Association of Pulse Pressure With New-Onset Atrial Fibrillation in Patients With Hypertension and Left Ventricular Hypertrophy

The Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study

Anne Cecilie K. Larstorp; Inger Ariansen; Knut Gjesdal; Michael H. Olsen; Hans Ibsen; Richard B. Devereux; Peter M. Okin; Björn Dahlöf; Sverre E. Kjeldsen; Kristian Wachtell

Abstract—Previous studies have found pulse pressure (PP), a marker of arterial stiffness, to be an independent predictor of atrial fibrillation (AF) in general and hypertensive populations. We examined whether PP predicted new-onset AF in comparison with other blood pressure components in the Losartan Intervention For Endpoint reduction in hypertension study, a double-blind, randomized (losartan versus atenolol), parallel-group study, including 9193 patients with hypertension and electrocardiographic left ventricular hypertrophy. In 8810 patients with neither a history of AF nor AF at baseline, Minnesota coding of electrocardiograms confirmed new-onset AF in 353 patients (4.0%) during mean 4.9 years of follow-up. In multivariate Cox regression analyses, baseline and in-treatment PP and baseline and in-treatment systolic blood pressure predicted new-onset AF, independent of baseline age, height, weight, and Framingham Risk Score; sex, race, and treatment allocation; and in-treatment heart rate and Cornell product. PP was the strongest single blood pressure predictor of new-onset AF determined by the decrease in the −2 Log likelihood statistic, in comparison with systolic blood pressure, diastolic blood pressure, and mean arterial pressure. When evaluated in the same model, the predictive effect of systolic and diastolic blood pressures together was similar to that of PP. In this population of patients with hypertension and left ventricular hypertrophy, PP was the strongest single blood pressure predictor of new-onset AF, independent of other risk factors. (Hypertension. 2012; 60:00-00.) ● Online Data Supplement

Key Words: arrhythmia ■ atenolol ■ blood pressure ■ hypertension ■ losartan ■ structural heart disease

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, and the prevalence is increasing.1 In the Rotterdam study, the prevalence of AF varied from 0.7% in the age group 55 to 59 years to 17.8% in those aged ≥85 years.2 AF incidence increases with age,3 and other risk factors include diabetes, obesity, hypertension, left ventricular hypertrophy (LVH), coronary heart disease, congestive heart failure, valvular heart disease, and increased left atrial size by echocardiography.3–6 AF is associated with a 4- to 5-fold increased risk of ischemic stroke2,8 and with a nearly doubled cardiovascular mortality risk.9 Prevention of AF is thus of great importance, and hypertension is currently the most prevalent, potentially modifiable risk factor, accounting for ≈14% to 22% of AF cases.4,10,11 Increased pulse pressure (PP), defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is a marker of arterial stiffness.12 Studies have found PP to be an independent predictor of new-onset AF in both general13 and hypertensive14 populations. Mitchell et al17 showed that increased baseline PP was the single blood pressure (BP) component most predictive of AF in 5331 participants (∼23% on antihypertensive treatment; ∼1.2% with electrocardiographic LVH [ECG-LVH]) during ≈20 years of follow-up in the Framingham Heart Study and indicated that the relation between BP and incident AF is potentially related, specifically, to the pulsatile component of BP as assessed by PP. In a study by Ciaroni et al,14 increased PP (measured by 24-hour ambulatory BP measurement)
During antihypertensive treatment was associated with an increased risk of new-onset AF, independent of age, sex, body mass index, and SBP in 597 patients with essential hypertension followed for \( \sim 7 \) years. A pathophysiological explanation may be that arterial stiffness increases with age, resulting in increased PP and increased pulsatile load on the heart,\(^\text{15}\) promoting LVH,\(^\text{16}\) left ventricular diastolic dysfunction,\(^\text{17,18}\) and increased left atrial size,\(^\text{19}\) possibly leading to fibrosis and electric remodeling in the left atrium and, eventually, AF. In a study by Goette et al.,\(^\text{20}\) patients with permanent AF had increased amount of atrial fibrosis; however, whether atrial fibrosis induces AF or is a consequence of AF is still unknown.

