Cardiovascular Outcome in Relation to Progression to Hypertension in the Copenhagen MONICA Cohort

Tine Willum Hansen, Jan A. Staessen, Haifeng Zhang, Christian Torp-Pedersen, Susanne Rasmussen, Lutgarde Thijs, Hans Ibsen, and Jørgen Jeppesen

Background: Previous studies of the risk associated with high–normal blood pressure (BP) determined BP category in a cross-sectional fashion.

Methods: In 1982–1984, we measured BP in a random sample of 2357 Danes without previous cardiovascular complications, aged 30 to 60 years. We determined progression from optimal (<120/80 mm Hg), normal (120 to 129/80 to 84 mm Hg), and high–normal (130 to 139/85 to 89 mm Hg) BP to hypertension (≥140/90 mm Hg or start of antihypertensive treatment) by follow-up until 1993–1994. We studied the prognostic significance of progression by subsequent follow-up until 2003.

Results: During 10.9 years (median), the crude progression rates to hypertension from optimal, normal, and high–normal BP were 10.4%, 37.3%, and 58.1%, respectively. During an additional 9.4 years (median), 218 first cardiovascular end points (cardiovascular death, nonfatal stroke, and nonfatal coronary heart disease) occurred. With sustained optimal or normal BP as reference, the multivariate-adjusted hazard ratios were similar ($P > .60$) for progression to high–normal BP (1.57; 95% confidence interval [CI], 1.06–2.33), for progression to hypertension (1.64; 95% CI, 1.19–2.26), and for sustained high–normal BP or hypertension (1.78; 95% CI, 1.39–2.29). The absolute 10-year cardiovascular risks were 5.1% for optimal or normal BP without progression, 11.1% and 13.9% for progression to high–normal BP or hypertension, respectively, and 18.7% for sustained high–normal BP or hypertension.

Conclusions: Progressing from optimal or normal BP to high–normal BP or hypertension carries nearly the same risk as sustained high–normal BP or hypertension. Am J Hypertens 2007;20:483–491 © 2007 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, cardiovascular disease, hypertension, population study, epidemiology.

The relation between cardiovascular outcome and blood pressure (BP) is log-linear without a critical level above which the risk suddenly increases.[1] However, for the diagnosis and management of hypertension, clinicians need operational thresholds. Therefore, the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC6)[2] and the World Health Organization and the International Society of Hypertension (WHO-ISH)[3] proposed a classification into optimal, normal, or high–normal BP and hypertension. In Framingham,[4] less than 65 years of age, 4-year progression rates from optimal, normal, and high–normal BP to hypertension were 5.3%, 17.6%, and 37.3%, and in older subjects 16.0%, 25.5%, and 49.5%, respectively.

In several large-scale cohort studies,[5–8] high–normal BP at baseline was associated with an increased rate of cardiovascular complications, compared with optimal BP. However, to our knowledge, no prior study prospectively assessed the progression rates from optimal or normal BP to high–normal BP or to hypertension and evaluated the

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From the Research Center for Prevention and Health (TWH), Copenhagen, Denmark; Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven (JAS, LT), Leuven, Belgium; Department of Cardiology, the First Affiliated Hospital, Nanjing Medical University (HZ), Nanjing, China; Department of Cardiology, Bispebjerg University Hospital (TWH, CT-P), Copenhagen, Denmark; and Medical Department M, Glostrup University Hospital (SR, HI, JJ), Copenhagen, Denmark.

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Address correspondence and reprint requests to Dr. Tine Willum Hansen, Bispebjerg Hospital, Y-forskning bygning 40, Bispebjerg Bakke, DK-2400 Copenhagen NV, Denmark; e-mail: tw@heart.dk

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incidence of cardiovascular complications during a subsequent period of follow-up in relation to progression status. We therefore determined in the Danish participants of the MONItoring of trends and determinants in Cardiovascular Disease (MONICA) the 10-year progression rates to high–normal BP and hypertension. Next, we predicted the incidence of cardiovascular events from the initial change in BP category, while adjusting for covariates. Here, we demonstrated that progression from optimal or normal BP to high–normal BP or hypertension carried nearly the same risk as high–normal BP or hypertension sustained throughout the initial follow-up.

Methods

Study Population

The Ethics Committee of Copenhagen County approved the MONICA health survey.[9] The study was conducted in accordance with the Helsinki Declaration. Participants gave informed written consent. In 1982–1984, we selected a random sample of the residents of Copenhagen County with the goal to recruit an equal number of women and men, aged 30, 40, 50, and 60 years.[10] At baseline, the participation rate was 82.6%. In 1993–1994, the 3785 former participants were invited for a follow-up examination at the Research Center for Prevention and Health in Glostrup, of whom 2656 (70.2%) renewed informed written consent and were examined.[10] For the present analysis, we excluded 299 subjects, because at baseline (1982–1984) or first follow-up (1993–1994) they had a history of myocardial infarction (n = 14 and 58, respectively) or stroke (n = 18 and 41), because they only attended the follow-up examination (n = 94), or because information on antihypertensive medication was missing either at baseline (n = 20) or at follow-up (n = 45). Thus, the number of subjects statistically analyzed totaled 2357 (88.7% of those with a follow-up examination).

