Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study


Summary

Background Patients with optimum (<120/80 mm Hg), normal (120–129/80–84 mm Hg), and high normal (130–139/85–89 mm Hg) blood pressure (BP) may progress to hypertension (>140/90 mm Hg) over time. We aimed to establish the best frequency of BP screening by assessing the rates and determinants of progression to hypertension.

Methods We assessed repeated BP measurements in individuals without hypertension (BP<140/90 mm Hg) from the Framingham Study (4200 men, 5645 women; mean age 52 years) who attended clinic examinations during 1978–94. The incidence of hypertension (or use of antihypertensive treatment) and its determinants were studied.

Findings A stepwise increase in hypertension incidence occurred across the three non-hypertensive BP categories; 5·3% (95% CI 4·4–6·3%) of participants with optimum BP, 17·6% (15·2–20·3%) with normal, and 37·3% (33·3–41·5%) with high normal BP aged below age 65 years progressed to hypertension over 4 years. Corresponding 4-year rates of progression for patients 65 years and older were 16·0% (12·0–20·9), 25·5% (20·4–31·4), and 49·5% (42·6–56·4), respectively. Obesity and weight gain also contributed to progression; a 5% weight gain on follow-up was associated with 20–30% increased odds of hypertension.

Interpretation High normal BP and normal BP frequently progress to hypertension over a period of 4 years, especially in older adults. These findings support recommendations for monitoring individuals with high normal BP once a year, and monitoring those with normal BP every 2 years, and they emphasise the importance of weight control as a measure for primary prevention of hypertension.

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ARTICLES

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Introduction

Blood pressure (BP) and the prevalence of hypertension increase with age in adults living in more-developed countries.1,2 Periodic screening of BP of adults has been recommended to detect the onset of hypertension,3 so that appropriate measures can be instituted to prevent the morbidity and the mortality associated with raised BP.4 Knowledge of the rates and determinants of progression to hypertension is critical for defining the optimum BP screening interval for individuals without hypertension. In the absence of definitive data regarding the time course of evolution of hypertension from lower values of BP, current international guidelines vary widely in their recommendations for the clinical monitoring of individuals without hypertension.5,6 For instance, the sixth report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure in the United States (JNC VI) recommends that people with high normal BP should undergo yearly monitoring, whereas those with normal or optimum BP should be screened every 2 years.7 By contrast, the European Task Force on Prevention of Coronary Disease proposes that all individuals without hypertension should be screened at least once every 5 years.4 The British Hypertension Society advocates an intermediate position: patients with a systolic BP of 135–139 mm Hg or a diastolic BP of 85–89 mm Hg should be reassessed yearly, whereas those with lower BP (ie, <135/85 mm Hg) should be assessed at 5–year intervals.8

Our objectives were to assess the rates of progression to hypertension and the determinants of progression among Framingham Heart Study participants without hypertension at baseline.

Methods

Study sample

The design and selection criteria of the original Framingham Heart Study and the Framingham Offspring Study have been described previously.9,10 Participants in the original cohort are examined every 2 years, while those in the offspring cohort are assessed once every 4 years. Participants in both studies are under continuous surveillance for the development of cardiovascular disease events and hypertension. Study participants were eligible for inclusion in the present investigation if they attended original cohort study examinations 16, 18, 20, or 22, or offspring cohort examinations 2 to 5, done between 1978 and 1994, and if they reached the next index examination free of the following exclusion criteria: hypertension (systolic BP >140 mm Hg, or a diastolic BP >90 mm Hg, or the use of antihypertensive medication11); or history of a myocardial infarction or of congestive heart failure at the index examinations; or age less than 35 or more than 94 years; or missing information on covariates used in multivariable analyses; or missing BP information from the next clinic examination.

