Atrial Fibrillation and Isolated Systolic Hypertension

The Systolic Hypertension in the Elderly Program and Systolic Hypertension in the Elderly Program-Extension Study

Tudor D. Vagaonescu, Alan C. Wilson, John B. Kostis

Abstract—We performed a post hoc analysis of the Systolic Hypertension in the Elderly Program database to assess the incidence of atrial fibrillation in the elderly hypertensive population, its influence on cardiovascular events, and whether antihypertensive treatment can prevent its onset. The Systolic Hypertension in the Elderly Program was a double-blind placebo-controlled trial in 4736 subjects with isolated systolic hypertension aged ≥60 years. Atrial fibrillation was an exclusion criterion from the trial. Participants were randomly assigned to stepped care treatment with chlorthalidone and atenolol (n=2365) or placebo (n=2371). The occurrence of atrial fibrillation and cardiovascular events over 4.7 years as well as the determination of cause of death at 4.7 and 14.3 years were followed. Ninety-eight subjects (2.06%) developed atrial fibrillation over 4.7 years mean follow-up, without significant difference between treated and placebo groups. Atrial fibrillation increased the risk for: total cardiovascular events (RR 1.69; 95% CI 1.21 to 2.36), rapid death (RR 3.29; 95% CI 1.08 to 10.00), total (RR 5.10; 95% CI 3.12 to 8.37) and nonfatal left ventricular failure (RR 5.31; 95% CI 3.09 to 9.13). All-cause and total cardiovascular death were significantly increased in the atrial fibrillation group at 4.7 years (HR 3.44; 95% CI 2.18 to 5.42; HR 2.39; 95% CI 1.05 to 5.43) and 14.3 years follow-up (HR 2.33; 95% CI 1.83 to 2.98; HR 2.21; 95% CI 1.54 to 3.17). Atrial fibrillation increased the risk for total cardiovascular events, rapid death, and left ventricular failure. All-cause mortality and total cardiovascular mortality were significantly increased in hypertensives with atrial fibrillation at 4.7 and 14.3 years follow-up. (Hypertension. 2008;51:1552-1556.)

Key Words: hypertension ▪ elderly ▪ atrial fibrillation ▪ chlorthalidone ▪ atenolol ▪ incidence ▪ death

Atrial fibrillation (AF) represents a major health problem, affecting more than 2 million patients in the United States.1 The prevalence of AF increases with age and it is estimated to be around 5% above age 70.2 In the Framingham study the incidence of AF in the general population approximately doubled for every 10-year increment in age beyond 50 years (approximately 10% in persons who reach age 803,4), and it was reported as high as 19.2 per 1000 person-years among adults above age 65 in the Cardiovascular Health Study.5 Arterial hypertension is an independent risk factor for developing AF3 and for an increased risk of stroke in patients with AF.6 However, no study addressed specifically the incidence of AF, the relationship of AF on cardiovascular events, and the effect of antihypertensive treatment versus placebo on the incidence of AF in a well-characterized hypertensive population. To answer these questions we performed a posthoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) database.

Methods

Participants and Study Design

SHEP was a double-blind, randomized, placebo-controlled trial design to test whether long-term administration of antihypertensive treatment to older persons with isolated systolic hypertension (SBP >160 mm Hg and DBP <90 mm Hg) reduces the combined incidence of fatal and nonfatal stroke during a 5-year follow-up. A cohort of 4736 men and women aged ≥60 years with hypertension as defined was followed up for an average of 4.7 years. Patients were randomized in a double-blind manner to a once-daily dose of either active drug treatment or matching placebo. The objective of the stepped care treatment program was to use the minimal amount of medication to maintain SBP at or below the goal (decrease in baseline SBP of at least 20 mm Hg and a SBP of less than 160 mm Hg). The first treatment step was chlorthalidone 12.5 mg/d (or matching placebo), which could be doubled if the participant’s SBP was not controlled at goal. If the SBP goal was not reached at the maximal dose (25 mg/d) of step 1 medication, atenolol 25 mg/d (or matching placebo) was added as the usual step 2 drug. Low-dose reserpine (0.05 mg/d) was substituted in those with contraindication to atenolol.7,8

Participants were followed monthly until SBP reached goal or until the maximum level of stepped-care treatment was achieved. All participants had quarterly visits from the date of randomization, at which they underwent measurement of blood pressure, heart rate, and body weight, and a medical history and detailed review of medication use were done.7 A 12 lead ECG (1 minute) and 2 minutes of rhythm strip were done at baseline and a 12 lead ECG was done at the second and final annual visits.7 All electrocardiograms collected in SHEP were read at the coding center using a protocol for
continuous voltage and duration measurement and categorical coding according to the Minnesota code.\(^9\)