Data Collection

In 1982–1984 and 1993–1994, the same trained nurse did all BP readings by auscultation of the Korotkoff sounds. After the subjects had rested for 5 min in the sitting position, she obtained two consecutive BP readings with a random zero mercury sphygmomanometer fitted with an appropriate cuff size. These two readings were averaged for analysis. At the baseline examination (1982–1984), we classified the participants with nonhypertensive BP values into those with optimal, normal, or high–normal BP by means of the thresholds proposed in the JNC6[2]/WHO-ISH[3] guidelines. Optimal BP was a level lower than 120 mm Hg systolic and 80 mm Hg diastolic. Normal BP ranged from 120 to 129 mm Hg systolic or from 80 to 84 mm Hg diastolic. High–normal BP encompassed 130 to 139 mm Hg systolic or 85 to 89 mm Hg diastolic. Patients who had a BP of at least 140 mm Hg systolic or 90 mm Hg diastolic[11] or were taking antihypertensive drugs were classified as hypertensive. At the follow-up examination in 1993–1994, we reclassified the participants applying the same criteria. In untreated subjects, whenever systolic or diastolic BP belonged to different categories, the higher category of the two values was used for classification. We did not combine subjects with normal and high–normal BP into a single group with prehypertension as proposed by the JNC7 guidelines,[11] to keep our results comparable with those of other reports,[5–8] including the initial Framingham study,[6] and because the European guidelines[12] do not support the idea of labeling subjects with normal BP as being prehypertensive. The nurse counted heart rate at the radial artery during 15 sec. Body mass index was weight in kilograms divided by height in meters squared.

The participants completed at baseline (1982–1984) and follow-up (1993–1994) the same self-administrated questionnaire, which inquired into their past and current medical history, intake of medications, social class, smoking habits, and alcohol consumption. We coded social class as high for participants with professional or intermediate occupations and as low for those with partly skilled or unskilled jobs. High alcohol intake was a consumption of more than five alcoholic beverages per day.[13] Venous blood samples, collected after an overnight fasting, were analyzed for serum lipids by standard enzymatic methods.

Ascertainment of Events

The Danish National Board of Health reviewed the legal and ethical implications of our study and granted permission to access the national registries. We obtained vital status from the Danish Civil Registration System, the cause of death from blinded adjudication of the diseases on the death certificates, and nonfatal events from the Danish National Health Register.[14] We assessed the incidence of a composite end point consisting of cardiovascular death, nonfatal stroke (ICD-8 codes 431, 433, or 434 or ICD-10 codes I61 or I63), and nonfatal coronary heart disease (ICD-8 code 410 to 414 or ICD-10 codes I20 to I25).

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.1 (SAS Institute, Cary, NC). For comparison of means and proportions at baseline (1982–1984), we applied the standard normal z-test for large samples and the χ^2 statistic, respectively.

In prospective analyses, we first assessed progression to high–normal BP or hypertension at follow-up (1993–1994) from lower BP values at baseline (1982–1984). We identified determinants of progression and we calculated adjusted 10-year progression rates, using multiple logistic regression. We stratified progression rates according to age, using 50 years as the cutoff. Next, we examined the incidence of the composite cardiovascular end point until September 30, 2003, in relation to the cross-classification of BP status at baseline (1982–1984) and follow-up

(1993–1994). In unadjusted analyses, we compared the incidence of cardiovascular events according to progression status by Kaplan-Meier survival function estimates and the log-rank test. Next, we applied multiple Cox regression to model these associations, only considering time to the first cardiovascular event. We ascertained that the proportional hazard assumption underlying Cox regression was fulfilled by testing the interaction between progression status and follow-up time. We presented hazard ratios as floating absolute risks and calculated their standard errors as described by Easton et al.[15] This approach allows calculation of a 95% confidence interval (CI) for the relative risk in the referent group. To identify significant predictors of outcome, we used forward and backward selection with the *P* value for independent covariates to enter or stay in the model set at .05. We tested as possible covariates baseline characteristics (1982–1984) including gender, age, body mass index, heart rate, smoking, alcohol intake, social class, diabetes mellitus, the total-to-HDL cholesterol ratio, serum triglycerides, and percentage change in weight from baseline until follow-up (1993–1994). In addition to significant covariates of outcome, we also forced body mass index into the Cox model as a possible intermediate causal factor on the path to a worse cardiovascular outcome. We evaluated differences between hazard ratios using the test statement in the PHREG procedure as implemented in the SAS package. Statistical significance was a *P* value of .05 or less on two-sided tests.