To our knowledge, the relation between baseline PP and PP during antihypertensive treatment and risk of new-onset AF has not yet been evaluated in high-risk patients with hypertension and ECG-LVH. Therefore, the goals of this prespecified Losartan Intervention For Endpoint (LIFE) reduction in hypertension substudy were to investigate the predictive value of higher baseline and in-treatment brachial PP for new-onset AF in patients with hypertension and LVH and to perform a thorough comparison of the predictive value of PP to that of other BP components such as SBP, DBP, and mean arterial pressure (MAP), using the Framingham study by Mitchell et al. as a model.\(^\text{13}\)

**Methods**

### Study Design and Population

The LIFE study\(^\text{21,22}\) enrolled 9193 patients with essential hypertension (mean sitting brachial BP: 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both) and ECG-LVH (determined by Cornell criteria,\(^\text{25}\)) randomized to losartan- versus atenolol-based therapy. (For further details, please see [http://hyper.ahajournals.org](http://hyper.ahajournals.org).) New-onset AF was a prespecified secondary end point. The present analyses included 8810 patients with neither a history of AF nor AF on their baseline ECG. New-onset AF was identified by Minnesota coding of AF was a prespecified secondary end point. The present analyses included 8810 patients with neither a history of AF nor AF on their baseline ECG. New-onset AF was identified by Minnesota coding of new-onset AF in patients with hypertension and LVH and to perform a thorough comparison of the predictive value of PP to that of other BP components such as SBP, DBP, and mean arterial pressure (MAP), using the Framingham study by Mitchell et al. as a model.\(^\text{13}\)

**Statistical Analyses**

Statistical analyses were performed by the investigators using SPSS version 16.0 (SPSS Inc). Data are presented as mean±standard deviation (SD) for continuous variables and as proportions for categorical variables. Brachial PP was calculated as the difference between SBP and DBP. MAP was calculated as DBP plus one third of PP. Baseline characteristics in patients grouped according to quartiles of baseline PP were compared using analysis of variance (ANOVA) for continuous variables and Pearson correlation coefficient. A 2-tailed \( P < 0.05 \) was required for statistical significance. All study data reside in a database with the authors.

### Results

#### Patient Population and Blood Pressures

In 8810 patients (46% men) at risk of developing new-onset AF, mean baseline PP was 76.5±15.5 mm Hg (74.6±15.6 mm Hg for men and 78.0±15.3 mm Hg for women), with a range of 23.5 to 134.0 mm Hg. Mean age at randomization was 65.9±6.9 years for men and 67.5±7.0 years for women. Elevated PP \( \geq 60 \) mm Hg at baseline was recorded in 7623 (86.5%) patients. Clinical characteristics according to quartiles of baseline PP (\( \geq 67.0 \) mm Hg, 67.0 to 77.0 mm Hg, 77.5 to 87.0 mm Hg, and \( \geq 87.5 \) mm Hg) are presented in Tables 1 and online-only Data Supplement S1 (see [http://hyper.ahajournals.org](http://hyper.ahajournals.org)).

Mean BP values at baseline and during follow-up are displayed in Figure 1. At baseline, mean SBP was 174.3±14.3 mm Hg, mean DBP was 97.9±8.8 mm Hg, and average MAP was 123.8±8.1 mm Hg. In patients followed for at least 4 years, 31.3% had a reduction in PP \( \geq 15.5 \) mm Hg (1 SD of the baseline mean), 79.8% had a reduction in SBP \( \geq 14.3 \) mm Hg (1 SD), 80.2% had a reduction in DBP \( \geq 8.8 \) mm Hg (1 SD), and 87.8% had a reduction in MAP \( \geq 8.1 \) mm Hg (1 SD).

Baseline PP was strongly correlated with SBP (Pearson correlation coefficient \( r = 0.83; P < 0.001 \)), moderately correlated with DBP \( (r = -0.41; P < 0.001) \), and more weakly correlated with MAP \( (r = 0.19; P < 0.001) \). Baseline MAP was strongly correlated with SBP \( (r = 0.71; P < 0.001) \) and DBP \( (r = 0.82; P < 0.001) \). There was a relatively weak correlation between baseline SBP and DBP \( (r = 0.17; P < 0.001) \).

### Multivariate Cox Regression Analyses

ECG confirmed new-onset AF in 353 (4.0%) of 8810 patients during a mean follow-up of 4.9±0.9 years. Figures 2 and 3 present the incidence of AF by quartiles of baseline PP.