The primary end point was fatal and nonfatal stroke, and secondary end points included transient ischemic attack, fatal and nonfatal myocardial infarction, left ventricular failure, sudden cardiac death, rapid cardiac death, other cardiovascular death. For combined end points, participants with multiple end points were counted only once.\(^7\)

Atrial fibrillation was an exclusion criterion at baseline. The occurrence of AF during follow-up was ascertained from the follow-up forms filed after each visit and at the final visit. Morbid and mortal events occurring after onset of AF were taken into account for the analysis relating these events to AF.

By the end of the study period, all subjects were advised to receive active treatment. Further determination of vital status and cause of death of all SHEP participants throughout the year 2000 was performed by National Death Index matching (SHEP-Extension [SHEP-X] study).

**Statistical Analysis**

Comparison of baseline characteristics of the participants who developed AF during follow-up to subjects who maintained sinus rhythm was done by \(\chi^2\) tests for categorical variables and standard \(t\) tests for continuous variables. For events occurring during follow-up relative risks and percentage differences were calculated by proportional hazards regression analysis\(^10\) using the entire duration of follow-up during the SHEP study. For the all-cause and the total cardiovascular mortality a separate analysis was performed for a duration of 14.3 years follow-up (SHEP-X) with atrial fibrillation as a time-dependent variable.

**Results**

**Baseline Characteristics and Incidence of Atrial Fibrillation**

Ninety-eight subjects (2.06\%) from the total 4736 participants developed AF over 4.5 years follow-up (21 312 patient-years). Characteristics of the participants who developed AF and of those who maintained sinus rhythm are presented in Table 1. Subjects who developed AF were significantly older and had more ECG abnormalities at baseline than participants who maintained sinus rhythm. The mean of all systolic BP measurements over the follow-up period was higher in participants who developed AF (153.1±14 mm Hg versus 149.4±14 mm Hg, \(P<0.01\)). The incidence of AF was 1.82\% in the active treatment group and 2.32\% in the placebo group (\(P=0.2\)). Seven (16.3\%) subjects randomized to the treated group and 17 (30.1\%) placebo group participants were placed on open label antihypertensive drugs. Subjects who developed AF were more likely to receive digoxin than the participants who maintained sinus rhythm (7.1\% versus 2\%, \(\chi^2=12.7, P=0.0004\)). Aspirin use did not differ significantly between the two groups (12.2\% versus 17.8\%, \(\chi^2=2, P=0.15\)).

**Cardiovascular Events and Mortality in the SHEP Participants**

The occurrence of cardiovascular events in the SHEP participants according to the AF status are presented in Tables 2 and 3. Subjects who developed AF were more likely to experience cardiovascular events, left ventricular failure, and rapid death than participants who maintained sinus rhythm. In 26 (26.5\%) of the 98 subjects who developed AF the arrhythmia preceded the occurrence of cardiovascular events, whereas in 15 (15.3\%) participants AF followed a cardiovascular event. There were no cardiovascular events observed in the remaining 57 (58.1\%) subjects who developed AF during the study follow-up.

All-cause and total cardiovascular mortality were significantly increased in the hypertensives who developed AF at both 4.7 years and 14.3 years follow-up (Table 3).

Participants who developed cardiovascular events after AF onset were mostly men and used alcohol daily or near daily (Table 4).

**Discussion**

**Atrial Fibrillation Incidence in the SHEP Participants**

The incidence of AF reported in the literature varies with the studied population. In a random sample of 487 subjects (215
men and 272 women aged 62 to 90 years) followed for 5 years AF incidence was 4%.11 In the Framingham study in subjects aged 55 to 94 years at baseline the biennial incidence of AF increased with age, ranging from 6.2 and 3.8 cases per 1000 person-examinations in men and women, respectively, aged 55 to 64 years, to 75.9 and 62.8 cases per 1000 person-examinations in men and women aged 85 to 94 years.3 In the Framingham study arterial hypertension (odds ratio 1.5 in men and 1.4 in women) and diabetes mellitus (odds ratio 1.4 in men and 1.6 in women) emerged as significant independent predictors of AF.4 In the Manitoba follow-up study AF incidence increased from less than 0.5 per 1000 person-years before age 50 to 9.7 per 1000 person-years after age 70. The rate of AF was 1.42 times higher in men with hypertension.12 In the Cardiovascular Health Study the incidence of AF was 19.2 per 1000 person years in adults over 65 years old. Higher levels of systolic BP were associated with an increased risk of AF.5