Results

Baseline Characteristics of the Participants

At baseline in 1982–1984 the 2357 participants had a mean age of 43.3±10.7 years and included 1194 women (50.7%). Table 1 lists the baseline characteristics of the participants by gender. In 1982–1984, 628 women (52.6%) and 400 men (34.4%) had optimal BP; 247 women (20.7%) and 313 men (26.9%) had normal BP; and 129 women (10.8%) and 191 men (16.4%) had high–normal BP. The remaining 190 women (15.9%) and 259 men (22.3%) had hypertension.

Progression to Hypertension

During a median of 10.9 years (interquartile range, 10.6 to 11.2 years), we examined the progression in BP from baseline (1982–1984) to follow-up (1993–1994). Table 2 shows the cross-classification of participants by age group according to their BP status in 1982–1984 and 1993–1994. Progression to hypertension from the three nonhypertensive groups was about twice as frequent in the older group (287 of 707 subjects [40.6%]) than the younger group (215 of 1201 subjects [17.9%]). In participants aged less than 50 years at enrollment, progression to hypertension occurred on the basis of an increase in systolic BP alone in 25 participants (11.6%); diastolic BP alone in 78 (36.3%); as a result of crossing both the systolic and diastolic BP thresholds in 74 (34.4%); and on the basis of the use of antihypertensive agents in 38 (17.7%). In the older group,

Table 1. Characteristics by gender

Characteristics	Women (*N* = 1194)	Men (*N* = 1163)	*P*
Baseline characteristics (1982–1984)			
Age (y)	43.2 ± 10.8	43.4 ± 10.6	.64
Weight (kg)	63.2 ± 10.5	78.2 ± 11.4	<.001
Body mass index (kg/m^2)	23.6 ± 3.8	25.2 ± 3.4	<.001
Systolic blood pressure (mm Hg)	119.8 ± 16.0	124.2 ± 14.5	<.001
Diastolic blood pressure (mm Hg)	73.9 ± 10.1	78.8 ± 10.3	<.001
Heart rate (beats/min)	71.7 ± 9.9	68.8 ± 10.0	<.001
Total/HDL cholesterol ratio	3.70 ± 1.15	4.75 ± 1.57	<.001
Triglycerides (mmol/L)	1.04 ± 0.52	1.44 ± 1.07	<.001
History of diabetes, *n* (%)	13 (1.0)	18 (1.5)	.33
Antihypertensive drug treatment, *n* (%)	56 (4.7)	42 (3.6)	<.001
Smokers, *n* (%)	592 (49.6)	669 (57.5)	<.001
>5 alcoholic beverages per day, *n* (%)	3 (0.3)	61 (5.2)	<.001
High social class, *n* (%)*	163 (13.7)	318 (27.3)	<.001
Follow-up (1993–1994)			
Change in weight (%)	6.8 ± 10.0	4.7 ± 8.0	<.001
Hypertensive, *n* (%)	397 (33.2)	488 (42.0)	.002
Treated, *n* (%)	107 (27.0)	96 (19.7)	.01
Diuretics, *n* (%)	49 (45.8)	31 (32.3)	.05
β-blockers, *n* (%)	25 (23.4)	19 (19.8)	.48
ACE inhibitors, *n* (%)	8 (7.5)	30 (31.3)	<.001
Calcium antagonist, *n* (%)	27 (25.2)	28 (29.2)	.54
Other, n (%)	2 (1.9)	6 (6.3)	.11
Treated and controlled, *n* (%)	27 (25.2)	17 (17.7)	.19

Plus–minus values are mean ± SD. Hypertension was a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic, or use of antihypertensive drugs.

* Social class was coded high for professional and intermediate occupations and low for partly skilled and unskilled jobs.

Table 2. Blood pressure category at baseline and on follow-up by age group

	Blood pressure category on follow-up (1993–1994)							
	Optimal		Normal		High–normal		Hypertension	
	N	%	*N*	%	*N*	%	*N*	%
Age <50 y (*n* = 1339)								
Optimal (*n* = 746)	424	56.8	185	24.8	81	10.9	56	7.5
Normal (*n* = 322)	69	21.4	93	28.9	70	21.7	90	28.0
High–normal (*n* = 133)	11	8.3	22	16.5	31	23.3	69	51.9
Hypertension (*n* = 138)	3	2.2	7	5.1	13	9.4	115	83.3
Age ≥50 y (*n* = 1018)								
Optimal (*n* = 282)	100	35.5	81	28.7	50	17.7	51	18.1
Normal (*n* = 238)	30	12.6	38	16.0	51	21.4	119	50.0
High–normal (*n* = 187)	14	7.5	24	12.8	32	17.1	117	62.6
Hypertension (*n* = 311)	4	1.3	10	3.2	29	9.3	268	86.2

progression to hypertension was determined on the basis of an increase in systolic BP alone in 120 participants (41.8%; $P < .0001$ compared to the younger group); diastolic BP alone in 27 (9.41%; $P < .0001$); as a result of crossing both the systolic and diastolic BP thresholds in 83 (28.9%; $P = .19$); and on the basis of the use of antihypertensive agents in 57 (19.9%; $P = .54$).

