

Long-Term Absolute Benefit of Lowering Blood Pressure in Hypertensive Patients According to the JNC VI Risk Stratification

Lorraine G. Ogden, Jiang He, Eva Lydick, Paul K. Whelton

Abstract—Blood pressure (BP) levels alone have been traditionally used to make treatment decisions in patients with hypertension. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recently recommended that risk strata, in addition to BP levels, be considered in the treatment of hypertension. We estimated the absolute benefit associated with a 12 mm Hg reduction in systolic BP over 10 years according to the risk stratification system of JNC VI using data from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. The number-needed-to-treat to prevent a cardiovascular event/death or a death from all causes was reduced with increasing levels of baseline BP in each of the risk strata. In addition, the number-needed-to-treat was much smaller in persons with ≥ 1 additional major risk factor for cardiovascular disease (risk group B) and in those with a history of cardiovascular disease or target organ damage (risk group C) than in those without additional major risk factors for cardiovascular disease (risk group A). Specifically, the number-needed-to-treat to prevent a death from all causes in patients with a high-normal BP, stage 1 hypertension, or stage 2 or 3 hypertension was, respectively, 81, 60, and 23 for those in risk group A; 19, 16, and 9 for those in risk group B; and 14, 12, and 9 for those in risk group C. Our analysis indicated that the absolute benefits of antihypertensive therapy depended on BP as well as the presence or absence of additional cardiovascular disease risk factors and the presence or absence of preexisting clinical cardiovascular disease or target organ damage. (*Hypertension*. 2000;35:539-543.)

Key Words: blood pressure ■ cardiovascular diseases ■ mortality ■ risk factors

Hypertension is an important public health challenge in the United States because of its high prevalence and the concomitant increase in the risk of cardiovascular/renal disease. As many as 43 million Americans have hypertension, which is defined as a systolic blood pressure (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) ≥ 90 mm Hg and/or taking antihypertensive medications.¹ According to the American Heart Association, in 1997, the estimated direct health costs (physician or other healthcare provider visits, hospital/nursing home stays, and antihypertensive medications) of the care of patients with hypertension in the United States were \$21.8 billion; the associated indirect costs (lost productivity due to morbidity and mortality) were \$8.2 billion.² Moreover, hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in the US population), stroke (the third leading cause of death), congestive heart failure, end-stage renal disease, and peripheral vascular disease.³⁻⁶

Prospective studies have repeatedly identified an increasing risk of cardiovascular disease, stroke, and renal insufficiency with progressively higher levels of both SBP and DBP.³⁻⁶ These studies have demonstrated a positive, contin-

uous, and independent association between BP and the incidence of coronary heart disease, stroke, congestive heart failure, and end-stage renal disease. They showed no evidence of a J-shaped relationship or a threshold below which increasing levels of BP are not associated with a corresponding increase in the risk of stroke, coronary heart disease, and renal disease. Furthermore, they suggest that the association of SBP with these outcomes is stronger than that of DBP. Randomized, controlled trials have demonstrated that antihypertensive drug therapy reduces the risk of cardiovascular disease and stroke among patients with mild hypertension.⁶⁻⁹

Traditionally, BP levels alone were used to make treatment decisions in patients with hypertension. This approach was based on the fact that elevated BP is an important indicator of the relative risk of cardiovascular disease among groups. This approach worked well for treatment decisions made in patients with moderate or more severe forms of hypertension (stages 2 to 3), but it is less well suited for treatment decisions in patients with milder elevations of BP. The recently published sixth report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) emphasized the importance of absolute, as

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opposed to relative, risk in clinical decision-making.¹⁰ For the first time, the JNC report presented a risk stratification system that was based not only on an individual's average BP level, but also on the presence or absence of target organ damage or other risk factors.¹⁰ The objectives of our study were to evaluate the absolute benefit derived from treating hypertension according to the JNC VI risk stratification system using the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHEFS) population.

