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 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; 60:347-353.) ● 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.4–6 AF is associated with a 4- to 5-fold increased risk of ischemic stroke7,8 and with a nearly doubled cardiovascular mortality risk.9 Prevention of AF is 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 al13 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)

Received March 9, 2012; first decision April 3, 2012; revision accepted June 2, 2012.
From the Department of Cardiology, Oslo University Hospital Ullevål, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway (A.C.K.L., I.A., K.G., S.E.K.); Department of Endocrinology, Odense University Hospital, Odense, Denmark (M.H.O.); Research Focus Area for Hypertension in Africa Research Team, Potchefstroom Campus, North West University, Potchefstroom, South Africa (M.H.O.); Division of Cardiology, Holbek Hospital, Holbek, Denmark (H.I.); Greenberg Division of Cardiology, Weill Cornell Medical College, New York, NY (R.B.D., P.M.O.); Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden (B.D.); Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark (K.W.). Clinical Trials Registration Information: URL: http://www.clinicaltrials.gov/ct2/show/NCT00338260 (Identifier NCT00338260).
The online-only Data Supplement is available with this article at http://hyper.ahajournals.orglookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.195032/DC1.

Correspondence to Anne Cecilie K. Larstorp, MD, Department of Cardiology, Oslo University Hospital Ullevål, Postboks 4956 Nydalen, N-0424 Oslo, Norway. E-mail a.c.k.larstorp@medisin.uio.no
© 2012 American Heart Association, Inc.
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 \( \approx 7 \) years. A pathophysiologic explanation may be that arterial stiffness increases with age, resulting in increased PP and increased pulsatile load on the heart, promoting LVH, left ventricular diastolic dysfunction, \([17,18]\) and increased left atrial size, \([19]\) possibly leading to fibrosis and electric remodeling in the left atrium and, eventually, AF. In a study by Goette et al, \([20]\) 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. \([13]\)

### Methods

#### Study Design and Population

The LIFE study \([21,22]\) 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 voltage-duration product \([23,24]\) and/or Sokolow-Lyon voltage criteria \([25]\) randomized to losartan- versus atenolol-based therapy. (For further details, please see 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 annual in-study ECGs at the core laboratory at Sahlgrenska University Hospital/Ostra, Göteborg, Sweden. \([21,26]\)

#### 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 the SD of baseline mean and per 10 mm Hg increments in BP. \([29,30]\) 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 \((df=\text{the number of covariates added to the model})\) 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.

### 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 ≥60 mm Hg at baseline was recorded in 7623 (86.5%) patients. Clinical characteristics according to quartiles of baseline PP \((≥76.0 \text{ mm Hg, 77.5 to 77.0 mm Hg, 77.5 to 87.0 mm Hg, and ≥87.5 mm Hg})\) are presented in Tables 1 and online-only Data Supplement S1 (see 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 123.3±8.1 mm Hg. In patients followed for at least 4 years, 41.3% had a reduction in PP ≥15.5 mm Hg (1 SD of the baseline mean), 79.8% had a reduction in SBP ≥14.3 mm Hg (1 SD), 80.2% had a reduction in DBP ≥8.8 mm Hg (1 SD), and 87.8% had a reduction in MAP ≥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 335 (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.

Results of the multivariate Cox regression model examining the predictive effect of baseline and in-treatment PP for new-onset AF are presented in Model 2 of Table 2 and in Table S2 (see http://hyper.ahajournals.org). Baseline PP was associated with a 39% (95% confidence interval [CI], 22% to
58%; \( P<0.001 \) increased risk of new-onset AF per 15.5 mm Hg (SD) increase, and in-treatment PP was associated with a 33% (95% CI, 18% to 50%; \( P<0.001 \) increased risk of new-onset AF per SD increase in a model adjusting for baseline age, height, weight, and Framingham Risk Score (FRS); sex, race, and a treatment group indicator (atenolol versus losartan), entered as continuous or categorical covariates; and in-treatment heart rate and ECG-LVH by Cornell product, entered as time-varying continuous covariates. Sex was a significant univariate predictor and was included in the multivariate Cox regression model for biological reasons, even though it was not significant in multivariate analyses. Smoking, diabetes, previous myocardial infarction, and body mass index did not predict new-onset AF; however, replacing height and weight with body mass index in the multivariate model did not alter the results. Baseline total cholesterol, potassium, and urine albumin-creatinine ratio were signifi-

![Figure 1](https://hyper.ahajournals.org/figure/1.png)

**Figure 1.** Mean blood pressure during 4.9 years of follow-up. The number of patients at each examination is noted in parentheses. \( P<0.001 \) for all blood pressure components (general linear models). BP indicates blood pressure; MAP, mean arterial pressure.