In the secondary analyses, we explored the relations between different BP components (PP, SBP, DBP, and MAP) as baseline and time-varying covariates and new-onset AF using the same multivariate Cox regression model and including a single BP component (PP, SBP, DBP, or MAP) or a combination of BP components (SBP and DBP, or PP and MAP). Hazard ratios (HR) for the incidence of new-onset AF associated with baseline and in-treatment PP, SBP, DBP, and MAP were computed per 1 SD of the baseline mean and per 10 mm Hg increments in BP.\(^\text{29,30}\) Wald \( \chi^2 \) statistics and \( P \) values were calculated. The decrease in the −2 Log likelihood statistic (a measure of model fit with data), caused by adding a single BP component (degrees of freedom \( df = 1 \)) or a combination of BP components (\( df \) equals the number of covariates added to the model) to the multivariate Cox regression model and \( \chi^2 \) tests, were used to evaluate and compare the relative importance and predictive effects of PP, SBP, DBP, and MAP. In addition, PP was also evaluated as a categorical variable with quartiles of baseline PP in multivariate analyses. Interaction analyses were performed using Cox regression models with 2 and 2 covariates and their cross-products.

Possible correlations between BP components were analyzed using Pearson correlation coefficient. A 2-tailed \( P < 0.05 \) was required for statistical significance. All study data reside in a database with the authors.
The number of patients at each examination is noted in parentheses. \( P < 0.001 \) for the trend across quartiles.

Fig. 2. Incidence of atrial fibrillation according to quartiles of baseline pulse pressure. \( P < 0.001 \) for the trend across quartiles (Pearson \( \chi^2 \)).
significant univariate predictors and were significant in the multivariate model; however, the model did not change when these covariates were excluded. Cox proportional hazards models for PP in comparison with other BP components are presented in Table 2. All 10 models were adjusted for baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product. Baseline PP quartile 4 (≥87.5 mm Hg) was associated with a 67% (95% CI, 32% to 211%; \( P=0.001 \)) higher risk of new-onset AF compared with quartiles 1 to 3. This result was strengthened when we also adjusted for in-treatment PP in the same model (HR, 1.98; 95% CI, 1.55 to 2.52; \( P<0.001 \)).

There were no significant interactions between baseline or in-treatment PP and other BP components or between baseline or in-treatment PP and baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product. Baseline PP quartile 4 (≥87.5 mm Hg) was associated with a highly significant increase in risk of developing AF during mean 4.9 years of follow-up compared with quartiles 1 to 3.

In comparison with SBP, DBP, and MAP as single BP components, PP was the strongest predictor of incident AF. When we considered the predictive effect of SBP and DBP together, model fit improved significantly and had the same \(-2 \log\text{likelihood} \chi^2 = 104.8; 2 \text{df}; P<0.01\).

In model 9, there were significant interactions between weight and in-treatment SBP and DBP (\( P=0.01 \)) and weight and in-treatment DBP (\( P=0.03 \)). In model 10, there were significant interactions between age and in-treatment MAP (\( P=0.02 \)) and weight and in-treatment MAP (\( P=0.004 \)).

**Discussion**

In the present study, increased baseline PP and PP during antihypertensive treatment were associated with an increased risk of incident AF, independent of other predictors of AF in this population (ie, baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product). Baseline PP quartile 4 (≥87.5 mm Hg) was associated with a highly significant increase in risk of developing AF during mean 4.9 years of follow-up compared with quartiles 1 to 3.

In comparison with SBP, DBP, and MAP as single BP components, PP was the strongest predictor of incident AF. When we considered the predictive effect of SBP and DBP together, model fit improved significantly and had the same \(-2 \log\text{likelihood} \chi^2 = 104.8; 2 \text{df}; P<0.01\).

In model 9, there were significant interactions between weight and in-treatment SBP and DBP (\( P=0.01 \)) and weight and in-treatment DBP (\( P=0.03 \)). In model 10, there were significant interactions between age and in-treatment MAP (\( P=0.02 \)) and weight and in-treatment MAP (\( P=0.004 \)).