Methods

Study Population

In the first National Health and Nutrition Examination Survey (NHANES I), a multistage, stratified, probability sampling design was used to select a representative sample of the US civilian noninstitutionalized population aged 1 to 74 years.^{11,12} Certain population subgroups, including those with a low income, women of childbearing age (25 to 44 years), and elderly persons (65 years or older) were oversampled. The NHEFS is a prospective cohort study of NHANES I participants who were 25 to 74 years of age when the survey was conducted (from 1971 to 1975).¹³⁻¹⁶ Of the 14 407 persons in this age range at baseline, 1473 were excluded because they had taken antihypertensive medication within the preceding 6 months, and 306 were excluded because information on important baseline covariables was missing. Of the remaining 12 628 participants, 359 (2.8%) were lost to follow-up, which left a total of 12 269 participants for inclusion in the current analysis.

Data Collection

Baseline data collection included information on medical history, standardized medical examinations, dietary history, laboratory tests, and anthropometric measurements.^{11,12} At the beginning of the baseline physical examination, a physician measured BP once with the examinee seated. With few exceptions, a standard mercury sphygmomanometer and a cuff that was at least 20% wider than the diameter of the arm (13 cm or 9.5 cm) was used to measure the participant's BP level. American Heart Association guidelines were followed. Blood samples were obtained, and frozen serum was sent to the Centers for Disease Control for the determination of serum total cholesterol. The baseline questionnaire on medical history included questions about selected health conditions and medications used for these conditions during the preceding 6 months. Baseline information on smoking status was obtained in a random subsample of 6142 participants who underwent more detailed baseline examination.^{11,12} For the remaining study participants, information on smoking status at baseline was derived from responses to questions on lifetime smoking history that were obtained during follow-up interviews in 1982 to 1984 or later.^{17,18} The validity of information obtained using this approach has been documented.^{17,18}

Follow-up data were collected between 1982 and 1984, and in 1986, 1987, and 1992.¹³⁻¹⁶ In preparation for each follow-up examination, a participant or his/her proxy was tracked to a current address. The examination included an in-depth interview with the participant or proxy. In addition, relevant hospital and nursing home records were obtained, including pathology reports and electrocardiograms. A death certificate was requested for all decedents. Mortality from cardiovascular disease was based on death certificate reports. Incident cardiovascular disease was based on documentation of an event that met prespecified study criteria and occurred during the period between the participant's baseline examination and the last follow-up interview. The validity of study outcome data from both sources has been documented.¹⁹

Cause-specific mortality was identified by means of underlying cause of death reports using the following codes from the *International Classification of Diseases*, Ninth Revision: 410 to 414 (coronary heart disease), 430 to 438 (stroke), and 390 to 459 (cardiovascular disease). A new cardiovascular disease event was based on a death certificate report in which the underlying cause of

death was recorded as code 390 to 459 or as ≥ 1 hospital and/or nursing home stays in which the participant had a discharge diagnosis with a code of 390 to 459.

Risk Stratification

Risk of cardiovascular disease in hypertensive patients is determined by the BP level and the presence or absence of target organ damage or other risk factors, such as cigarette smoking, dyslipidemia, and diabetes. The JNC VI report recommended a risk stratification system that is based on 3 categories of BP and 3 risk groups (A, B, and C).¹⁰ The 3 BP categories (SBP/DBP) are as follows: high-normal (130 to 139/85 to 89 mm Hg), stage 1 hypertension (140 to 159/90 to 99 mm Hg), and stages 2 or 3 hypertension ($\geq 160/\geq 100$ mm Hg). Risk group A includes patients who do not have clinical cardiovascular disease, target organ damage, or other cardiovascular disease risk factors. Risk group B includes patients who do not have clinical cardiovascular disease, target organ damage, or diabetes but who do have ≥ 1 other cardiovascular disease risk factor, such as smoking, dyslipidemia, age > 60 years, male sex, postmenopausal status (in women), or a family history of cardiovascular disease. Risk group C includes patients with diabetes mellitus, clinically manifest cardiovascular disease, or target organ damage.¹⁰ In the present analysis, risk group B included men, postmenopausal women, or those who were ≥ 60 years of age, current smokers, or had a serum total cholesterol ≥ 240 mg/dL. Risk group C included participants who had a self-reported history of diabetes, heart attack, heart failure, stroke, or renal disease or who had evidence of these conditions during their baseline examination.

