Upper Normal Blood Pressures Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men
A 35-Year Follow-Up Study

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See Editorial Commentary, pp 184–185

Abstract—Hypertension is the most prevalent risk factor for incident atrial fibrillation (AF). Recently, even high normal blood pressures (BPs) have been established as predictive of AF in women. We aimed to study the long-term impact of upper normal BP on incident AF in a population-based study of middle-aged men. From 1972 to 1975, 2014 healthy Norwegian men were included in a prospective cardiovascular survey and underwent a comprehensive clinical examination including standardized BP measurements. During up to 35 years of follow-up, 270 men were documented with AF by scrutinizing all hospital discharges. Risk estimations for incident AF were analyzed in quartiles of BP using multivariate adjusted Cox proportional hazards. Men with baseline systolic BP ≥140 mm Hg and upper normal BP 128 to 138 mm Hg had 1.60-fold (95% CI 1.15–2.21) and 1.50-fold (1.10–2.03) risk of AF, respectively, compared with men with BP <128 mm Hg. Baseline diastolic BP ≥80 mm Hg increased the risk of incident AF 1.79-fold (95% CI 1.28–2.59) compared with diastolic BP <80 mm Hg. When adjusting for the occurrence of diabetes mellitus or cardiovascular diseases before an AF event, the results still maintained significance. Additional analyses, on average 7 years after baseline, including men still healthy, showed that sustained upper normal systolic BP remained a significant predictor of subsequent AF. In conclusion, upper normal blood pressures are long-term predictors of incident AF in initially healthy middle-aged men. (Hypertension. 2012;59:198-204.) ◆ Online Data Supplement

Key Words: arrhythmia ▪ cardiac disease ▪ epidemiology ▪ hypertension ▪ men

The incidence of atrial fibrillation (AF) is increasing in the general population.1-3 Currently, there is growing awareness of AF as a major health problem mainly because of its strong association with heart failure and stroke.4-6 Rhythm control strategies for sinus rhythm maintenance are unfortunately not optimal in clinical practice.7,8 Therefore, additional knowledge of AF prevention by identifying possible treatable risk factors has important clinical relevance.9,10

The Framingham Heart Study, as well as other population-based cohort studies, has shown that arterial hypertension is a strong independent risk factor for AF.8,11-14 Furthermore, a recent study by Conen et al showed that even systolic and diastolic blood pressure (BP) within the nonhypertensive range was independently associated with AF in a large cohort of middle-aged women.15 Another recent study from the prospective follow-up in the Framingham cohort demonstrated that pulse pressure, reflecting arterial stiffness, was the most important predictor of AF.16

In our study cohort, we have previously established baseline systolic BP as a strong predictor of cardiovascular death, but potential association with AF has never been assessed.17 In the present study, we aimed to test the long-term impact of systolic BP, in particular upper normal systolic BP, on the risk of developing AF in healthy middle-aged men. Second, we aimed to assess the associations between incident AF and diastolic BP and pulse pressure.

Methods

Study Population
From 1972 to 1975, 2014 apparently healthy men aged 40 to 59 years from 5 governmental institutions in Oslo were included in a prospective cardiovascular survey after careful screening of health information. The presence of any of the following diseases caused primary exclusion: known or suspected coronary heart disease; diagnosed hypertension requiring drug treatment; diabetes mellitus; thyroid disorders; cancer; advanced pulmonary, renal, or liver...
diseases; or other serious disorders. The participants underwent clinical examinations, blood tests, chest x-ray, resting ECG, and symptom-limited bicycle exercise ECG test. Physical fitness was defined as the total bicycle exercise capacity calculated as the sum of work at all workloads, divided by body weight. Left ventricular hypertrophy (LVH) was defined by the Minnesota Code classification system for ECG (codes 3.1 and 3.5).16

The same study investigators performed a consecutive follow-up examination, survey 2, in 1980 to 1982, on average 7 years after baseline, with a total of 1758 participants. According to baseline inclusion criteria, 1423 men remained healthy. Detailed description of the inclusion process and examination procedure is given elsewhere19–21 and is further elaborated in the online Data Supplement, available at http://hyper.ahajournals.org.