In the present study, increased baseline PP and PP during antihypertensive treatment were associated with an increased risk of incident AF, independent of other predictors of AF in this population (ie, baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product). Baseline PP quartile 4 (≥87.5 mm Hg) was associated with a highly significant increase in risk of developing AF during mean 4.9 years of follow-up compared with quartiles 1 to 3.

In comparison with SBP, DBP, and MAP as single BP components, PP was the strongest predictor of incident AF. When we considered the predictive effect of SBP and DBP together, model fit improved significantly and had the same \(-2 \log\text{likelihood} \chi^2 = 104.8; 2 \text{df}; P<0.01\).

In model 9, there were significant interactions between weight and in-treatment SBP and DBP (\( P=0.01 \)) and weight and in-treatment DBP (\( P=0.03 \)). In model 10, there were significant interactions between age and in-treatment MAP (\( P=0.02 \)) and weight and in-treatment MAP (\( P=0.004 \)).

In the present study, increased baseline PP and PP during antihypertensive treatment were associated with an increased risk of incident AF, independent of other predictors of AF in this population (ie, baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product). Baseline PP quartile 4 (≥87.5 mm Hg) was associated with a highly significant increase in risk of developing AF during mean 4.9 years of follow-up compared with quartiles 1 to 3.

In comparison with SBP, DBP, and MAP as single BP components, PP was the strongest predictor of incident AF. When we considered the predictive effect of SBP and DBP together, model fit improved significantly and had the same \(-2 \log\text{likelihood} \chi^2 = 104.8; 2 \text{df}; P<0.01\).

In model 9, there were significant interactions between weight and in-treatment SBP and DBP (\( P=0.01 \)) and weight and in-treatment DBP (\( P=0.03 \)). In model 10, there were significant interactions between age and in-treatment MAP (\( P=0.02 \)) and weight and in-treatment MAP (\( P=0.004 \)).
In-treatment MAP was associated with incident AF when adjusted for baseline MAP and the above-mentioned AF risk factors. Entering MAP into the same model as PP did not improve model fit; baseline and in-treatment MAP were not significant, and the HRs of baseline and in-treatment PP were unaltered. Thus, PP predicted incident AF independent of MAP.

AF is associated with increased risk of cardiovascular morbidity and mortality. It is highly important to identify modifiable risk factors, as both men and women have an approximate 25% overall lifetime risk of AF. To our knowledge, this is the first study to report a strong, independent association between brachial PP and new-onset AF in patients with hypertension and ECG-LVH. Our results are in agreement with a Framingham Heart Study investigation evaluating PP as a predictor for incident AF in a general population with normal or moderately increased BP. Furthermore, Mitchell et al demonstrated that there is a potential weakness of concentrating on SBP alone and ignoring DBP and PP, and our data support this finding. When evaluating the risk of incident AF in a hypertensive population with ECG-LVH, PP should be considered or, alternatively, SBP and DBP together. PP is simple to calculate as the absolute difference between SBP and DBP.

Increased PP, a marker of advanced vascular aging and arterial stiffness, may contribute to the structural and electric remodeling of the myocardium, leading to the development of AF, possibly through increased pulsatile load on the heart and increased left atrial size. Studies have shown that reduced distensibility of large arteries parallel cardiac hypertrophy and remodeling in patients with hypertension. Large artery stiffness may increase the workload on the heart similar to volume overload and, perhaps, represent one of the mechanisms by which hypertension leads to eccentric hypertrophy and left atrial enlargement. In a LIFE substudy, there was a significant correlation between baseline brachial PP and left atrial size, independent of age, sex, and body surface area (data not shown). Furthermore, there is much evidence for linking brachial PP to microvascular damage in the heart and other target organs, which, again, may lead to increased peripheral resistance and MAP, further increasing arterial stiffness and central PP. Increased central PP may then further damage small arteries and lead to LVH. Studies have found brachial PP to be a powerful predictor of cardiovascular morbidity and mortality, and the predictive effect increases with age. The present study evaluated brachial PP and not central PP. Noninvasive central PP has been shown to better predict cardiovascular outcomes than brachial PP and to be closer associated with extent of atherosclerosis (carotid plaque burden and intimal-medial thickness, and vascular mass).