Statistical Analysis

Poisson regression analysis was used to model the relationship between SBP and mortality from all-cause or cardiovascular diseases. Categorization and quadratic terms were used to test the linearity of log mortality on SBP. In addition, the differences in regression coefficients of log mortality on SBP among the 4 BP categories ($< 130/< 85$ mm Hg, 130 to 139/85 to 89 mm Hg, 140 to 159/90 to 99 mm Hg, and $\geq 160/\geq 100$ mm Hg) were tested by using interaction terms. Because no evidence of deviation from linearity or of interaction among the different levels of BP existed, an overall model was used for each outcome. Risk differences among the 3 groups were modeled using separate intercepts and interaction terms. SBP levels were centralized to their mean value before performing regression analyses to stabilize the estimates of regression coefficients on total and cardiovascular mortality and cardiovascular incidence. The Poisson regression models for cumulative log mortality (event rate) over a 10-year period were as follows:

$$\begin{aligned} \text{Total Mortality} = & -3.6517 + (1.8379 \times \text{risk group B}) \\ & + (2.4632 \times \text{risk group C}) + [0.0343 \times (\text{SBP} - 132)] \\ & - [0.0133 \times (\text{SBP} - 132) \times \text{risk group B}] \\ & - [0.0179 \times (\text{SBP} - 132) \times \text{risk group C}] \end{aligned}$$

$$\begin{aligned} \text{Cardiovascular Mortality} = & -5.7325 + (3.0247 \times \text{risk group B}) \\ & + (3.9434 \times \text{risk group C}) \\ & + [0.0613 \times (\text{SBP} - 132)] \\ & - [0.0342 \times (\text{SBP} - 132) \times \text{risk group B}] \\ & - [0.0434 \times (\text{SBP} - 132) \times \text{risk group C}] \end{aligned}$$

$$\begin{aligned} \text{Cardiovascular Event Rate} = & -2.3035 + (0.9649 \times \text{risk group B}) \\ & + (1.6462 \times \text{risk group C}) \\ & + [0.0285 \times (\text{SBP} - 132)] \\ & - [0.0080 \times (\text{SBP} - 132) \times \text{risk group B}] \\ & - [0.0131 \times (\text{SBP} - 132) \times \text{risk group C}] \end{aligned}$$

To estimate the absolute reduction in the risk of mortality associated with a 12 mm Hg drop in SBP over a 10-year period of follow-up among the 9 groups defined by different BP levels and cardiovascular disease risk, we first calculated the 10-year probability of death using observed data from the NHEFS population. We then calculated the

TABLE 1. Distribution of NHANES I Epidemiologic Follow-up Study Participants With a High-Normal BP or Hypertension at Baseline According to BP Level and Risk Categorization

SBP/DBP, mm Hg	Risk Group A	Risk Group B	Risk Group C
130–139/85–89	276 (3.9)	1371 (19.3)	300 (4.2)
140–159/90–99	257 (3.6)	2208 (31.1)	603 (8.5)
≥160/≥100	107 (1.5)	1505 (21.2)	463 (6.5)
Total	640 (9.0)	5084 (71.7)	1366 (19.2)

Values are n (%).

Risk group A includes participants with no evidence of target organ damage, clinical cardiovascular disease, or additional major risk factors for cardiovascular disease. Risk group B includes participants who were men or postmenopausal women ≥60 years of age, current smokers, or had a serum total cholesterol ≥240 mg/dL. Risk group C includes participants who had a self-reported history of diabetes, heart attack, heart failure, stroke, or renal disease at baseline or had used medication for these conditions during the preceding 6 months.