BP Measurements
During baseline examinations BP was measured manually to the nearest even 2 mm Hg with a calibrated mercury sphygmomanometer after 5 minutes in the supine position in a quiet room. The same physician (J.E.) performed all measurements in all participants. Detailed description of this procedure is given in online supplement.

In the present article, the term "upper normal BP" is used for BP values in the upper part of the normal range corresponding to our distribution into quartiles and hence is at variance with current BP guidelines, where systolic BP 130 to 139 mm Hg and diastolic BP 85 to 89 mm Hg are categorized as high-normal BP.22

Morbidity and Mortality Data
Morbidity data were consecutively obtained from 1 questionnaire survey in 1987. 2 clinical surveys in 1989 to 1990 (survey 3) and 1994 to 1995 (survey 4), and 2 nationwide surveys of patient records from all Norwegian hospitals in 1995 to 1996 and 2005 to 2008.23,24 The medical records were scrutinized by 2 investigators from the study group (J.E., J.B.), and data were obtained from all available sections of the medical records, eg, ECG readings, outpatient notes, and admission and discharge letters. After necessary permissions from the health authorities, mortality data were obtained from the database of Statistics Norway completed up to December 31, 2007. No participants were lost to follow-up.

AF
The first event of AF was registered from the hospital medical records almost exclusively by ECG documentation of paroxysmal, persistent, or permanent AF or atrial flutter. Atrial flutter, although there were only a few cases, was included because this arrhythmia shares the same code number as AF (I48) in the International Classification of Diseases. Episodes of AF after coronary artery bypass grafting or valve replacement were not included, nor was AF related to acute myocardial infarction. Among 270 patients with AF, information about date of new onset AF was unavailable in 17 men, and they were therefore excluded in the survival analyses. The participants with diagnosed AF were censored solely at the first event of AF.

Statistical Methods
For continuous variables, analysis of variance including tests, in addition to regression and correlation methods, were applied. Categorical variables were tested by the Fisher exact test or by χ² tests. The Kendall rank test was used to assess correlation (trend) between quartiles of systolic BP and baseline data.

Univariate analyses of the risk of developing AF were estimated with Kaplan-Meier plots and tested with log-rank tests. Cox regression models were used to study associations between selected potential predictors and incident AF. Significant variables in univariate analyses were entered into multivariate analysis, and a final model was reached by stepwise backward variable selection. As expected, the BP components were so closely correlated that they canceled each other out in a concurrent multivariate analysis; we therefore analyzed BP components separately in the multivariate model. The final Cox proportional hazards models included adjustments for age, LVH, and body mass index (BMI). In addition, variables with prognostic power in comparable studies (current smoking, total cholesterol, physical fitness, and resting heart rate) were entered into the model, but none of these latter variables influenced the results. Finally, in a subsequent model, multivariate Cox proportional hazard analyses were performed after censoring at first occurrence of diabetes mellitus or cardiac diseases (myocardial infarction, coronary artery bypass grafting, aortic valve replacement, heart failure), before an AF event.

Probability values were 2-sided, and values <0.05 were considered statistically significant. We calculated 95% CIs throughout the analyses. Data were analyzed using the statistical package of JMP version 9 (SAS Institute Inc, Cary, NC).

Results
Study Characteristics
Average age at baseline was 50 years, and 44% were current smokers. During follow-up of up to 35 years (median 30 years), 270 men (13%) developed AF representing an incidence rate of 5.1 per 1000 person-years. Mean age at first appearance of AF was 71 years. At the end of follow-up, 59% of the men in the sinus rhythm group and 56% in the AF group had died, with no significant difference between the groups. Men who later developed AF had higher baseline BMI, higher resting systolic and diastolic BP, and higher prevalence of LVH. No difference was observed regarding pulse pressure, resting heart rate, PR interval, or physical fitness (Table 1).