Individuals with myocardial infarction or congestive heart failure at baseline were excluded because these disorders can directly lower BP, and these patients are likely to be on medications that could further decrease BP.
the baseline examination.3,9 If systolic and diastolic BP (systolic 130–139 mm Hg or diastolic 85–89 mm Hg) at the end of the period of observation was crosstabulated against their BP category at the beginning of the period, all participants underwent a physical examination (with a medical history), anthropometric measurements, laboratory tests, and electrocardiography. A physician measured the systolic and diastolic BPs of seated participants twice, with a mercury column sphygmomanometer, an appropriately sized cuff, and by a standard protocol. Participants rested for at least 5 min in a seated position before the initial BP reading was obtained. The average of these three non-hypertensive JNC VI or World Health Organization-International Society of Hypertension (WHOISH) BP categories: optimum (systolic <120 mm Hg or diastolic <80 mm Hg), normal (systolic 120–129 mm Hg or diastolic 80–84 mm Hg), or high normal BP (systolic 130–139 mm Hg or diastolic 85–89 mm Hg) at the end of the 4-year period. We examined the crude 4-year incidence rates of hypertension for participants in each of the three non-hypertensive BP categories in two baseline age groups: 35–64 years, and 65–94 years.

Multivariable logistic regression (stratified by time period) was used to compute the 4-year probabilities of developing hypertension (and 95% CI) for each BP category. To investigate the optimum frequency of BP screening, we derived annual rates of hypertension incidence for each non-hypertensive BP category from the corresponding 4-year rate, assuming constant risk. Thus, if R is the 4-year rate of progression to hypertension, then Q = (1–R)^4, indicating the annual probability of not progressing to hypertension. The annual probability of progression to hypertension, Pp equals 1–Q. Similarly, 2-year (P2) and 3-year (P3) probabilities of developing hypertension are: P2 = 1–Q2, and P3 = 1–Q3.

We used multivariable logistic regression models (stratified by examination cycle) to examine the association of select variables with incidence of hypertension over the 4-year interval of observation. Since hypertension incidence rates were considerably different for younger individuals compared with older ones, but did not vary between the two sexes, pooled sex analyses were done for the two age groups. Individuals with optimum BP served as the reference group. We included the following covariates: BP category, age, sex, body-mass index, percent change in weight over the 4-year interval, smoking status (yes/no), and heart rate. These variables have been associated with increased risk of hypertension incidence. Odds ratios (and 95% CI) were computed for increments (for continuous variables) or for change in category (for categorical variables) of these variables.

### Table 1: Baseline characteristics of study sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=4670)</th>
<th>Men (n=3574)</th>
<th>Women (n=975)</th>
<th>Men (n=626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>Optimum</td>
<td>Normal</td>
<td>High normal</td>
<td>Optimum</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 (8)</td>
<td>50 (8)</td>
<td>52 (8)</td>
<td>47 (8)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>107 (8)</td>
<td>122 (5)</td>
<td>132 (5)</td>
<td>111 (6)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>69 (6)</td>
<td>77 (5)</td>
<td>81 (6)</td>
<td>71 (5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 (4)</td>
<td>26 (5)</td>
<td>27 (5)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>65 (10)</td>
<td>67 (10)</td>
<td>69 (11)</td>
<td>60 (10)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>5.28 (1.06)</td>
<td>5.59 (1.11)</td>
<td>5.79 (1.22)</td>
<td>5.35 (1.01)</td>
</tr>
<tr>
<td>Smoker</td>
<td>29%</td>
<td>28%</td>
<td>27%</td>
<td>28%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0-8%</td>
<td>1-7%</td>
<td>4-5%</td>
<td>1-9%</td>
</tr>
<tr>
<td>Weight change*</td>
<td>+3-7% (8)</td>
<td>+2-3% (7)</td>
<td>+1-8% (7)</td>
<td>+2-5% (7)</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index. *Change over follow-up period of 4 years as a percent of baseline weight; +=weight gain, -=weight loss. All values are mean (SD) unless indicated.

### Table 2: Change in BP category on follow-up according to baseline BP category

<table>
<thead>
<tr>
<th>Age 35-64 years (n=8244)</th>
<th>Age 65-94 years (n=1601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum</td>
<td>Normal</td>
</tr>
<tr>
<td>Age 35-64 years (n=8244)</td>
<td>2619 (64.4%)</td>
</tr>
<tr>
<td>Optimum</td>
<td>660 (27.5%)</td>
</tr>
<tr>
<td>Normal</td>
<td>195 (11.0%)</td>
</tr>
<tr>
<td>High normal</td>
<td>165 (38.2%)</td>
</tr>
<tr>
<td>High normal</td>
<td>115 (21.1%)</td>
</tr>
<tr>
<td>Age 65-94 years (n=1601)</td>
<td>49 (7.9%)</td>
</tr>
</tbody>
</table>