### Table 2. Cox Proportional Hazards Models for PP and other BP Components as Independent Predictors of New-Onset AF in Patients With Hypertension and ECG-LVH

<table>
<thead>
<tr>
<th>Model</th>
<th>-2 Log Likelihood</th>
<th>BP Components</th>
<th>HR (95% CI) per 10 mm Hg Increase</th>
<th>HR (95% CI) per 1 SD Increase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>5762.0</td>
<td>Baseline PP</td>
<td>1.14 (1.06–1.23)</td>
<td>1.23 (1.09–1.38)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>5739.6</td>
<td>Baseline PP</td>
<td>1.24 (1.14–1.34)</td>
<td>1.39 (1.22–1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>5764.5</td>
<td>Baseline SBP</td>
<td>1.13 (1.04–1.23)</td>
<td>1.20 (1.06–1.34)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 4</td>
<td>5750.2</td>
<td>Baseline SBP</td>
<td>1.18 (1.08–1.28)</td>
<td>1.27 (1.12–1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5</td>
<td>5772.7</td>
<td>Baseline DBP</td>
<td>0.94 (0.84–1.07)</td>
<td>0.95 (0.86–1.06)</td>
<td>0.35</td>
</tr>
<tr>
<td>Model 6</td>
<td>5772.6</td>
<td>Baseline DBP</td>
<td>0.95 (0.84–1.08)</td>
<td>0.96 (0.85–1.07)</td>
<td>0.45</td>
</tr>
<tr>
<td>Model 7</td>
<td>5772.6</td>
<td>Baseline MAP</td>
<td>1.07 (0.94–1.22)</td>
<td>1.06 (0.95–1.18)</td>
<td>0.33</td>
</tr>
<tr>
<td>Model 8</td>
<td>5767.4</td>
<td>Baseline MAP</td>
<td>1.11 (0.97–1.27)</td>
<td>1.09 (0.97–1.22)</td>
<td>0.14</td>
</tr>
<tr>
<td>Model 9</td>
<td>5739.4</td>
<td>Baseline SBP</td>
<td>1.24 (1.14–1.36)</td>
<td>1.36 (1.20–1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 10</td>
<td>5739.4</td>
<td>Baseline PP</td>
<td>1.24 (1.14–1.35)</td>
<td>1.39 (1.22–1.59)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All models are adjusted for baseline age, height, weight, and Framingham Risk Score; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product. One SD of the baseline mean was 15.5 mm Hg for PP, 14.3 mm Hg for SBP, 8.8 mm Hg for DBP, and 8.1 mm Hg for MAP.

PP indicates pulse pressure; BP, blood pressure; AF, atrial fibrillation; ECG-LVH, electrocardiographic left ventricular hypertrophy; HR, hazard ratio; CI, confidence interval; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
In conclusion, in patients with hypertension and ECG-LVH in the LIFE study, increased baseline and in-treatment PP were independently associated with increased risk of new-onset AF. PP was (in comparison with SBP, DBP, and MAP) the single BP component with the strongest predictive effect.

Limitations
Patients evaluated in the LIFE study were predominantly white and from Western countries. They had hypertension and ECG-LVH and increased risk of cardiovascular events compared with hypertensive subjects without LVH. The results may not be generalizable to normotensives and hypertensives without LVH. BP was measured with a sphygmomanometer, which is considered less accurate than 24-hour ambulatory BP measurement. New-onset AF was a pre-specified secondary end point; however, the LIFE study was designed and had statistical power for the primary composite end point, and the HRs for AF require careful interpretation.

Perspectives
In patients with hypertension and ECG-LVH in the LIFE study, increased baseline and in-treatment PP were independently associated with new-onset AF. PP was (in comparison with SBP, DBP and MAP) the single BP component with the strongest predictive effect, supporting the hypothesis that the relation between BP and incident AF is related specifically to the pulsatile component of BP as assessed by PP. Furthermore, SBP and DBP together had a predictive effect similar to the predictive effect of PP, reflecting the definition of PP. In-treatment MAP was significantly associated with new-onset AF when adjusted for baseline MAP and the mentioned risk factors; however, the predictive effect was weaker than for PP or for SBP and DBP evaluated together. This result may imply that the association between MAP (the steady component of BP) and AF is weak. When evaluating risk of AF in patients with hypertension and ECG-LVH, both baseline PP and PP during antihypertensive treatment, alternatively SBP and DBP together, should be considered. Furthermore, lowering of PP may prevent new-onset AF in patients with hypertension and LVH; however, this must be further explored in randomized clinical trials.