Table 1. Baseline Characteristics for Men Who Developed Atrial Fibrillation Compared With Men in Sinus Rhythm (n=2014)
Systolic BP at baseline was divided in quartiles (Q), and Table 2 demonstrates a strong significance for trend across the quartiles with respect to age, BMI, diastolic BP, pulse pressure, and resting heart rate and for the exercise variables physical fitness and maximum exercise systolic BP. The presence of LVH was predominant in the highest quartile.

Predictors of Incident AF
In univariate analyses age, all the BP components, BMI, LVH, maximum exercise heart rate, and physical fitness were significantly associated with AF. Age, systolic BP, diastolic BP, LVH, and BMI remained significant predictors in multivariate analyses, and age was the strongest predictor (Table 3).

Table 2. Baseline Characteristics in Quartiles of Systolic BP (n=2014)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 (88–116 mm Hg), n=492</th>
<th>Q2 (118–126 mm Hg), n=478</th>
<th>Q3 (128–138 mm Hg), n=518</th>
<th>Q4 (140–220 mm Hg), n=526</th>
<th>P Value (for Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>48.6 (5.1)</td>
<td>48.8 (5.4)</td>
<td>50.1 (5.5)</td>
<td>51.7 (5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body height, cm (SD)</td>
<td>177 (6)</td>
<td>177 (6)</td>
<td>177 (6)</td>
<td>176 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Body weight, kg (SD)</td>
<td>75 (9)</td>
<td>76 (9)</td>
<td>78 (10)</td>
<td>79 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>24 (3)</td>
<td>24 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>239 (49)</td>
<td>201 (42)</td>
<td>226 (44)</td>
<td>217 (41)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>106 (22)</td>
<td>104 (22)</td>
<td>124 (24)</td>
<td>114 (22)</td>
<td>ns</td>
</tr>
<tr>
<td>Examinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg (SD)</td>
<td>110 (6)</td>
<td>122 (3)</td>
<td>133 (3)</td>
<td>154 (13)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg (SD)</td>
<td>77 (7)</td>
<td>84 (6)</td>
<td>89 (6)</td>
<td>98 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg (SD)</td>
<td>33 (6)</td>
<td>39 (6)</td>
<td>44 (6)</td>
<td>56 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate, bpm (SD)</td>
<td>58 (8)</td>
<td>60 (8)</td>
<td>62 (9)</td>
<td>65 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR interval, ms (SD)</td>
<td>171 (26)</td>
<td>171 (25)</td>
<td>172 (25)</td>
<td>172 (24)</td>
<td>ns</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>19 (4)</td>
<td>17 (4)</td>
<td>17 (3)</td>
<td>53 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum ex. heart rate, bpm (SD)</td>
<td>163 (14)</td>
<td>164 (13)</td>
<td>163 (13)</td>
<td>162 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>Maximum ex. systolic BP, mm Hg (SD)</td>
<td>204 (18)</td>
<td>209 (20)</td>
<td>217 (19)</td>
<td>232 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical fitness, kJ/kg (SD)</td>
<td>2.2 (0.9)</td>
<td>2.0 (0.8)</td>
<td>1.9 (0.8)</td>
<td>1.6 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>6.4 (1.2)</td>
<td>6.6 (1.1)</td>
<td>6.7 (1.2)</td>
<td>6.8 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose, mmol/L (SD)</td>
<td>4.4 (0.5)</td>
<td>4.4 (0.5)</td>
<td>4.5 (0.6)</td>
<td>4.6 (0.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD or numbers (n) and percentages. BP indicates blood pressure; Q, quartile; ns, not significant; bpm, beats per min; ex., exercise; LVH, left ventricular hypertrophy.

Predictors of Incident AF
In univariate analyses age, all the BP components, BMI, LVH, maximum exercise heart rate, and physical fitness were significantly associated with AF. Age, systolic BP, diastolic BP, LVH, and BMI remained significant predictors in multivariate analyses, and age was the strongest predictor (Table 3).