10-year probability of death for each participant assuming a 12 mm Hg reduction in SBP throughout the period. The difference between the 2 probabilities represents the reduction in absolute risk that could be expected from a 12 mm Hg reduction in SBP. The number-needed-to-treat was calculated by taking the reciprocal of the absolute reduction in risk, which represents the number of patients who would have to be treated to prevent 1 outcome event. The number-needed-to-treat is a useful way of expressing the degree of benefit that can be expected from a healthcare intervention.^{20,21} To correct for regression dilution bias, we calculated the coefficient of reliability using BP measurements at baseline and at the 10-year follow-up examination.

Results

Table 1 shows the distribution of the 7090 NHEFS participants who had high-normal BP or hypertension according to their baseline level of BP and category of presumed cardiovascular risk. Slightly less than a third of the participants (27.9%) had high-normal BP, 43.3% had stage 1 hypertension, and 29.3% had stage 2 or 3 hypertension. A small minority (9.0%) of the study participants had no other risk factors for cardiovascular disease and no evidence of target organ damage or clinical cardiovascular disease (risk group A). The vast majority, however, had ≥1 other risk factor for cardiovascular disease (71.7%; risk group B), and a substantial minority had a current history of diabetes or of other cardiovascular or renal diseases (19.2%; risk group C).

The number-needed-to-treat to prevent a cardiovascular disease event, with or without correction for regression dilution bias, is presented in Table 2. The number was determined using an average reduction of 12 mm Hg in SBP over 10 years of

follow-up. As expected, the number was reduced with increasing levels of baseline BP in each of the risk groups. The number-needed-to-treat was also smaller among persons who had major risk factors or who had a history of cardiovascular diseases (risk groups B and C) compared with their counterparts in risk group A, who did not have additional risk factors for cardiovascular disease. For example, to prevent a cardiovascular event, the number-needed-to-treat for high-normal BP, stage 1 hypertension, or stage 2 or 3 hypertension, respectively, was 25, 20, and 10 in risk group A; 13, 11, and 7 in risk group B; and 10, 9, and 8 in risk group C.

The number-needed-to-treat to prevent a cardiovascular death was also reduced with increasing levels of baseline BP in each of the risk groups (Table 3). However, this reduction was particularly prominent in those without a major risk factor for cardiovascular disease (risk group A). In this group, the number-needed-to-treat was 486 for persons with high-normal BP, 273 for those with stage 1 hypertension, and 34 for their counterparts with stage 2 or 3 hypertension. The number-needed-to-treat to prevent a cardiovascular death was much smaller among persons with major risk factors or with a history of cardiovascular diseases (risk groups B and C) than in those who did not have additional risk factors for cardiovascular disease (risk group A). For example, the number-needed-to-treat for persons with high-normal BP, stage 1 hypertension, or stage 2 or 3 hypertension, respectively, was 36, 27, and 12 for risk group B and 21, 18, and 11 for risk group C.

The number-needed-to-treat to prevent a death from all causes is presented in Table 4. In each of the risk groups, the number-needed-to-treat was reduced with increasing levels of baseline BP. In addition, the number was much smaller in persons who had ≥1 additional major risk factor for cardiovascular disease (risk group B) and in those with a history of cardiovascular disease or target organ damage (risk group C) than in those in risk group A. Specifically, the number-needed-to-treat for persons with high-normal BP, stage 1 hypertension, or stage 2 or 3 hypertension, respectively, was 81, 60, and 23 for those in risk group A; 19, 16, and 9 for those in risk group B; and 14, 12, and 9 for those in risk group C.