Sources of Funding
The LIFE study was originally sponsored by Merck & Co, Inc, Whitehouse Station, NJ. This sub-study was partially funded by a grant from South-Eastern Norway Regional Health Authority.

Disclosures
Drs Gjesdal, Olsen, Devereux, and Wachtell were investigators and Drs Devereux, Ibsen, Kjeldsen, and Dahlöf were steering committee members for the LIFE Study. Drs Dahlöf, Devereux, and Wachtell have received grant support from Merck & Co, Inc, the sponsor for the LIFE Study. Drs Gjesdal, Olsen, Ibsen, Devereux, Okin, Dahlöf, Kjeldsen, and Wachtell have received occasional speaker honoraria from Merck & Co, Inc.

References
Pulse Pressure and Risk of Atrial Fibrillation

What Is New?

- To our knowledge, this is the first study to report a strong, independent association between baseline pulse pressure and pulse pressure during antihypertensive treatment and new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy.

What Is Relevant?

- In 8810 patients in this randomized (losartan versus atenolol) treatment trial, pulse pressure (the pulsatile component of blood pressure and a marker of arterial stiffness) was the strongest single blood pressure predictor for atrial fibrillation compared with systolic blood pressure, diastolic blood pressure, and mean arterial pressure.

Summary

When evaluating risk of atrial fibrillation in patients with hypertension and left ventricular hypertrophy, both baseline pulse pressure and pulse pressure during antihypertensive treatment should be considered.
Association of Pulse Pressure With New-Onset Atrial Fibrillation in Patients With Hypertension and Left Ventricular Hypertrophy: The Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study
Anne Cecilie K. Larstorp, Inger Ariansen, Knut Gjesdal, Michael H. Olsen, Hans Ibsen, Richard B. Devereux, Peter M. Okin, Björn Dahlöf, Sverre E. Kjeldsen and Kristian Wachtell

Hypertension. published online July 2, 2012;

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/2012/06/29/HYPERTENSIONAHA.112.195032

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2012/07/02/HYPERTENSIONAHA.112.195032.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
ONLINE SUPPLEMENT:

Association of Pulse Pressure With New-Onset Atrial Fibrillation in Patients With Hypertension and Left Ventricular Hypertrophy
The Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study

Anne Cecilie K. Larstorp, MD1, 2, Inger Ariansen, MD, PhD1, 2, Knut Gjesdal, MD, PhD1, 2, Michael H. Olsen, MD, PhD3, 4, Hans Ibsen, MD, PhD5, Richard B. Devereux, MD6, Peter M. Okin, MD6, Björn Dahlöf, MD, PhD7, Sverre E. Kjeldsen, MD, PhD1, 2, Kristian Wachtell, MD, PhD8.

1Oslo University Hospital Ullevål, Department of Cardiology and 2University of Oslo, Institute of Clinical Medicine, Oslo, Norway, 3Odense University Hospital, Department of Endocrinology, Odense, Denmark and 4North West University, The Research Focus Area for Hypertension in Africa Research Team, Potchefstroom Campus, South Africa, 5Holbæk Hospital, Division of Cardiology, Holbæk, Denmark, 6Weill Cornell Medical College, Greenberg Division of Cardiology, New York City, United States of America, 7Sahlgrenska University Hospital/Östra, Department of Medicine, Göteborg, Sweden, 8Gentofte University Hospital, Department of Cardiology, Hellerup, Denmark.

Short title: Pulse Pressure and risk of Atrial Fibrillation

Online supplement word count of text: 1006   Tables: 2

Correspondence to Anne Cecilie K. Larstorp, M.D., Department of Cardiology, Oslo University Hospital Ullevål, Postboks 4956 Nydalen, N-0424 Oslo, Norway.
Telephone: +4722119100, Fax: +4722119181
E-mail: a.c.k.larstorp@medisin.uio.no
Clinical Trials Registration: NCT00338260
Expanded Methods:

Study Design and Population
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, as described in detail elsewhere (1-3), enrolled 9193 patients aged 55 through 80 years (mean 67 years) with essential hypertension (mean sitting brachial blood pressure (BP) in the range of 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both after placebo run-in) having ECG-LVH determined by Cornell voltage-duration product (4;5) and/or Sokolow-Lyon voltage criteria (6) on a screening ECG in a prospective, double-blind, parallel group study with randomization to losartan- vs. atenolol-based therapy targeting a BP of 140/90 mm Hg or lower (1). Patients were followed for mean 4.8 years and the main outcome was the composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction. New-onset atrial fibrillation was a pre-specified secondary endpoint.