Table 3. Possible Predictors of Atrial Fibrillation in Univariate (Ranked by χ²) and Multivariate Analysis (n=1997)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
<td>χ²</td>
</tr>
<tr>
<td>Age at baseline (10 y)</td>
<td>1.95</td>
<td>(1.55–2.45)</td>
<td>&lt;0.001</td>
<td>31.9</td>
</tr>
<tr>
<td>Systolic BP (1 SD)</td>
<td>1.35</td>
<td>(1.20–1.51)</td>
<td>&lt;0.001</td>
<td>22.8</td>
</tr>
<tr>
<td>Diastolic BP (1 SD)</td>
<td>1.33</td>
<td>(1.17–1.49)</td>
<td>&lt;0.001</td>
<td>20.3</td>
</tr>
<tr>
<td>Physical fitness (1 SD)</td>
<td>0.78</td>
<td>(0.68–0.90)</td>
<td>&lt;0.001</td>
<td>12.8</td>
</tr>
<tr>
<td>Exercise maximum heart rate (1 SD)</td>
<td>0.79</td>
<td>(0.70–0.90)</td>
<td>&lt;0.001</td>
<td>12.6</td>
</tr>
<tr>
<td>Pulse pressure (1 SD)</td>
<td>1.25</td>
<td>(1.10–1.41)</td>
<td>&lt;0.001</td>
<td>12.0</td>
</tr>
<tr>
<td>BMI (1 SD)</td>
<td>1.22</td>
<td>(1.08–1.38)</td>
<td>&lt;0.005</td>
<td>10.3</td>
</tr>
<tr>
<td>LVH (yes/no)</td>
<td>2.09</td>
<td>(1.33–3.14)</td>
<td>&lt;0.005</td>
<td>9.4</td>
</tr>
<tr>
<td>Exercise maximum systolic BP (1 SD)</td>
<td>1.19</td>
<td>(1.05–1.35)</td>
<td>&lt;0.05</td>
<td>7.3</td>
</tr>
<tr>
<td>Total cholesterol (1 SD)</td>
<td>1.11</td>
<td>(0.98–1.26)</td>
<td>ns</td>
<td>2.8</td>
</tr>
<tr>
<td>PR interval (1 SD)</td>
<td>1.07</td>
<td>(0.95–1.21)</td>
<td>ns</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart rate at rest (1 SD)</td>
<td>0.98</td>
<td>(0.86–1.11)</td>
<td>ns</td>
<td>0.1</td>
</tr>
<tr>
<td>Blood glucose (1 SD)</td>
<td>1.02</td>
<td>(0.89–1.16)</td>
<td>ns</td>
<td>0.1</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>1.01</td>
<td>(0.78–1.30)</td>
<td>ns</td>
<td>0.1</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; BP, blood pressure; BMI, body mass index; ns, not significant; LVH, left ventricular hypertrophy.

*BP components were analyzed separately in multivariate analyses; in the final multivariate model, systolic BP is applied.
Risk of Incident AF Related to BP Quartiles

**Systolic BP**
Multiple adjusted risk estimates of AF are presented in Table 4 and Figure 1. Compared with the reference quartile, with systolic BP <118 mm Hg (Q1), the long-term risks of AF were 1.51-fold and 1.62-fold for men with baseline systolic BP 128 to 138 mm Hg (Q3) and 140 to 220 mm Hg (Q4), respectively. When using BP <128 mm Hg as the reference, Q3 had a 1.50-fold and Q4 a 1.60-fold risk of incident AF.

**Diastolic BP**
Multivariable adjusted risk estimates showed that diastolic BP <80 mm Hg (Q1) was associated with the lowest risk of incident AF, and when using this quartile as reference, the risks of AF were 1.69-fold, 1.81-fold, and 1.94-fold in Q2, Q3, and Q4, respectively (Table 4 and Figure 2).

**Pulse Pressure**
The quartile with the highest pulse pressure showed a 1.49-fold increase in age-adjusted AF risk compared with the reference quartile (Table 4). Multivariable analyses, however, did not establish pulse pressure as predictive of AF in the present study.

