Hypertensive Therapy: Part I

Veronica Franco, MD; Suzanne Oparil, MD; Oscar A. Carretero, MD

Cardiovascular disease (CVD), including stroke, is the most common cause of death and disability in developed countries, and hypertension is one of the most important modifiable risk factors for these outcomes. The relationship between blood pressure (BP) and CVD mortality is positive, strong, continuous, graded, and predictive, for those with or without coronary heart disease, and it increases with age. A meta-analysis of observational studies involving more than 1 million individuals without prior histories of stroke or heart disease carried out by the Prospective Studies Trialists’ Collaboration demonstrated that death from coronary heart disease and stroke increases continuously and linearly from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic. An increment of 20 mm Hg in systolic BP (SBP) or 10 mm Hg in diastolic BP (DBP) in middle-aged and elderly persons is associated with a 2-fold increase in cardiovascular (coronary heart disease and stroke) mortality throughout the entire range of BP (Figure 1). In addition, data from the Framingham Heart Study showed that, when compared with “optimum” BP (SBP <120 mm Hg and DBP <80 mm Hg), “normal” BP (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg) is associated with a 2- to 4-fold increase in risk of developing hypertension, and “high normal” BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg) is associated with a 5-fold increased risk.

Hypertension, defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg or the use of antihypertensive medications, is a major public health problem, affecting almost 29% of the adult US population, according to the US National Health and Nutrition Examination Survey (NHANES), and 44% of the population in Europe. Importantly, there has been an increase in the prevalence of hypertension in the United States between 1988 to 1991 and 1999 to 2000, a reversal of the previously reported declining trend in hypertension prevalence between 1960 and 1991.

Although NHANES assessed trends in the cross-sectional prevalence of hypertension in the US population, long-term risk of an individual is best determined by the lifetime risk statistic, which is the probability of developing hypertension during the remaining years of life. Data from the Framingham Heart Study indicated a lifetime risk for developing hypertension of 90% for men and women who were not hypertensive at age 55 or 65 years and survived to age 80 to 85 (Figure 2). Even after adjusting for competing causes of mortality, the remaining lifetime risks of hypertension were 86% to 90% in women and 81% to 83% in men. More than half of the 55-year-old participants developed hypertension within 10 years. Furthermore, the 4-year rates of progression to hypertension in the Framingham cohort were 50% for those 65 years and older with BPs in the 130– to 139–/85– to 90–/89–mm Hg range and 26% for those with BPs in the 120– to 129–/80– to 84–/85–mm Hg range. These rates of hypertension are of great concern, especially because BP control in the United States, although better than in other countries, is still unacceptable: 70% of hypertensives have not achieved their goal (<140/90 mm Hg overall) BP per the 1999 to 2000 NHANES report. Furthermore, almost 30% of all hypertensives are unaware of their illness, and 42% are not being treated with medication. Control levels are even lower in the European countries, only 8% on average. The relative impact of hypertension treatment strategies in Europe, Canada, and the United States was estimated by using sample surveys conducted in the 1990s. Among persons 35 to 64 years of age, 29% of hypertensives in the United States had their BP “controlled” at 140/90 mm Hg, compared with 17% in Canada and ≤10% in Europe. At the 140/90–mm Hg cut-point, two thirds to three fourths of the hypertensives in Canada and Europe were untreated, compared with slightly less than half in the United States. Undiagnosed, untreated, and uncontrolled hypertension clearly places a significant strain on the healthcare delivery system. Rates of decline of death from CVD have slowed in the past decade, and major complications of hypertension, including heart failure and end-stage renal disease, have actually risen over that time period.

In this review, we will summarize the important clinical trials and guidelines for the treatment of hypertension that have been published recently and will outline the most significant developments and key messages in the field that should guide evidence-based medical practice in the coming years.