**BP at baseline**

**BP on follow-up**

**Optimum**

**Normal**

**High normal**

**Hypertension**

<table>
<thead>
<tr>
<th>Age 35-64 years (n=8244)</th>
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</tr>
</tbody>
</table>
Table 4: 4-year rates of hypertension (95% CI)*

<table>
<thead>
<tr>
<th>Baseline BP category</th>
<th>Age 35–64 years</th>
<th>Age 65–94 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum</td>
<td>5.3 (4.4–6.3)</td>
<td>16.0 (12.0–20.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>17.6 (15.2–20.3)</td>
<td>25.5 (20.4–31.4)</td>
</tr>
<tr>
<td>High normal</td>
<td>37.3 (33.4–41.5)</td>
<td>49.5 (42.6–56.4)</td>
</tr>
</tbody>
</table>

*Rates are per 100, and are adjusted for sex, age, body-mass index, baseline examinations, and baseline systolic and diastolic BP.

Table 3: Adjusted 4-year incidence of hypertension according to baseline BP category

We computed the incidence rate of stage II or greater hypertension (systolic pressure ≥160 mm Hg, or a diastolic BP >100 mm Hg; or the use of antihypertensive medication on follow-up) for each non-hypertensive baseline BP category. We examined several interaction terms (age-BP category, sex-BP category, body-mass-index-BP category, and percent weight change-BP category). We did all analyses with the SAS system (SAS Institute, Cary, NC) procedures LOGISTIC on a SUN Sparc 2 workstation (release 6.11). All p values reported are two-sided.

Results

Of 22 301 eligible attendees, 12 456 were excluded because of hypertension (9623); history of myocardial infarction or coronary heart failure (339); age less than 35 years or more than 94 years (1144); missing information on covariates used in multivariate analyses (117); or missing BP information (1233). There were 9845 eligible people (5645 women, 4200 men; mean age 52·1 years). At baseline, 2967 women (53%) and 1532 men (36%) had optimum BP; 30% had normal BP (1542 [27%] of women, 1402 [33%] of men), whereas the remaining 24% had high normal BP (1136 [20%] of women, 1226 [30%] of men).

Table 1 shows the clinical characteristics of participants in the two age groups at baseline according to BP category. Table 2 shows the BP category of participants on follow up at 4 years, according to their baseline BP category.

Progression to hypertension was determined on the basis of an increase in systolic BP alone in 853 participants (45%); diastolic BP alone in 202 (11%); as a result of crossing both the systolic and diastolic BP thresholds in 234 (12%); and on the basis of start of antihypertensive agents in 618 (32%). Progression to hypertension was about twice as frequent in the older age group (1341 of 8244 [16%]).

We examined annual incidence rates of hypertension in the community, 10–12,15,16 to our knowledge only one previous study has provided information on short-term rates of progression to hypertension using JNC VI/WHO-ISH BP categories.17 Information on the short-term rates of development of hypertension for non-hypertensive BP categories, however, is limited. Consequently, current recommendations for follow-up BP screening of individuals without hypertension are empirical rather than evidence-based, and vary widely across guidelines.1,5,6

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Table 5: Odds ratios for multivariable logistic regression

and women (p=0.31). 273 (15·4%) individuals with high normal BP in the younger age group and 144 (23·1%) individuals with high normal BP in the older age group progressed to stage II or greater hypertension.

Estimates of 1-year, 2-year, and 3-year incidence rates of hypertension are presented in table 4. Annual incidence rates were highest for older individuals with high normal BP (16%) and lowest in young individuals with optimum BP (below 2%).

Comparison of optimum BP, a normal BP at baseline was associated with a two-fold to four-fold increased risk of hypertension, while high normal BP was associated with a five-fold to 12-fold raised odds (table 5). A 5% increase in weight over the 4–year interval (equivalent to a gain of 4 kg in an average man, or 3 kg in a woman) was associated with a 20–30% increased odds of being hypertensive on follow-up.

None of the interaction terms was significant as a predictor of incident hypertension.