BP was measured at follow-up examinations; in the present study we have used yearly recordings. After patients had been seated for 5 minutes, BP was measured as the average of two recordings with a 1 minute interval with the arm positioned so that the location of the stethoscope head was at the level of the heart.

The trial protocol was approved by all ethics committees concerned, in accordance with the Declaration of Helsinki, and was overseen by an independent data and safety monitoring board. All participants provided written informed consent.

A total of 362 patients with a history of AF and/or AF on their baseline ECG and 21 patients with missing baseline PP were excluded from the present analyses.

Electrocardiography
Electrocardiograms were obtained at study baseline, at 6 months, and at yearly follow-up intervals until study termination or patient death. All ECGs were interpreted at the core laboratory at Sahlgrenska University Hospital/Östra, Göteborg, Sweden, by experienced readers blinded to clinical information. The QRS durations were measured to the nearest 4 msec and the QRS amplitudes to the nearest 0.5 mm (0.05 mV). Cornell product higher than 2440 mm × msec (4;5) and/or Sokolow-Lyon voltage higher than 38 mm (6) were used to identify LVH (7;8).

Statistical Analyses
Serum glucose, serum creatinine and urine albumin-creatinine ratio were log₁₀ or reciprocally transformed owing to skewed distributions.

In the primary analyses, possible associations between baseline PP or PP during antihypertensive therapy and the risk of developing new-onset AF were analyzed according to a pre-specified statistical analysis plan using Cox proportional hazards regression analyses (7;9) and based on the intention-to-treat principle (3).

Interaction analyses were performed using Cox regression models with two and two covariates (either between a BP component and an adjustment covariate, between two adjustment covariates or between two BP components included in the same model) and their cross-products (interaction terms). Significant interaction terms were then entered into separate Cox regression models that included all the covariates in the multivariate model.
References


(4) Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. *J Am Coll Cardiol.* 1992;20:1180-1186.