New BP Classification

The goal of antihypertensive treatment is to reduce CVD risk and thus morbidity and mortality rates. Because of the new data on lifetime risk of hypertension and the impressive rise
in the risk of cardiovascular complications associated with levels of BP previously considered to be normal, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has introduced a new classification that includes the term **prehypertension** for those with SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg (Tables 1 and 2). Prehypertension is not a disease category. Rather, it is a designation

**Figure 1.** Coronary heart disease (A) and stroke (B) mortality rate in each decade of age versus usual BP at the start of that decade. Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. For DBP, each age-specific regression line ignores the left-hand point (ie, at slightly less than 75 mm Hg), for which the risk lies significantly above the fitted regression line (as indicated by the broken line below 75 mm Hg). This figure shows that the relationship of coronary heart disease and stroke mortality to usual BP is strong and direct at all ages, with no good evidence of a threshold at any age in the range of usual SBP above 115 mm Hg or of usual DBP above 75 mm Hg. A “doubling” (ie, proportional, or log) scale has been used for mortality rates, with a 95% CI for each point that reflects the amount of information underlying each risk estimate. Reprinted with permission from Elsevier from Lewington et al.3
chosen to identify individuals at high risk of developing hypertension, so that both patients and healthcare providers are alerted to this risk and encouraged to intervene and prevent or delay hypertension from developing. Individuals who are prehypertensive are not candidates for drug therapy on the basis of their BP and should be firmly advised to practice lifestyle modification to reduce their risk of developing hypertension in the future. However, persons with BPs in the prehypertensive range and comorbid conditions, eg, diabetes or chronic kidney disease, that require intensive BP lowering should be treated aggressively with antihypertensive medications. Specific choices of therapy in this situation should be guided by the nature of the comorbid conditions.

In clinical practice, the diagnosis of hypertension should be made on the basis of SBP more often than on DBP; SBP in the population increases with advancing age, whereas DBP tends to plateau or fall after age 60. As a result, knowledge of BP alone correctly classified the stage of hypertension in 99% of persons 60 years of age or older in the Framingham Heart Study cohort who were not on antihypertensive medication. In contrast, knowledge of DBP alone correctly classified the hypertension stage in only 47% of these persons. Importantly, SBP is a better predictor of events (coronary heart disease, CVD, heart failure, stroke, end-stage renal disease, and all-cause mortality) than is DBP, especially among older persons. Furthermore, SBP is a more difficult therapeutic target than DBP; as will be discussed later, randomized controlled outcome trials of antihypertensive treatment generally have reported much greater success (>

TABLE 1. Changes in Blood Pressure Classification (JNC 6 and 7)

<table>
<thead>
<tr>
<th>JNC 6 Category</th>
<th>SBP/DBP</th>
<th>JNC 7 Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120/80</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129/80–84</td>
<td>Prehypertension</td>
</tr>
<tr>
<td>Borderline</td>
<td>130–139/85–89</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypertension</td>
<td>≥140/90</td>
<td>Stage 1</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140–159/90–99</td>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160–179/100–109</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>≥180/110</td>
<td></td>
</tr>
</tbody>
</table>

Reproduced with permission from Chobanian et al. 13

TABLE 2. Key Messages From JNC 7

- In individuals older than age 50 years, SBP is a more important CVD risk factor than DBP.
- Beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg throughout the BP range.
- Those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.
- Those with SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg should be considered prehypertensive and require health-promoting lifestyle modifications to prevent a progressive rise in blood pressure and CVD.
- Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with drugs from other classes.
- Certain specific high-risk conditions are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, \( \beta \)-blockers, calcium channel blockers).
- Two or more antihypertensive medications will be required to achieve goal BP in most hypertensive patients.
- For patients with BP >20/10 mm Hg above the BP goal, initiation of therapy using two agents, one of which will usually be a thiazide diuretic, should be considered.
- Hypertension will be controlled only if patients are motivated to stay on their treatment plan. Positive experiences, trust in the clinician, and empathy improve patient motivation and satisfaction.

Information derived from Chobanian et al. 12,13

Figure 2. Residual lifetime risk of hypertension in women and men aged 65 years. Cumulative incidence of hypertension in 65-year-old women and men. Data for 65-year-old men in the 1952 to 1975 period are truncated at 15 years because there were few participants in this age category who were followed up beyond this time interval. Reprinted with permission from Vasan et al. 9
or absence of risk factors or target-organ damage for the purpose of defining treatment thresholds and goals. Although we recognize the importance of total CVD risk in making treatment recommendations, risk stratification does have major challenges that may limit its use in clinical practice: (1) Many busy practitioners consider the time and effort needed to compile the required data on each patient and to perform the risk stratification calculation to be so excessive that they do not routinely do so, despite recommendations in treatment guidelines. (2) Biological variability is such that risk stratification schemes may yield inexact and incorrect predictions.18

In the worst case, this would result in erroneous classification of an individual as low risk, leading to inappropriate withholding of treatment. For these reasons, and because elevated BP per se is such a robust CVD risk factor, JNC 7 recommends that all people with hypertension be treated with antihypertensive medications as well as lifestyle modification.