**Table 2. Cardiovascular Events in the SHEP Participants According to Occurrence of AF**

<table>
<thead>
<tr>
<th>Cardiovascular Events</th>
<th>Present AF</th>
<th>Absent AF</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>6 (6.12%)</td>
<td>249 (5.4%)</td>
<td>1.15 (0.52 to 2.51)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0 (0%)</td>
<td>24 (0.5%)</td>
<td>0.95 (0.06 to 14.98)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>6 (6.1%)</td>
<td>231 (5%)</td>
<td>1.24 (0.55 to 2.80)</td>
</tr>
<tr>
<td>TIA</td>
<td>2 (2%)</td>
<td>141 (3%)</td>
<td>0.66 (0.16 to 2.68)</td>
</tr>
<tr>
<td>Total LV failure</td>
<td>15 (15.3%)</td>
<td>139 (3%)</td>
<td>5.10 (3.12 to 8.37)</td>
</tr>
<tr>
<td>Fatal LV failure</td>
<td>1 (1%)</td>
<td>9 (0.2%)</td>
<td>4.87 (0.75 to 31.61)</td>
</tr>
<tr>
<td>Nonfatal LV failure</td>
<td>14 (14.3%)</td>
<td>130 (2.8%)</td>
<td>5.31 (3.09 to 9.13)</td>
</tr>
<tr>
<td>Total MI</td>
<td>6 (6.1%)</td>
<td>151 (3.2%)</td>
<td>1.88 (0.85 to 4.15)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1 (1%)</td>
<td>40 (0.9%)</td>
<td>1.18 (0.17 to 8.26)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>5 (5.1%)</td>
<td>114 (2.5%)</td>
<td>2.09 (0.86 to 5.04)</td>
</tr>
<tr>
<td>Total cardiovascular events</td>
<td>34 (34.7%)</td>
<td>928 (20%)</td>
<td>1.69 (1.21 to 2.36)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0 (0%)</td>
<td>46 (0.9%)</td>
<td>0.50 (0.03 to 7.87)</td>
</tr>
<tr>
<td>Rapid death</td>
<td>3 (3%)</td>
<td>42 (0.9%)</td>
<td>3.29 (1.08 to 10.00)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; LV, left ventricular; MI, myocardial infarction; TIA, transient ischemic attack.

The incidence of AF in SHEP reported here (2.06% during 4.5 years average follow-up) is similar to that previously published. A slightly lower incidence of AF than in the Framingham study may be explained by a selection bias attributable to the initial inclusion criteria in the SHEP trial (clinical trial patients being with less comorbidities at baseline, and as such being less likely to develop AF). Subjects who developed AF in the SHEP were significantly older and were more likely to have ECG abnormalities at baseline when compared with the participants who maintained sinus rhythm. These data suggest that ECG abnormalities in elderly persons with isolated systolic hypertension identify a subset with higher risk of developing AF.

The incidence of AF did not differ significantly between subjects randomized to active treatment or placebo. The mean of all systolic BP measurements during 4.5 years of

![Table 3. All-Cause Mortality and Total Cardiovascular Mortality in the SHEP Participants According to the Atrial Fibrillation Status at 4.7 Years and at 14.3 Years Follow-Up](image)

<table>
<thead>
<tr>
<th>Mortality Follow-Up</th>
<th>Present AF (%96)</th>
<th>Absent AF (%4638)</th>
<th>Adjusted Hazard Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7 Years follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>21 (21.43%)</td>
<td>434 (9.36%)</td>
<td>3.44 (2.18 to 5.42)</td>
</tr>
<tr>
<td>Total cardiovascular mortality</td>
<td>7 (7.14%)</td>
<td>195 (4.20%)</td>
<td>2.39 (1.05 to 5.43)</td>
</tr>
<tr>
<td>14.3 Years follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>30 (71.43%)</td>
<td>1920 (41.40%)</td>
<td>2.33 (1.83 to 2.98)</td>
</tr>
<tr>
<td>Total cardiovascular mortality</td>
<td>33 (33.67%)</td>
<td>935 (20.16%)</td>
<td>2.21 (1.54 to 3.17)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation. #
follow-up was significantly higher in the AF group. This suggests that a poor blood pressure control increases the risk of developing AF.