In multivariate logistic regression (Table 3), compared with optimal BP, normal BP at baseline was associated with 4.32 and 4.90 increased risks of hypertension in the younger and older groups, respectively. High–normal BP was associated with 11.9 and 7.74 higher risks. Percent change in weight from baseline to follow-up (1993–1994) significantly and independently predicted the transition to hypertension. Among the other characteristics at enrolment, higher age and low social class were forerunners of hypertension in younger participants, whereas higher body mass index and higher total-to-HDL-cholesterol ratio predicted hypertension in the older group. In the younger age group, the 10-year incidence rates of hypertension with adjustments, applied as in Table 3, were 6.5% (95% CI, 4.9–8.6), 23.5% (CI, 18.9–28.9), and 46.0% (CI, 36.5–55.8) for subjects with optimal, normal, and high–normal BP at baseline. In the older age group, the corresponding adjusted rates were 16.9% (CI, 12.7–22.0), 50.2% (CI, 43.5–56.8), and 61.4% (CI, 53.6–68.6), respectively.

Progression as Predictor of Outcome

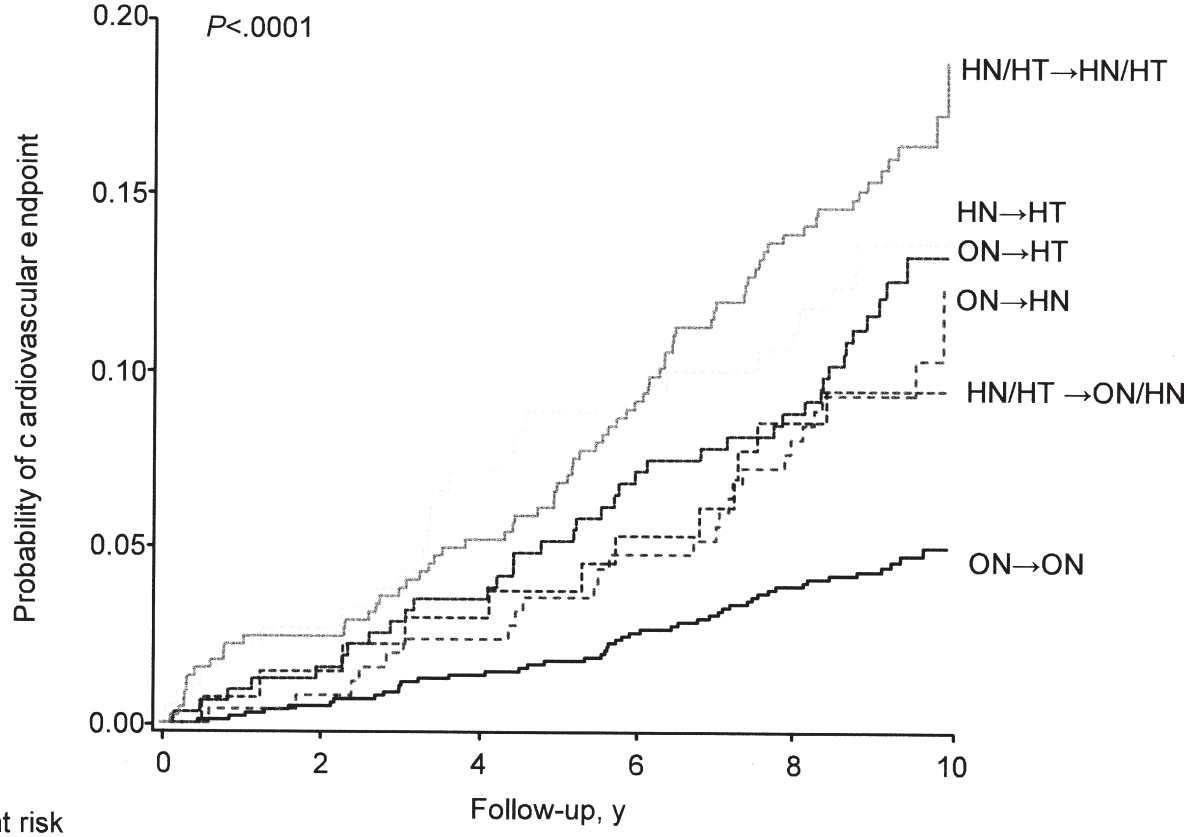
During follow-up from 1993–1994 until 2003 (median, 9.4 years; 5th to 95th percentile interval, 3.9 to 10.1 years), 20,883 person-years accrued. Of 249 deaths, 89 (35.7%) were due to cardiovascular illness. Two hundred eighteen subjects experienced at least one cardiovascular event, including 58 cardiovascular deaths, 30 strokes, and 130 coronary events.