As described, BP quartiles were applied in the present study, but we also analyzed clinical BP groups according to current guidelines; the group with high-normal systolic BP (ie, 130 to 139 mm Hg) demonstrated a significant increased

### Table 4. Relative Risk of Atrial Fibrillation in Quartiles of Baseline BP Compared With the Lowest Quartile (n=1997)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>1.04 (0.70–1.54)</td>
<td>1.57 (1.10–2.27)</td>
<td>1.75 (1.22–2.52)</td>
</tr>
<tr>
<td>Multiple adjusted*</td>
<td>1.00</td>
<td>1.02 (0.69–1.53)</td>
<td>1.51 (1.05–2.20)</td>
<td>1.62 (1.10–2.39)</td>
</tr>
<tr>
<td>Multiple adjusted and adj.</td>
<td>1.00</td>
<td>1.26 (0.74–2.14)</td>
<td>1.98 (1.22–3.27)</td>
<td>1.84 (1.07–3.19)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>1.70 (1.16–2.53)</td>
<td>1.81 (1.21–2.74)</td>
<td>2.05 (1.41–3.05)</td>
</tr>
<tr>
<td>Multiple adjusted*</td>
<td>1.00</td>
<td>1.69 (1.15–2.53)</td>
<td>1.81 (1.20–2.76)</td>
<td>1.94 (1.30–2.95)</td>
</tr>
<tr>
<td>Multiple adjusted and adj.</td>
<td>1.00</td>
<td>1.67 (1.00–2.85)</td>
<td>1.76 (1.01–3.11)</td>
<td>2.36 (1.38–4.15)</td>
</tr>
<tr>
<td><strong>Pulse pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.00</td>
<td>1.22 (0.84–1.76)</td>
<td>1.13 (0.79–1.63)</td>
<td>1.49 (1.04–2.16)</td>
</tr>
<tr>
<td>Multiple adjusted*</td>
<td>1.00</td>
<td>1.18 (0.81–1.71)</td>
<td>1.08 (0.75–1.55)</td>
<td>1.34 (0.92–1.96)</td>
</tr>
<tr>
<td>Multiple adjusted and adj.</td>
<td>1.00</td>
<td>1.11 (0.67–1.84)</td>
<td>1.25 (0.78–2.04)</td>
<td>1.53 (0.92–2.57)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; Q, quartile; DM, diabetes mellitus.
*Multiple adjusted: Adjusted for age, body mass index, left ventricular hypertrophy, current smoking, total cholesterol, physical fitness, and resting heart rate.
†Multiple adjusted and adjusted for cardiac disease (myocardial infarction, coronary artery bypass grafting, valve replacement, heart failure) or DM.

Figure 1. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of systolic blood pressure during 35 years of follow-up.

Figure 2. Kaplan-Meier curves show survival (%) free from AF among 1997 initially healthy middle-aged men according to quartiles of diastolic blood pressure during 35 years of follow-up.
risk of AF compared with optimal systolic BP = 120 mm Hg (multiple adjusted HR 1.67; further data not shown).

Analyses at Follow-Up

Before the occurrence of incident AF, 115 men developed diabetes mellitus or 1 of the following cardiac events: myocardial infarction, coronary artery bypass grafting, aortic valve replacement, and heart failure. Adjustments for the occurrence of these disorders in the multivariate model did not appreciably change the previous established risk of AF associated with baseline systolic and diastolic BP (Table 4).

When extending analyses from baseline to survey 2, on average 7 years later, 82 men (4%) had been diagnosed with hypertension. Only men considered still healthy and free of any chronic drug regimen at survey 2 were included in further analyses. At baseline, 26% of the total population had measured systolic BP ≥140 mm Hg (which corresponds to Q4); at survey 2, this number had increased to 31%. Thus, the measured BP at survey 2, not the diagnosis of hypertension, was used to exclude all men with hypertensive values. Among the men with upper normal systolic BP at baseline (Q3), 70% (265 of 380 men examined at survey 2) had sustained BP below 140 mm Hg. Table 5 demonstrates that this normotensive group through 7 years of follow-up still has a significant increased AF risk compared with men with lower systolic BP.