**Cardiovascular Events and Atrial Fibrillation in the SHEP Study**

In the general population AF has been associated with an increased mortality (relative risk of 1.92 for all causes and 1.82 for cardiovascular death excluding stroke\(^{11}\); relative risk of 1.31 for total and 1.41 for cardiovascular mortality\(^{12}\); odds ratio of 1.5 in men and 1.9 in women for total mortality\(^{14}\)). In the SHEP study hypertensives with AF had a higher total cardiovascular death rate than participants who maintained sinus rhythm at both 4.7 and 14.3 years. This was, most likely, one of the contributors of a significantly higher all cause mortality in the subjects who developed AF at 4.7 and 14.3 years.

Atrial fibrillation has been reported to increase the risk for both fatal (RR 6.9 in men\(^{15}\); RR 2.7 in men and 5.6 in women\(^{13}\); RR 2.48 in men\(^{12}\)) and nonfatal (RR 2.6 to 4.5\(^{16}\)). However, the rates of fatal and nonfatal stroke and of TIAs did not differ between participants with and without AF in the SHEP study.

SHEP participants with AF had a significantly higher risk for total (RR 5.10; 95% CI 3.12 to 8.37) and nonfatal (RR 5.31; 95% CI 3.09 to 9.13) left ventricular failure when compared with subjects who maintained sinus rhythm. Hypertension control prevents heart failure in the elderly hypertensives.\(^{17}\) It is possible that the higher SBP observed during the study in the subjects with AF is responsible for the increased risk for left ventricular failure. The relative risk for left ventricular failure in the participants with AF (5.10 for total, 4.87 for fatal, and 5.31 for nonfatal left ventricular failure) in SHEP was higher than the RR for congestive heart failure (2.98) in AF subjects reported in previous studies.\(^{13}\)

This observation suggests that hypertension and AF may have a synergistic effect for the development of congestive heart failure.

In SHEP, participants with AF had a higher risk for total (RR 1.88; 95% CI 0.85 to 4.15) and nonfatal (RR 2.09; 95% CI 0.86 to 5.04) myocardial infarction than subjects who maintained sinus rhythm. This finding can be explained by the higher prevalence of baseline ECG abnormalities in the former group (80.4% versus 60.6%, \(P<0.001\)), as a possible marker of extensive coronary artery disease in hypertensives with AF.

The LIFE study revealed that losartan (when compared with atenolol) significantly reduced the onset of AF as well as the risk of cardiovascular events in hypertensives with history of AF.\(^ {18}\) Chlorthalidone and atenolol, used in the SHEP trial, failed to decrease the incidence of AF as well as its association with more cardiovascular events in the elderly hypertensives when compared with placebo. However, the SHEP study was not designed to prevent occurrence of AF in hypertensives (the actual detected power in our analysis was 23%, corresponding to a reduction of AF from 2.32% in the placebo group to 1.82% in the treated group).

**Limitations**

This analysis of the SHEP database is a retrospective study and as such presents several limitations. Atrial fibrillation was not one of the major prespecified outcomes in SHEP, and its occurrence was retrieved from follow-up forms. Treatment of new onset AF (rate control or cardioversion) and anticoagulation for chronic AF were not specifically addressed in SHEP. It is also unclear how many other subjects developed AF after completion of the original SHEP study. Our conclusions cannot be generalized to other groups of hypertensives which were not represented in the SHEP. With all these limitations, the design of the SHEP study (double-blind, randomized, placebo-controlled trial, exclusion of AF subjects at enrollment, close monitoring of cardiovascular events) makes it an appropriate database for studying AF in the elderly with isolated arterial hypertension. It offers also the unique opportunity to assess the effects of chlorthalidone or atenolol versus placebo in influencing the onset and course of AF in the elderly hypertensives.

**Perspectives**

In SHEP the incidence of AF was 2.06% over 4.5 years mean follow-up. Although the incidence of AF did not differ according to assignment to active treatment or placebo, poorer blood pressure control and baseline electrocardiographic abnormalities predicted AF. Elderly hypertensives with AF had significantly more total cardiovascular events, rapid death, total and nonfatal left ventricular failure than hypertensives who maintained sinus rhythm. The presence of AF in elderly hypertensives was associated with a significant increase in all cause and total cardiovascular mortality at 4.7 and 14.3 years follow-up.

**Acknowledgment**

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**Disclosures**

None.

**References**


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