We evaluated to what extent the cross-classification of the BP status in 1982–1984 and 1993–1994 predicted the incidence of the composite cardiovascular end point. For this analysis, we included 63 patients with high–normal BP at baseline and follow-up (four events) into the group of patients with sustained hypertension. Fig. 1 shows the unadjusted cumulative events rates according to the cross-

Table 3. Odds ratios from multiple logistic regression models for incident hypertension

	Age <50 y (*n* = 1202)		Age ≥50 y (*n* = 709)	
Predictor variables	**Odds ratio (95% CI)**	***P***	**Odds ratio (95% CI)**	***P***
Baseline blood pressure category				
Optimal	Referent		Referent	
Normal	4.32 (2.90–6.45)	<.001	4.90 (3.20–7.50)	<.001
High–normal	11.9 (7.23–19.6)	<.001	7.74 (4.85–12.4)	<.001
Other baseline characteristics				
Age (+10 y)	2.08 (1.46–2.97)	<.001	1.40 (0.98–2.02)	.07
Body mass index (+2 kg/m^2)	1.11 (0.99–1.23)	.07	1.21 (1.09–1.35)	<.001
Total/HDL cholesterol ratio (1 unit)	1.01 (0.85–1.21)	.88	1.23 (1.05–1.45)	.01
Social class* (low versus high)	1.67 (1.08–2.58)	.02	0.84 (0.53–1.33)	.45
Change in weight (+5%)	1.40 (1.27–1.54)	<.001	1.33 (1.20–1.47)	<.001

* Social class was coded high for professional and intermediate occupations and low for partly skilled and unskilled occupations. Other variables tested but not reaching statistical significance were sex, heart rate, smoking, alcohol intake, history of diabetes, and serum triglycerides.



No. at risk						
ON→ON	1020	1009	993	968	944	170
HN/HT→ON/HN	137	130	127	120	113	31
ON→HN	252	250	246	235	224	36
ON→HT	316	307	296	282	269	23
HN→HT	186	178	164	157	149	19
HN/HT→HN/HT	446	429	412	389	354	53

FIG. 1. Abbreviations indicate cross-classification by blood pressure categories in 1982–1984 and 1993–1994: ON→ON sustained optimal/normal blood pressure; HN/HT→ON/HN regression from high–normal blood pressure or hypertension to optimal/normal or high–normal blood pressure; ON→HN progression from optimal/normal to high–normal blood pressure; ON→HT progression from optimal/normal blood pressure to hypertension; HN→HT progression from high–normal blood pressure to hypertension; and HN/HT→HN/HT sustained high–normal blood pressure or hypertension. The *P* value is for trend across the blood pressure groups.

classification of BP. The 10-year cardiovascular risk increased from 5.1% for optimal or high–normal BP without progression, to 11.1% and 13.9% for progression from optimal–normal BP to high–normal BP or to hypertension, respectively. The 10-year risk was 18.7% in patients with high–normal BP or hypertension at baseline and follow-up. Next, in multivariate Cox regression models, we adjusted for significant covariates (Fig. 2). These included gender, age, heart rate, smoking, the total-to-HDL cholesterol ratio at baseline (1982–1984), and the percentage change in weight from baseline until follow-up (1993–1994). We also forced body mass index into these models. Subjects with optimal or normal BP at baseline and follow-up were the referent group. Participants who progressed from optimal or normal BP to high–normal BP or to hypertension had a significantly increased risk (Fig. 2). The hazard ratio in subjects progressing from optimal or normal BP to high–normal BP was similar to that in subjects progressing from optimal or normal BP to hypertension ($P = .92$), as well as to that in patients with