Discussion

There are ≈22.7 million US residents aged ≥18 years who take medications that have been prescribed for the treatment of high BP.¹ Only a small proportion of the almost 55 million US adults with either known high BP (43.2 million) or a history of high BP (12.7 million) have clinical symptoms, and

TABLE 2. Estimated Effect of a 12 mm Hg Reduction in SBP Over 10 Years on the Number-Needed-to-Treat to Prevent a Cardiovascular Disease Event Among NHANES I Epidemiologic Follow-Up Study Participants According to Baseline BP Level and Category of Presumed Cardiovascular Risk

SBP/DBP, mm Hg	Risk Group A		Risk Group B		Risk Group C	
	Uncorrected	Corrected*	Uncorrected	Corrected*	Uncorrected	Corrected*
130–139/85–89	41	25	23	13	19	10
140–159/90–99	33	20	19	11	17	9
≥160/≥100	16	10	13	7	15	8

See text or Table 1 for definition of risk groups.

*Corrected for regression dilution bias using a reliability coefficient of 0.53 to correct for imprecision in the measurement of SBP.

TABLE 3. Estimated Effect of a 12 mm Hg Reduction in SBP Over 10 Years on the Number-Needed-to-Treat to Prevent a Cardiovascular Disease Death Among NHANES I Epidemiologic Follow-Up Study Participants According to Baseline BP Level and Category of Presumed Cardiovascular Risk

SBP/DBP, mm Hg	Risk Group A		Risk Group B		Risk Group C	
	Uncorrected	Corrected*	Uncorrected	Corrected*	Uncorrected	Corrected*
130–139/85–89	701	486	60	36	37	21
140–159/90–99	394	273	44	27	31	18
≥160/≥100	49	34	21	12	20	11

See text or Table 1 for definition of risk group.

*Corrected for regression dilution bias using a reliability coefficient of 0.53 to correct for imprecision in the measurement of SBP.

most are asymptomatic. The main objective in lowering BP is to reduce the patient's absolute risk of premature death and disease, primarily by reducing their risk of cardiovascular diseases. In the US, ≈13% and 14% of the adult population, respectively, has high-normal BP or stage 1 hypertension.¹ In contrast, only ≈4% and 1% of the adult population, respectively, has stages 2 to 3 hypertension.¹ Epidemiological studies and randomized trials have repeatedly demonstrated that the relative risk of cardiovascular disease increases continuously with increasing levels of BP.^{3–9} However, no specific BP level identifies the need for antihypertensive treatment in an individual patient. We compared the expected absolute benefits of BP lowering in the patients in the 9 groups characterized by baseline BP level and cardiovascular disease risk. Our results indicate that the clinical decision to treat high BP should be based on a person's average BP levels as well as on the presence or absence of other cardiovascular disease risk factors.

An important strength of our study is that we were able to calculate the number-needed-to-treat to prevent an event using a large representative sample of the US general population. An additional strength was that the outcomes of interest (cardiovascular and total mortality) were assessed over a prolonged period of follow-up, which averaged 20 years. A 12 mm Hg reduction in SBP was chosen as the treatment effect of interest because it represents the average BP reduction that has been achieved in the major randomized controlled trials that have been conducted to determine the efficacy of antihypertensive drug treatment in reducing cardiovascular disease risk.⁶ If a larger reduction in SBP were achieved in hypertensive patients, a greater benefit on morbidity and mortality might be observed. Likewise, the BP-lowering benefit might be increased with more prolonged treatment for hypertension than was the case in the databases

we used. Previous analyses have indicated that the reduction in stroke risk observed in clinical trials is similar to that expected on the basis of the risk associated with high BP in observational studies.^{3,7} However, the reduction in risk for coronary heart disease in clinical trials is less than expected when based on results from observational studies. One explanation for the latter discrepancy is that the clinical trials from which the estimates of coronary heart disease risk reduction were derived had a much shorter average duration (3 to 5 years) than the corresponding experience in observational studies (>10 years).

Our analysis supports the JNC VI recommendation to prescribe drug treatment as the initial therapy in patients with stages 2 to 3 hypertension and in those who have lower BP levels when these persons have diabetes, target organ disease, or cardiovascular disease.¹⁰ Moreover, our results suggest that treatment of those with high-normal BP or stage 1 hypertension who concurrently have ≥1 other major risk factor for cardiovascular disease is cost-effective. In such patients, the number-needed-to-treat was similar to that noted in their counterparts with stages 2 to 3 hypertension who did not have an additional major risk factor for cardiovascular disease.