Discussion

We followed 2014 initially healthy middle-aged men for more than 50,000 person-years, and 270 AF events occurred. Sample size, total person-years, and event rate in our study are fairly comparable to those of large AF trials. Men with baseline systolic BP ≥140 mm Hg or upper normal BP had 1.60-fold and 1.50-fold risk of incident AF, respectively, compared with men with BP <128 mm Hg. Baseline diastolic BP ≥80 mm Hg increased AF risk 1.80-fold compared with diastolic BP <80 mm Hg. Baseline pulse pressure was not a significant predictor of AF in the present study, possibly because of an initially healthy and relatively young population.

Our intention with the present observational study was not to establish a firm BP threshold but to assess possible associations between BP below what we today register as hypertension and an increased AF risk. For this purpose, we applied BP quartiles, traditionally used in this kind of epidemiological research, and the levels of 128 mm Hg for systolic BP and 80 mm Hg for diastolic BP follow this quartile classification.

Comparison With Related Studies

The overall incidence rate of AF in our study during 53,062 person-years of observation was 5.1 per 1000 person-years. In comparison, the Manitoba Follow-Up Study, 1948 to 1992, with 154,000 person-years had a lower incidence of AF, 2 per 1000 person-years in a population approximately 20 years younger at inclusion. In the Framingham Heart Study, 253 AF events occurred in men during 32,544 person-years of follow-up in a study cohort aged 45 to 95 years (6.3 per 1000 age-adjusted person-years). This is comparable with our study, as the cohort had mean age at baseline 10 years higher than our population. All studies referred to above have shown that the incidence of AF increases with advancing age.

Because of its high prevalence in the population, hypertension is by far the most prevalent risk factor for development of AF.8,11–14 Still, it has remained unknown at what level BP starts to impose an increased risk of AF.22 Conen et al15 showed that even systolic and diastolic BP levels within the nonhypertensive range were independently associated with incident AF in nearly 35,000 initially healthy women with mean age at baseline 55 years, median follow-up of 12 years, and AF incidence rate of 1.9%. Age at follow-up appears to be the most important cause of the substantial difference in incidence rate compared with our study. Women with high-normal systolic BP at baseline (130–139 mm Hg) had 28% increased risk of AF compared with women with optimal systolic BP <120 mm Hg, which is in line with the results of our study in middle-aged men.

Pathophysiological Aspects

Low BP, both systolic and diastolic, is associated with low incidence of AF in recent studies, and pathophysiological understanding of the development of AF is essential. Increased BP over time may cause a slow but progressive process of structural and electrophysiological remodeling in both ventricles and atria. Elevated end-diastolic left ventricular pressure and subsequently increased left atrial pressure may cause atrial stretch and eventually dilatation, which may favor the development of AF.8

Follow-Up

The assessment of data from survey 2 revealed that almost one third of still-healthy study participants had measured
systolic BP ≥140 mm Hg. However, despite analyses on a lower number of subjects caused by the exclusion of men with high systolic BP, sustained upper normal systolic BP remained a significant predictor of incident AF.

There are several important questions to address in the present study. Primarily, do the nonhypertensive men at baseline have an increased AF risk because they subsequently develop hypertension, or is there an independent increased AF risk associated with upper normal BP? Our results indicate that upper normal systolic BP is a significant predictor of incident AF both at baseline and at 7 years of follow-up, but the majority of the study participants developed AF late in life, on average 20 years from baseline. Additionally, in studies with a long follow-up duration, the strength of a disease-specific predictor often weakens with time when other risk factors or diseases become increasingly important. Unfortunately, additional data from survey 3, on average 16 years after baseline, were not considered accessible because of the substantially reduced number of participants and hence lack of power for survival analysis.

Limitations
Our study included apparently healthy, middle-aged Norwegian men in daily work. The results cannot necessarily be generalized to men of different ethnicity or age, men with concomitant diseases, or women. Only 18 men reported current participation in competition sports, and the results cannot be generalized to athletes.

