence of CV events compared with atenolol therapy, despite a similar reduction in BP.<sup>37</sup> Losartan was better tolerated than atenolol and was associated with a 25% lower incidence of new-onset diabetes compared with atenolol ( $P = .001$ ). These results suggest that ARBs—the newest class of antihypertensive agents—may represent a significant advance in antihypertensive therapy.

## The Future of Antihypertensive Therapy

Based on recent trends in hypertension management, a number of reasonable predictions can be made for the content of the next JNC report. It is likely that the definition and treatment recommendations for hypertension will continue to evolve. The recent tendency has been a downward shift not only in the BP levels established as the threshold for the diagnosis of hypertension and the initiation of treatment in various high-risk groups, but also for the target goals of therapy. Furthermore, there will likely be an increased focus on monitoring and treatment of elevated SBP and PP; on combination therapy as first-line treatment in high-risk patients, such as those with diabetes or with higher BP levels; and on the value of renin-angiotensin-aldosterone system blockade. The emphasis on monotherapy will undoubtedly be replaced by emphasis on the concomitant use of multiple antihypertensive agents to achieve increasingly lower BP target goals. Increased attention will be placed on using agents with ancillary properties—most importantly, on those providing protection against target organ disease. Finally, improving patient education and expectations will likely be highlighted, consistent with the current state of knowledge regarding the risks and treatment of uncontrolled hypertension. Patients must be knowledgeable about their own target BP and the fact that multiple agents may well be necessary for them to reach their BP goal.

## References

- Lewis O: Stephen Hales and the measurement of blood pressure. *J Hum Hypertens* 1994;8:865–871.
- O'Brien E, Fitzgerald D: The history of blood pressure measurement. *J Hum Hypertens* 1994;8:73–84.
- Riva-Rocci S. Un sfigomanometro nuovo. *Gaz Med Torino* 1896; 47:981–996, 1001–1017 (in Italian).
- Cantwell JD; Nicolai S. Korotkoff (1874–1920). *Clin Cardiol* 1989; 12:233–235.
- Cameron JS, Hicks J: Frederick Akbar Mahomed and his role in the description of hypertension at Guy's Hospital. *Kidney Int* 1996;49: 1488–1506.
- White PD: *Heart Disease*, 2nd ed. Macmillan, New York, 1937.
- Piot O, Gallois H, Baguet JP, Mallion JM: First-line treatment of hypertension: from monotherapy to fixed low-dose combination therapy. *J Hum Hypertens* 2001;15:443–446.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970;213:1143–1152.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *JAMA* 1967;202:1028–1034.
- Jones DW, Hall JE: The National High Blood Pressure Education Program: thirty years and counting. *Hypertension* 2002;39:941–942.
- Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: a cooperative study. *JAMA* 1977;237:255–261.
- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157: 2413–2446.
- World Health Organization–International Society of Hypertension Guidelines Subcommittee: 1999 World Health Organization–International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999;17:151–183.
- Deedwania PC: The changing face of hypertension: is systolic blood pressure the final answer? *Arch Intern Med* 2002;162:506–508.
- Stamler J, Stamler R, Neaton JD: Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993;8:598–615.
- Neaton JD, Kuller L, Stamler J, Wentworth DN: Impact of systolic and diastolic blood pressure on cardiovascular mortality, in Laragh JH, Brenner BM (eds): *Hypertension: Pathophysiology, Diagnosis and Management*. Raven, New York, 1995, p. 127–144.
- Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D: Does the relation of blood pressure to coronary heart disease risk change with aging? *Circulation* 2001;103:1245–1249.
- Domanski M, Mitchell G, Pfeiffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J, for the MRFIT Research Group: Pulse pressure and cardiovascular disease-related mortality. *JAMA* 2002;287:2677–2683.
- Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D: Impact of high normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–1297.
- Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1980 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1980;140:1280–1285.
- Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1984 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1984;144:1045–1057.
- Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988;148:1023–1038.

23. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;153:154–183.
24. Burt VL, Whelton P, Rocella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D: Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313.
25. Joffres MR, Ghadirian P, Fodor JG, Petrasovits A, Chockalingam A, Hamet P: Awareness, treatment, and control of hypertension in Canada. *Am J Hypertens* 1997;10:1097–1102.
26. Colhoun HM, Dong W, Poulter NR: Blood pressure screening, management and control in England: results from the health survey for England 1994. *J Hypertens* 1998;16:747–752.
27. Chamontin B, Poggi L, Lang T, Ménard J, Chevalier H, Gallois H, Crémier O: Prevalence, treatment and control of hypertension in the French population: data from a survey on high blood pressure in general practice, 1994. *Am J Hypertens* 1998;11:759–762.
28. Marques-Vidal P, Tuomilehto J: Hypertension awareness, treatment and control in the community: is the ‘rule of halves’ still valid? *J Hum Hypertens* 1997;11:213–220.
29. Waeber B, Burnier M, Brunner HR: How to improve adherence with prescribed treatment in hypertensive patients? *J Cardiovasc Pharmacol* 2000;35(Suppl):S23–S26.
30. Hyman DJ, Pavlik VN: Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med* 2000;160:2281–2286.
31. Oparil S, Calhoun DA: Managing the patient with hard-to-control hypertension. *Am Fam Physician* 1998;57:1007–1014, 1019–1020.
32. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA: Inadequate management of blood pressure in a hypertensive population. *N Engl J Med* 1998;339:1957–1963.
33. Neutel JM, Smith DH, Weber M: Low-dose combination therapy: an important first-line treatment in the management of hypertension. *Am J Hypertens* 2001;14:286–292.
34. Neutel JM: Clinical studies of CS-866, the newest angiotensin II receptor antagonist. *Am J Cardiol* 2001;87(Suppl):37C–43C.
35. Ball KJ, Williams PA, Stumpe KO: Relative efficacy of an angiotensin II antagonist compared with other antihypertensive agents: olmesartan medoxomil vs antihypertensives. *J Hypertens* 2001;19(Suppl 1):S49–S56.
36. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J: Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens* 2001;3:283–291, 318.
37. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, for the LIFE Study Group: Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002;359:995–1003.