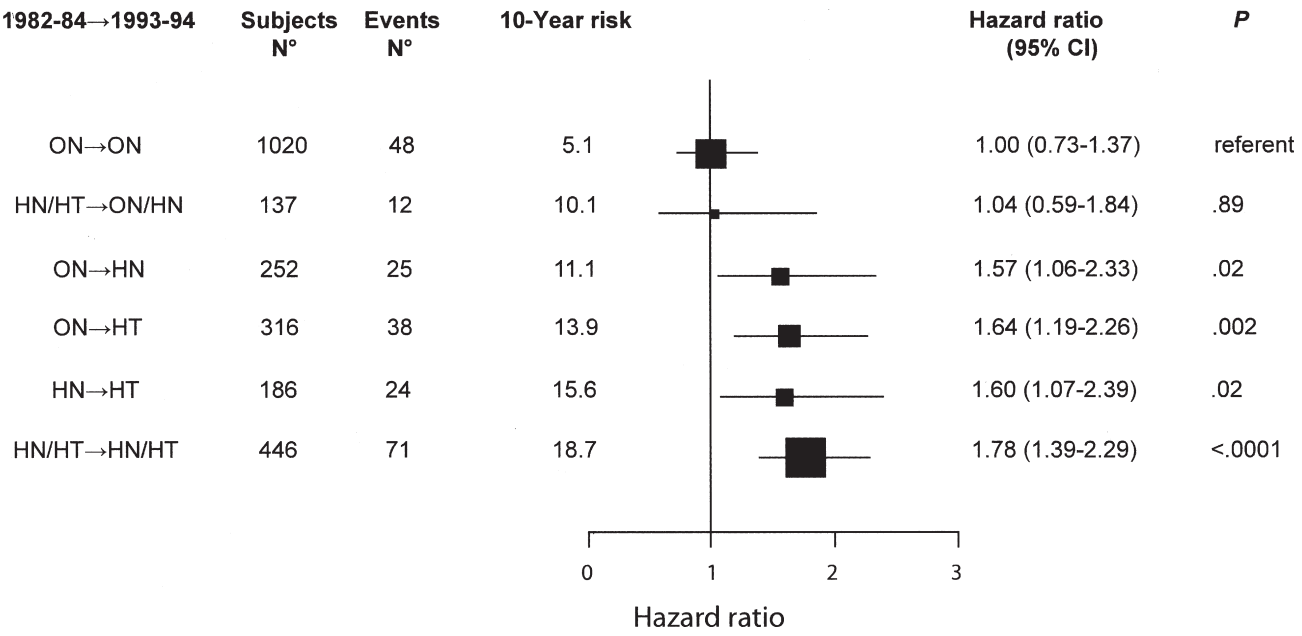


FIG. 2. Abbreviations indicate cross-classification by blood pressure categories in 1982–1984 and 1993–1994: ON→ON sustained optimal/normal blood pressure; HN/HT→ON/HN regression from high–normal blood pressure or hypertension to optimal/normal or high–normal blood pressure; ON→HN progression from optimal/normal to high–normal blood pressure; ON→HT progression from optimal/normal blood pressure to hypertension; HN→HT progression from high–normal blood pressure to hypertension; and HN/HT→HN/HT sustained high–normal blood pressure or hypertension. The hazard ratios were adjusted for baseline characteristics (1982–1984), including gender, age, heart rate, smoking, total-to-HDL cholesterol ratio, body mass index, and percentage change in weight during follow-up until 1992–1993. Squares are proportional to the number of events in each group. Horizontal lines denote the 95% confidence interval. All hazard ratios higher than unity were not significantly different from one another ($.60 < P < .92$).

sustained high–normal BP or hypertension throughout the initial follow-up ($P = .69$).

Sensitivity analyses (Table 4) addressed the risk associated with progression status in various groups or with adjustments for additional or alternative sets of covariates. To keep a meaningful number of end points in each stratum, we combined participants who progressed from the three nonhypertensive BP categories at baseline (1982–1984) to hypertension at follow-up (1993–1994). All sensitivity analyses were confirmatory, although some hazard ratios in progressors did not reach statistical significance due to the lower number of subjects and events.

Discussion

The key finding of our study was that in middle-aged and older subjects without previous cardiovascular complications, progression from optimal or normal BP to high–normal BP or hypertension carried about the same cardiovascular risk as high–normal BP or hypertension sustained during the initial follow-up. Our current study differs from other surveys,[5–8] which investigated the risk associated with high–normal BP, in that during the initial 10 years of follow-up we first determined progression from optimal or normal BP to high–normal BP or to hypertension, and that we subsequently kept our participants in follow-up for another 9.4 years to determine the prognostic significance of progression.

The investigators of the Framingham Heart Study[6] classified participants into one of the three nonhypertensive BP categories and assessed the incidence of first major cardiovascular events, using subjects with optimal BP at enrolment as the referent group. In adjusted analyses, the hazard ratios associated with a high–normal BP at baseline were 2.5 (95% CI, 1.6–4.1; $P < .001$) in women and 1.6 (95% CI 1.1–2.2; $P < .05$) in men. In supplementary analyses, which accounted for BP category and other risk factors as time-dependent covariates, the corresponding hazard ratios were 1.8 (95% CI, 1.0–3.1; $.05 < P < .10$) and 1.6 (95% CI, 1.1–2.3; $P < .05$), respectively. In a more recent analysis of the same cohort,[16] the Framingham investigators applied the JNC7 guidelines[11] to compare the risks associated with prehypertension (120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic) and normal BP (<120 mm Hg systolic and <80 mm Hg diastolic). In fully adjusted Cox models, that included BP status as a time-dependent covariate, the hazard ratios were 2.3 (95% CI, 0.8–6.3) and 3.5 (95% CI, 1.6–7.5) for stroke and for fatal and nonfatal myocardial infarction, respectively.