Discussion

The BP of adults in western societies increases with age,1 and that the extent of this age-related increase depends on the initial value of BP.11 Framingham Heart Study investigators have reported that patients with a normal or high normal diastolic BP are two to three times more likely to progress to hypertension than individuals with optimum diastolic BP.12 Information on the short-term rates of development of hypertension for non-hypertensive BP categories, however, is limited. Consequently, current recommendations for follow-up BP screening of individuals without hypertension are empirical rather than evidence-based, and vary widely across guidelines.1,5,6

We determined the incidence rate of stage II or greater hypertension across the three non-hypertensive BP categories. Older individuals and those with high normal BP were more likely to progress to hypertension than younger people and those with normal or optimum BP, as has been reported previously.1,11 Incidence rates of hypertension were similar for men and women.

Multivariable analyses identified baseline body-mass index and weight gain as important determinants of future hypertension. In addition, systolic rather than diastolic was the major determinant of progression to hypertension.

Although several investigators have assessed the incidence of hypertension in the community,10–12,15,16 to our knowledge only one previous study has provided information on short-term rates of progression to hypertension using JNC VI/WHO-ISH BP categories.17 Although that study was based on a small sample of individuals with high normal BP, the annual incidence of hypertension varied from 9·6% (ages 35–54 years) to 15·3% (ages 55–75 years), figures that are remarkably
similar to ours. Rates of progression to hypertension from normal or optimum BP are unavailable in published studies.

Incidence rates of hypertension in individuals without hypertension are likely to vary depending on the initial BP value, the variance of BP measurements, the duration of follow-up, and the presence of factors predisposing to hypertension. There are several potential reasons for the high incidence of hypertension in individuals with high normal BP relative to the other two groups. First, risk factors for hypertension (such as baseline age and a higher body-mass index) were more common in this group. Second, individuals with high normal BP needed a smaller increment of BP on follow-up (by definition) to progress to hypertension than the other two groups. Third, it has been well documented that change in systolic BP during follow-up varies directly with the initial level. Fourth, it is possible that some participants with hypertension were misclassified as having high normal BP at baseline, and these individuals were most likely to have hypertension on follow-up.

Body-mass index at baseline and weight gain on follow-up were important determinants of future hypertension. These findings add to the substantial data linking obesity and weight gain to the future risk of hypertension. Our results serve to re-emphasise the importance of weight control in the primary prevention of hypertension.

Sex was not an important determinant of risk of hypertension in our sample. These findings are consistent with those noted in the NHANES study; however, some other studies have reported a higher incidence of hypertension in women. Although the strengths of our study are that we used a large community-based sample and short-term progression rates to hypertension specific to BP category, it is important to acknowledge certain limitations. Foremost among these is the variability of BP measurements. Such variability could have introduced error to the stratification of people into hypertensive and non-hypertensive categories. Additionally, the predictive value is lower for single occasion BP measurements (such as in our study) compared with readings obtained on multiple occasions. Furthermore, rates of progression to hypertension in people with high normal BP may be overestimated in our study if misclassification of hypertension at the follow-up visit was considerable. Lastly, the predominant Caucasian sample limits the generalisability of our findings to other ethnic groups.

The optimum frequency of screening individuals without hypertension for the early detection of hypertension depends on several factors, such as the rates of progression to hypertension, the accuracy of clinical assessment, the costs of screening, the risks associated with new-onset hypertension and the benefits of BP lowering. Our findings indicate that a substantial proportion of participants with high normal BP develop hypertension over a 1–year period, suggesting that yearly screening might be desirable for this group. Conversely, a follow-up interval of up to 5 years, as recommended by the European Task Force on Prevention of Coronary Disease, would seem long for this group given that their rate of progression to hypertension was 37–50% after only 4 years. A sizeable proportion of individuals with normal BP develop hypertension over a period of 2 (older individuals) to 3 years (younger individuals),

Empirically, it would seem that a strategy of screening every 2 years might be reasonable in this group. In our study, young people with optimum BP emerged as the sole group that can be monitored less frequently. Overall, our observations call into question guidelines that recommend follow-up of people with normal and high normal BP at an interval of 5 years, and underscore the need for additional research (including cost-effectiveness analyses) to determine the optimum strategy for screening individuals without hypertension.

Contributors R S Vasan, D Levy, M G Larson, and W B Kannel designed the study and planned the analyses. M G Larson and E Leip did the statistical analyses. All investigators contributed to the interpretation of data and the writing of the paper.

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