Table S1. Baseline Characteristics by Quartiles of Baseline Pulse Pressure (n= 8810)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 (≤67.0 mm Hg)</th>
<th>Q2 (67.5-77.0 mm Hg)</th>
<th>Q3 (77.5-87.0 mm Hg)</th>
<th>Q4 (≥87.5 mm Hg)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=2334</strong></td>
<td><strong>n=2189</strong></td>
<td><strong>n=2139</strong></td>
<td><strong>n=2148</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>1234 (53)</td>
<td>1019 (47)</td>
<td>928 (43)</td>
<td>833 (39)</td>
<td>‡</td>
</tr>
<tr>
<td>Age, y</td>
<td>64±7</td>
<td>66±7</td>
<td>68±7</td>
<td>70±6</td>
<td>†</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>2115 (91)</td>
<td>2016 (92)</td>
<td>1998 (93)</td>
<td>2013 (94)</td>
<td>‡</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81±15</td>
<td>79±15</td>
<td>78±16</td>
<td>76±14</td>
<td>†</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169±10</td>
<td>168±9</td>
<td>167±9</td>
<td>166±9</td>
<td>†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2±4.7</td>
<td>28.0±4.8</td>
<td>28.2±5.1</td>
<td>27.7±4.6</td>
<td>†</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>391 (17)</td>
<td>378 (17)</td>
<td>347 (16)</td>
<td>324 (15)</td>
<td>ns</td>
</tr>
<tr>
<td>No exercise, n (%)</td>
<td>464 (20)</td>
<td>429 (20)</td>
<td>502 (24)</td>
<td>531 (25)</td>
<td>‡</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>213 (9)</td>
<td>235 (11)</td>
<td>296 (14)</td>
<td>359 (17)</td>
<td>‡</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td>268 (12)</td>
<td>293 (13)</td>
<td>276 (13)</td>
<td>322 (15)</td>
<td>‡</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>27 (1.2)</td>
<td>31 (1.4)</td>
<td>37 (1.7)</td>
<td>33 (1.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Isolated systolic hypertension, n (%)</td>
<td>0 (0)</td>
<td>121 (6)</td>
<td>406 (19)</td>
<td>721 (34)</td>
<td>‡</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>159±10</td>
<td>171±7</td>
<td>179±9</td>
<td>189±10</td>
<td>†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>102±6</td>
<td>99±7</td>
<td>97±9</td>
<td>93±10</td>
<td>†</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>57±8</td>
<td>72±3</td>
<td>82±3</td>
<td>96±7</td>
<td>na</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>121±6</td>
<td>123±7</td>
<td>125±9</td>
<td>125±9</td>
<td>†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75±11</td>
<td>74±11</td>
<td>74±11</td>
<td>73±11</td>
<td>†</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>28.4±9.9</td>
<td>29.7±10.1</td>
<td>30.2±10.5</td>
<td>31.7±10.7</td>
<td>†</td>
</tr>
<tr>
<td>Cornell product, mm x msec</td>
<td>2738±910</td>
<td>2828±1093</td>
<td>2849±1037</td>
<td>2851±1021</td>
<td>†</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.86±2.03</td>
<td>5.88±1.98</td>
<td>6.08±2.31</td>
<td>6.21±2.37</td>
<td>†</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>87.4±19.1</td>
<td>86.2±18.8</td>
<td>86.2±21.3</td>
<td>86.6±21.1</td>
<td>†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.99±1.13</td>
<td>6.06±1.10</td>
<td>6.09±1.12</td>
<td>6.09±1.13</td>
<td>†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.48±0.44</td>
<td>1.50±0.43</td>
<td>1.50±0.44</td>
<td>1.51±0.44</td>
<td>ns</td>
</tr>
<tr>
<td>Serum uric acid, μmol/L</td>
<td>336±79</td>
<td>329±76</td>
<td>326±77</td>
<td>324±78</td>
<td>†</td>
</tr>
<tr>
<td>UACR, mg/mmol</td>
<td>5.7±30.7</td>
<td>5.6±20.7</td>
<td>7.3±29.1</td>
<td>9.8±35.5</td>
<td>†</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>144.4±11.8</td>
<td>142.8±11.5</td>
<td>141.9±12.2</td>
<td>140.1±12.0</td>
<td>†</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>20±8</td>
<td>22±9</td>
<td>23±10</td>
<td>25±10</td>
<td>†</td>
</tr>
</tbody>
</table>

*Values are mean±SD or numbers (n) and percentages. †P <0.01 (ANOVA). ‡P <0.01 (Pearson Chi-Square). CHD indicates coronary heart disease; ns, not significant; na, not applicable; bpm, beats per minute; HDL, high density lipoprotein; UACR, urine albumin-creatinine ratio.
<table>
<thead>
<tr>
<th>Variable in Multivariate Model</th>
<th>$\chi^2$</th>
<th>Hazard Ratio (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline pulse pressure per 15.5 mm Hg (1 SD)</td>
<td>25.3</td>
<td>1.39 (1.22 - 1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-treatment pulse pressure per 15.5 mm Hg (1 SD)</td>
<td>21.7</td>
<td>1.33 (1.18 - 1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-treatment Cornell product per 1050 mm x msec (1 SD)</td>
<td>8.3</td>
<td>1.13 (1.04 - 1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-treatment heart rate (bpm)</td>
<td>70.9</td>
<td>1.03 (1.02 - 1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (atenolol vs. losartan)</td>
<td>27.4</td>
<td>1.79 (1.44 - 2.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>103.1</td>
<td>1.10 (1.08 - 1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.3</td>
<td>1.23 (0.85 - 1.85)</td>
<td>0.25</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>17.0</td>
<td>1.02 (1.01 - 1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>13.2</td>
<td>1.03 (1.02 - 1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (white vs. black)</td>
<td>8.2</td>
<td>3.26 (1.45 - 7.35)</td>
<td>0.004</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>7.7</td>
<td>0.98 (0.96 - 0.99)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PP indicates pulse pressure; AF, atrial fibrillation; ECG-LVH, electrocardiographic left ventricular hypertrophy; $\chi^2$, Chi-Square (Wald Score); CI, confidence interval; SD, standard deviation; bpm, beats per minute.