The researchers of the Atherosclerosis Risk in Communities Study (ARIC)[8] also applied a time-dependent strategy and reported in a fully adjusted Cox model a hazard ratio of 2.33 (95% CI, 1.85–2.92) for high–normal BP relative to optimal BP. The Chicago Heart Association Detection Project in Industry[5] as well as the National Health and Nutrition Examination Survey (NHANES I)[7]

Table 4. Sensitivity analysis of hazard ratios according to changes in blood pressure status

	Hazard ratios (95% CI)			
	HN/HT→ON/HN*	ON→HN*	Non-HT→HT*	HN/HT→HN/HT*
Baseline characteristic				
Women (n = 72/1194)	1.48 (0.68–3.25)	1.89 (0.93–3.83)	0.94 (0.55–1.61)	1.89 (1.22–2.91)§
Men (n = 146/1163)	0.67 (0.28–1.63)	1.56 (0.97–2.51)	2.00 (1.52–2.64)§	1.76 (1.29–2.41)§
≥50 y (n = 160/1018)	1.00 (0.53–1.87)	1.38 (0.85–2.23)	1.29 (0.97–1.73)	1.61 (1.23–2.12)§
<50 y (n = 58/1339)	0.85 (0.21–3.47)	1.97 (0.98–3.95)	2.80 (1.77–4.41)§	1.95 (1.00–3.68)‡
Never treated (n = 179/2131)	1.11 (0.63–1.98)	1.60 (1.08–2.38)‡	1.59 (1.22–2.08)§	1.70 (1.24–2.34)§
Alternative adjustments (n = 218/2357)				
Excluding body mass index	1.01 (0.57–1.79)	1.56 (1.05–2.31)‡	1.61 (1.25–2.06)§	1.74 (1.36–2.24)§
Additional risk factors†	1.07 (0.60–1.90)	1.58 (1.07–2.35)‡	1.63 (1.27–2.09)§	1.79 (1.34–2.39)§
Smoking and alcohol intake as time-dependent covariates	1.05 (0.59–1.85)	1.61 (1.08–2.38)‡	1.70 (1.33–2.17)§	1.84 (1.43–2.36)§

* HN/HT→ON/HN indicates regression from high–normal blood pressure or hypertension to optimal/normal or high–normal blood pressure; ON→HN indicates progression from optimal/normal to high–normal blood pressure; non-HT→HT indicates progression from nonhypertensive blood pressure to hypertension; and HN/HT→HN/HT indicates sustained high–normal blood pressure or hypertension. Subjects with optimal/normal blood pressure through out the follow up were the reference group. All hazard ratios were adjusted for baseline characteristics (1982–1984), including sex (if applicable), age, heart rate, smoking, total-to-HDL cholesterol ratio, body mass index, and percentage change in weight during follow-up until 1992–1993; † Additional risk factors were serum triglycerides, alcohol intake, social class, history of diabetes, and antihypertensive drug treatment at baseline (1982–1984) or follow-up (1993–1994). Significance of the hazard ratios: ‡ $P < .01$; § $P < .001$.

investigated outcome only in relation to BP categories at baseline without time-dependent covariates. In the former study,[5] a high–normal BP predicted mortality from coronary heart disease with hazard ratios relative to optimal BP of 1.34 (95% CI, 0.74–2.53) in women and 1.77 (95% CI, 1.12–2.79) in men. In the NHANES I survey,[7] the corresponding hazard ratio for fatal and nonfatal cardiovascular complications was 1.42 (95% CI, 1.09–1.84).

To our knowledge, all previously published studies[5–8] assessed the risk of high–normal BP in comparison with optimal BP and considered BP category as a risk factor either at baseline[5,7] or as a time-dependent covariate during the same follow-up period during which the events accumulated.[6,8] In the current study, we first evaluated progression from optimal or normal BP, and we predicted the incidence of cardiovascular complications during subsequent follow-up. The pathogenesis of hypertension and cardiovascular complications is interrelated and the underlying pathophysiologic mechanisms can similarly affect BP and the probability of an event. For instance, stiffening of the large arteries with aging may at the same time increase systolic BP and lower the diastolic perfusion pressure in the coronary arteries.[17] Conversely, coronary heart disease can decrease left ventricular performance, leading to a decrease in the BP before a coronary event occurs.[18] A well-established adage in epidemiology is that prediction from risk factors separated in time from the event is stronger than prediction from concurrent risk factors.[19,20] Our analysis of outcome might therefore be less confounded by concurrent changes in BP than the previous studies.[5–8] Moreover, because of the current thresholds for medical intervention in hypertension[11] and their insufficient application,[21] using both optimal and normal BP as the referent group might be more relevant to current clinical practice than only considering optimal BP.

In addition to Framingham,[4] two other surveys[22,23] reported on the incidence of hypertension according to the JNC6[2]/WHO-ISH[3] criteria, but provided less detailed information. In accordance with Framingham[4] and several other previous studies,[23–27] we found that the percentage change in weight was a consistent predictor of the risk of hypertension. That higher age and lower social class were predictors of hypertension below age 50 years is also in line with previous reports.[27] Finally, a higher body mass index[4,24,25] and a higher serum cholesterol[25,26,28] have previously been shown to be predictors of the risk of hypertension.