The European Society of Hypertension–European Society of Cardiology guidelines for the management of hypertension17 differ in substance from those of JNC 7.12,13 The European classification of hypertension is complex, including the 3 stages of hypertension (BP ≥140/90, ≥160/100, and ≥180/110) from JNC 6, plus a special class for isolated systolic hypertension (ISH), and the categories of “optimal, normal, and high normal” BP. The European guidelines classify hypertensive individuals into “low, moderate, high, and very high added risk,” to indicate an approximate absolute 10-year risk of CVD of <15%, 15% to 20%, 20% to 30%, and >30%, respectively, according to Framingham criteria.19 Risk stratification is based on the presence or absence of target-organ damage, concomitant risk factors for CVD, history of diabetes, and associated clinical conditions. This classification is used to determine the threshold for antihypertensive drug treatment. According to the European guidelines, some persons with stage 1 or even stage 2 hypertension would be recommended for monitoring and lifestyle modifications only. This represents a substantially less aggressive approach to antihypertensive treatment than that recommended by JNC 7.12,13

The US and European guidelines also differ in the extent to which they provide specific recommendations to the practitioner for choosing treatments. JNC 7 provides specific recommendations (choice of drugs) for the pharmacological treatment of elevated BP, whereas the European guidelines defer drug choices to the healthcare provider’s judgment with consideration of the individual patient’s personal, medical, and cultural characteristics.

### Thresholds and Targets for BP Reduction Therapy

On the basis of evidence from multiple clinical trials, JNC 7 recommends that the threshold for pharmacological treatment of hypertension should be BP ≥140/90 mm Hg, except in the presence of diabetes or chronic kidney disease, in which case prehypertensive persons should be started on appropriate drug therapy, particularly if a trial of lifestyle modification fails to reduce their BP to goal (Table 3).2 The BP goal for the general population of hypertensives is <140/90 mm Hg; for persons with diabetes or chronic kidney disease, it is <130/80 mm Hg. However, because myocardial infarction, stroke, and other cardiovascular events occur in many individuals with BPs below these (admittedly arbitrary) goals, an “ideal” BP, based on epidemiological data, would appear to be 115/75 mm Hg or lower.1 This has prompted many to advocate a “go as low as the patient will tolerate” strategy of antihypertensive treatment. Expert committees and treatment guidelines have not embraced such a radical approach because evidence from randomized controlled outcome trials with low BP targets is sparse. It is not clear that optimal BP achieved by pharmacological means has a risk profile similar to naturally occurring optimal BP. Furthermore, the risks associated with antihypertensive drug therapy in the high doses needed to reduce BP to optimal levels are uncertain, as is the cost of this approach.

Interestingly, data from a number of sources, including the Western Infirmary in Glasgow and NHANES, have shown that hypertensive persons have higher mortality rates than normotensive persons, even when their BP is controlled with antihypertensive medications. The 9-year follow-up data

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**TABLE 3.** Lifestyle Modifications to Manage Hypertension*†

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate Systolic BP Reduction, Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI 18.5–24.9)</td>
<td>5–20 mm Hg/10-kg weight loss20,21</td>
</tr>
<tr>
<td>Adopt DASH diet eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a</td>
<td>8–14 mm Hg22–23</td>
</tr>
<tr>
<td></td>
<td>reduced content of saturated and total fat</td>
<td></td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g</td>
<td>2–8 mm Hg22,24</td>
</tr>
<tr>
<td></td>
<td>sodium chloride)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least</td>
<td>4–9 mm Hg23,24</td>
</tr>
<tr>
<td></td>
<td>30 minutes per day, most days of the week)</td>
<td></td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol)</td>
<td>2–4 mm Hg27</td>
</tr>
<tr>
<td></td>
<td>[eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>more than 1 drink per day in women and lighter-weight persons</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index calculated as weight in kilograms divided by the square of height in meters; DASH, Dietary Approaches to Stop Hypertension.