Only a minority (9.0%) of those with a high-normal BP or hypertension did not have additional risk factors for cardiovascular disease. The number-needed-to-treat was high in this group, especially in persons with high-normal BP or stage 1 hypertension. Therefore, lifestyle modification may provide a more meaningful approach for lowering BP in this group.

Overall, antihypertensive treatment is a cost-effective approach to the reduction of cardiovascular disease and total mortality compared with the treatment of other cardiovascular disease risk factors. For example, pooling the experience of the 5 major trials evaluating the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors indicated

TABLE 4. Estimated Effect of a 12 mm Hg Reduction in SBP Over 10 Years on the Number-Needed-to-Treat to Prevent An All-Cause Death Among NHANES I Epidemiologic Follow-Up Study Participants According to Baseline BP Level and Category of Presumed Cardiovascular Risk

SBP/DBP, mm Hg	Risk Group A		Risk Group B		Risk Group C	
	Uncorrected	Corrected*	Uncorrected	Corrected*	Uncorrected	Corrected*
130–139/85–89	130	81	33	19	25	14
140–159/90–99	97	60	27	16	22	12
≥160/≥100	37	23	17	9	16	9

See text or Table 1 for definition of risk groups.

*Corrected for regression dilution bias using a reliability coefficient of 0.53 to correct for imprecision in the measurement SBP.

that an average decrease of 20% in total serum cholesterol and of 28% in LDL cholesterol was associated with an absolute risk reduction of 14 deaths from cardiovascular disease and 16 deaths from all causes per 1000 persons treated over the 5-year follow-up period.²² Therefore, the number-needed-to-treat to prevent a death over 10 years of follow-up would likely be 35 for mortality from cardiovascular diseases and 30 for mortality from all causes. On the basis of our analysis, the number-needed-to-treat to prevent mortality from cardiovascular disease or all causes in patients with stages 2 to 3 hypertension or in patients with high-normal BP or hypertension who had ≥ 1 other major risk factor for cardiovascular disease or a prior history of cardiovascular disease is similar or even lower. Results from the recently published UK Prospective Diabetes Study indicate that the number-needed-to-treat to prevent 1 death related to diabetes is 15 for an average reduction in SBP/DBP of 10/5 mm Hg over 10 years among type 2 diabetic patients with hypertension.²³ The benefit of BP control may be greater than blood-glucose control among these patients.^{23,24}

In our study participants, only a single BP measurement was obtained at the baseline examination. This imperfect measurement of BP might have resulted in a misclassification of our study participants into the different BP categories and a consequent dilution of our estimates of absolute risk. Because of this, we entered SBP as a continuous variable in the risk equations to avoid estimating absolute risk based on BP category. Furthermore, a repeated measurement of BP at the 10-year follow-up was used to correct for the possibility of regression dilution bias. These strategies should have minimized the potential for bias due to imperfections in the measurement of BP at the baseline examination.

In conclusion, our analysis demonstrates that the absolute benefits of antihypertensive therapy depend not only on BP but also on the presence or absence of additional cardiovascular disease risk factors and the presence or absence of preexisting clinical cardiovascular disease or target organ damage. These findings have important implications for clinical practice and public health. To make an informed decision regarding the wisdom of initiating antihypertensive drug treatment for high BP, the practicing clinician must assess the absolute risk of an individual patient by determining the presence or absence of other cardiovascular disease risk factors and the presence or absence of clinical cardiovascular disease or target organ damage. To improve the cost-effectiveness of antihypertensive interventions in community programs, an emphasis should be placed on targeting high-risk populations. Our study also suggests that a need exists for more aggressive BP lowering among those with high-normal or stage 1 hypertension who concurrently have ≥ 1 additional major risk factors for cardiovascular disease.

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