The current study must be interpreted within the context of its potential limitations and strengths. First, we classified the participants based on two BP readings obtained on a single occasion at baseline (1982–1984) and initial follow-up (1993–1994). However, some previous studies also relied on two readings[6] or even on a single measurement.[5,7] Second, we assessed progression from only two contacts. Thus, we do not know when during the interval between the two visits the transition in BP status took place. Third, we might have underestimated the risk

of progression to hypertension, because untreated or high-risk patients were more likely to die before follow-up in 1993–1994. Survival bias might therefore have led to an underestimation of the risk in patients with sustained hypertension. Fourth, our initial follow-up examination (1993–1994) preceded the publication of the findings of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[29,30] by more than a decade. In patients with normal cholesterol levels, ASCOT showed that the combination of newer antihypertensive drugs with statins, compared with older agents without active lipid-lowering therapy, nearly doubled the benefit in terms of the prevention of coronary heart disease or the composite of all cardiovascular events.[29,30] Finally, as in all longitudinal studies, the subjects remaining under investigation decreased over time, were self selected, and in our study represented only 70.2% of those originally recruited. On the other hand, follow-up of our participants in terms of fatal and nonfatal cardiovascular events was complete and in contrast to other studies[5–8] predictor and outcome variables were assessed during two distinct periods of follow-up.

Our current findings, taken together with those of other researchers,[5–8] identify a potential agenda for future clinical research. The JNC7 guidelines[11] highlighted that prehypertension, that is the combination of normal and high–normal BP, represents a major public health problem. The Trial of Preventing Hypertension (TROPHY)[31] recently demonstrated that pharmacologic treatment of this condition is feasible and well tolerated. Candesartan given for 2 years, during the subsequent 2 years, postponed the incidence of hypertension with a relative risk reduction of 15.5%.[31] However, the key question whether subjects with high–normal BP should be pharmacologically treated before they progress to hypertension remains unanswered. The TROPHY trial[31] was not powered to prove benefit in terms of a reduction of cardiovascular complications. Moreover, a healthy lifestyle maintained during 132 to 633 months can reduce BP in normotensive subjects[32,33] and hypertensive patients[32] alike.

In the current study, progression from optimal or normal BP to high–normal BP or hypertension carried nearly the same risk as sustained high–normal BP or hypertension. The current standard of care is to keep prehypertensive patients without an associated condition or history of cardiovascular disease in follow-up with BP measurements at yearly or two-yearly intervals and to only institute pharmacologic treatment once hypertension develops.[11] This conservative policy should not be revised, unless randomized controlled trials indisputably prove that intervening at an earlier stage of the disease process results in a clinically meaningful reduction of cardiovascular complications without loss of quality of life, and at a cost for which society is willing to pay.

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Reviewer Critique

Prehypertension. To Treat, or not to Treat: That Is the Question

Betram Pitt

Individuals with prehypertension, especially the elderly, are at increased risk of progressing to hypertension and suffering cardiovascular (CV) events.[1,2] Hansen et al[3] provide further evidence concerning the natural history of patients with "optimal" (<120/80 mm Hg), "normal" (120 to 129/80 to 84 mm Hg), and "high normal" (130 to 139/85 to 89 mm Hg) blood pressure (BP). In the first part of this study more than 2300 individuals without a prior history of CV complications, aged 30 to 60 years, were followed for a median of 10.9 years to observe the progression to hypertension. In the second part of this study these individuals were followed for an additional 9.4 years to determine the effect of progression from one category to another on CV events. They found that progression from optimal or normal to high normal or hypertension carries nearly the same risk for CV events as sustained high normal BP or hypertension. On the basis of their findings they suggest that patients with prehypertension without a history of CV disease be followed periodically but not be treated unless they develop hypertension or further data show that therapy reduces CV events and is cost effective.

Although I would agree that there is insufficient evidence to treat individuals with prehypertension to reduce CV events, the TROPHY study[4] has suggested that treatment with an angiotensin receptor blocker might be effective in slowing the rate of progression to hypertension. This study was not, however, powered to provide information on the effect of treatment on CV events. A larger-scale, randomized trial powered to show whether therapy with an inhibitor of the renin-angiotensin-aldosterone system (RAAS) is effective in preventing CV events in patients with borderline hypertension and risk factors for CV disease is currently being planned. Before considering therapy in individuals with prehypertension, further information is needed on a number of questions, including: prediction of who will progress; which individuals will develop target organ damage; how the presence of target organ damage relates to subsequent CV events; and whether strategies can be developed to implement and sustain exercise, diet, and lifestyle changes before pharmacologic therapy. The fact that 70 million individuals in the US alone >20 years of age were estimated to have prehypertension in the 1999–2000 National Health and Nutrition Examination Survey (NHANES),[5] along with the likelihood that this number will increase in the near future, makes the effort to answer these questions imperative.

See related article on page 483.

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From the University of Michigan School of Medicine, Ann Arbor, Michigan.

Address correspondence and reprint requests to Dr. Betram Pitt, Taubman Medical Center, 1500 East Medical Center Dr., Ann Arbor, MI 48109; e-mail: bpitt@umich.edu

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