The morbidity data, including diagnosed AF, were collected from hospital medical records and not from the primary health care system. If a participant never had been in contact with an outpatient clinic or hospitalized, which is exceedingly uncommon in the Norwegian health care system, a diagnosis of AF could have been missed.

Perspectives
Both systolic BP ≥128 mm Hg and diastolic BP ≥80 mm Hg are found to be long-term predictors of incident AF in initially healthy middle-aged men. The present results imply that even middle-aged men with nonhypertensive BP levels according to current guidelines have an increased risk of developing AF compared with men with lower BP. However, it is not yet resolved whether the subsequent development of hypertension among persons with upper normal BP is the essential pathway to incident AF. A few recent studies, 1 of them the randomized trial from the Cardio-Sis investigators, have reported that tight BP control compared with usual BP control in the treatment of hypertension reduces the incidence of cardiovascular events, including new-onset AF.25,26 We therefore propose further randomized clinical trials with improved BP control to aid in the challenge of preventing increasing AF in the general population.

Sources of Funding
This study was supported by unrestricted grants from Stein Erik Hagens Foundation for Clinical Heart Research; Oslo University Hospital, Ullevaal; and the Norwegian Council for Cardiovascular Diseases.

Disclosures
S.E.K. and H.A. have received honoraria for ad hoc lectures and advisory board meetings. J.B. holds a position as an epidemiologist at AstraZeneca.

References


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Hypertension. published online January 17, 2012;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2012/01/17/HYPERTENSIONAHA.111.179713

Data Supplement (unedited) at:
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Upper Normal Blood Pressures Predict Incident Atrial Fibrillation in Healthy Middle-aged Men

A 35 Year Follow-up Study

Grundvold: Upper normal blood pressure and atrial fibrillation

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Methods

Study population
Men aged 40-59 years working in five Governmental agencies in Oslo, Norway, were recruited for a cardiovascular health survey which took place between August 28, 1972 and March 21, 1975. Only employees working in agencies practicing annual or biennial health examinations of all their employees were chosen for the study. Eligibility of each man was decided after a joint scrutiny of his health records by the Chief Medical Officer of each agency and the survey leader (JE). Presence of any of the following diseases caused primary exclusion: Known or suspected coronary heart disease, diagnosed hypertension requiring drug treatment, diabetes mellitus, thyroid disorders, cancer, advanced pulmonary, renal, or liver diseases, or other serious disorders. Subjects on any chronic drug regimen were also excluded, as were those who for various reasons were judged unable to properly conduct a symptom limited bicycle exercise ECG test (e.g. for orthopedic, neurological, or muscular reasons). In all 2341 men fulfilled these health criteria, and 2014 (86%) agreed to participate.

Men who at arrival for the study reported that any of the above mentioned diseases/disorders had been diagnosed elsewhere after their last visit to the company health office, underwent a full survey examination, but were later excluded from our files. Accordingly our study population was judged to represent a group of apparently healthy men aged 40-59 years.

Current and former smoking habits were registered, and the participants were asked if they had consumed alcohol the last two days before examination. All men were employed and none reported alcohol abuse.

Blood pressure measurements
The fifth phase of Korotkoff sounds established diastolic BP. BP was measured three times, where the first measurement established approximately the pressure level. The second measurement was a very careful procedure with first elevating the arm for venous draining, and then lowering the arm with measurements during inspiration followed by relaxed expiration. The third measurement was identical to the second. There was a systematic minimal fall in BP from the first to the second reading, and then on average a minimal rise in BP (<1 mm Hg) from the second to the third reading. The second reading was therefore considered the most basic recording, and has therefore been used as baseline value.

Hypertensive BP values refer to standard definitions (≥140 mm Hg and/or ≥90 mm Hg). Pulse pressure was defined as the difference between systolic and diastolic BP for each individual.

Morbidity and Mortality data
With permissions from the Norwegian Data Inspectorate, the Norwegian Board of Health and all Norwegian hospitals, all 2014 subjects in the study were linked with the patient journal system using a unique personal identification number (Norwegian social security number).