*For overall cardiovascular risk reduction, stop smoking.

†The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.

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from NHANES I, obtained between 1982 and 1984, showed 30% (for women) and 36% (for men) increases in risk of death in persons previously diagnosed as hypertensive and treated with medication, where BP was not elevated on follow-up examination, compared with normotensive persons surveyed. Whether these numbers could be improved with more aggressive BP goals and more modern treatment modalities remains to be determined.

The major randomized controlled trial that addressed the issue of BP treatment targets in essential hypertension is the Hypertension Optimal Treatment (HOT) study. HOT evaluated the effects on clinical outcomes of various target DBPs (\(\leq 80\) mm Hg versus \(\leq 85\) mm Hg versus \(\leq 90\) mm Hg) in 18 790 hypertensive individuals. In the study as a whole, the lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6 mm Hg, and the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg. However, among the 1501 diabetics enrolled in HOT, there was a 50% reduction in major cardiovascular events in the target group \(\leq 80\) mm Hg compared with the \(\leq 90\) mm Hg group. Achieved DBPs in these two treatment groups in the study as a whole were 81 and 85 mm Hg, respectively, indicating exquisite sensitivity of diabetic persons to small differences in BP.

The UK Prospective Diabetes Study Group (UKPDS) carried out a randomized, controlled trial in 1148 hypertensive type 2 diabetics that evaluated the effects of tight BP control (target DBP \(\leq 85\) mm Hg; achieved BP 144/82 mm Hg) versus less tight BP control (target DBP \(\leq 105\) mm Hg; achieved BP 154/87 mm Hg) on mortality and CVD outcomes. Tight BP control resulted in statistically significant and clinically important reductions in the risk of death related to diabetes (52%), complications related to diabetes (24%), stroke (44%), and microvascular disease (37%). Thus, both UKPDS and HOT showed major reductions in clinical outcomes associated with relatively small decreases in BP in persons with type 2 diabetes. These data have been used to justify the lower BP goal (\(< 130/80\) mm Hg) for hypertensive diabetics proposed in recent guidelines.

In addition to diabetes, chronic kidney disease, defined as either reduced excretory function with an estimated glomerular filtration rate \(< 60\) mL/min per 1.73 m\(^2\) (approximately corresponding to a creatinine of \(> 1.5\) mg/dL in men or \(> 1.3\) mg/dL in women) for \(\geq 3\) months or the presence of albuminuria (\(> 300\) mg/d or \(> 200\) mg/g creatinine), is another condition in which prognosis is extremely sensitive to BP. A meta-analysis of randomized controlled trials of antihypertensive treatment in persons with predominantly nondiabetic kidney disease has shown that the lowest risk for disease progression was at SBP levels of 110 to 129 mm Hg; after adjustment for SBP, DBP was not a risk factor. Importantly, the relationship between SBP and risk of kidney disease progression was dependent on urinary protein excretion: At levels of protein excretion \(\geq 1.0\) g/d, risk increased sharply at SBPs \(> 120\) to 130 mm Hg, whereas at excretion levels \(< 1.0\) g/d, risk did not increase until SBP exceeded 160 mm Hg (Figure 3). The National Kidney Foundation and JNC 7 recommend a goal BP of \(< 130/80\) mm Hg for all individuals with chronic kidney disease.

Benefit from more intensive versus less intensive antihypertensive therapy on clinical outcomes was shown in the meta-analysis of the Blood Pressure Lowering Treatment Trialists’ Collaboration, which included a total of 13 948 individuals enrolled in 4 trials. There was a 23% (95% CI 5 to 37) reduction in the risk of stroke and a 15% (95% CI 5 to 24) reduction in major cardiovascular events with more intensive compared with less intensive treatment. There was not clear evidence of benefit for coronary heart disease (5% [95% CI −11 to 19]), heart failure (16% [95% CI −18 to 41]) or total mortality (4% [95% CI −9 to 16]), but the 95% CIs did not exclude moderate advantages for participants assigned more intensive therapy. Although the level of BP at which disease risks are minimized (the optimal goal BP) cannot be determined from these overviews, the benefits were seen at BP levels substantially lower than those routinely achieved in clinical practice.

Acknowledgments

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References


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