![Figure 2](https://hyper.ahajournals.org/figure/2.png)

**Figure 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. When comparing single BP components in parallel multivariate models, adjusting for the same covariates, baseline and in-treatment PP (Models 1 and 2) and baseline and in-treatment SBP (Models 3 and 4), in addition to in-treatment MAP adjusted for baseline MAP (Model 8), were significant independent predictors of new-onset AF. Baseline and in-treatment DBP were not significant predictors (Models 5 and 6). The initial $-2 \log$ likelihood was 5773.6 for the multivariate model, with baseline age, height, weight, and FRS; sex, race, and treatment allocation; and in-treatment heart rate and ECG-LVH by Cornell product. This model was used as a basis to evaluate decrease in $-2 \log$ likelihood when introducing BP measures. Baseline and in-treatment PP (Model 2) were the strongest single component predictors ($-2 \log$ likelihood 5739.6; $\chi^2 = 34.0$; 2 df, $P<0.001$); however, when entering baseline and in-treatment SBP and DBP into 1 model (Model 9), the model fit was equally good as for the baseline and in-treatment PP model: $-2 \log$ likelihood 5739.4 ($\chi^2 = 34.2$; df = 4; $P<0.001$) compared with 5739.6. The model with baseline and in-treatment SBP alone (Model 4) had a $-2 \log$ likelihood of 5750.2, and adding baseline and in-treatment DBP to the model (Model 9) thus induced a significant improvement ($\chi^2 = 10.8$; df = 2; $P<0.01$). In model 9, baseline and in-treatment SBP and DBP were all significant predictors of new-onset AF; however, the effects of SBP and DBP were opposite. Adding baseline and in-treatment MAP to the model with baseline and in-treatment PP did not change the model fit ($-2 \log$ likelihood 5739.4 for Model 10 and 5739.6 for Model 2), and baseline and in-treatment MAP were not significant predictors in this model. When forcing baseline and in-treatment PP, SBP, and DBP into the same model, the HRs for DBP were not calculated owing to excess colinearity ($r \approx 1.0$) with PP and SBP. In the same model, baseline PP had a higher $\chi^2$ (Wald score) than baseline SBP ($\chi^2 = 8.7$ versus 0.01), and in-treatment PP was a stronger predictor than in-treatment SBP ($\chi^2 = 7.2$ versus 0.08).

PP was also computed as a categorical variable, with quartiles of baseline PP (quartile 4 versus quartiles 1 to 3). When 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 ($\geq 87.5$ 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. There were significant interactions between in-treatment heart rate and weight ($P=0.03$) and in-treatment heart rate and race ($P=0.003$) in all 10 models (Table 2). In model 9, there were significant interactions between weight and in-treatment SBP ($P=0.03$) and weight and in-treatment DBP ($P=0.01$). 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 ($\geq 87.5$ 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 $-2 \log$ likelihood as the PP model. This is a consequence of the mathematical calculation of PP as the difference between SBP and DBP. When evaluated in the same model, the effects of SBP and DBP were significant but opposite, suggesting that, for a certain value of SBP, lower DBP was associated with an increased risk of new-onset AF. When evaluating PP, SBP, and DBP in the same model, both baseline and in-treatment PP had higher $\chi^2$ (Wald score) than SBP. This supports the finding that PP is the strongest single BP measure for predicting incident AF in our study; however, it should be interpreted with caution, considering the high correlations between the BP components in this specific model.
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 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

### 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>Multivariate Model</th>
<th>-2 Log Likelihood for Model</th>
<th>BP Components in Model*</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>In-treatment PP</td>
<td>1.20 (1.11–1.30)</td>
<td>1.33 (1.18–1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4</td>
<td>5750.2</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 5</td>
<td>5772.7</td>
<td>In-treatment 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 6</td>
<td>5772.6</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 7</td>
<td>5772.6</td>
<td>In-treatment DBP</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>In-treatment MAP</td>
<td>1.13 (1.02–1.25)</td>
<td>1.10 (1.01–1.20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 10</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></td>
<td></td>
<td>In-treatment SBP</td>
<td>1.20 (1.11–1.30)</td>
<td>1.30 (1.17–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline DBP</td>
<td>0.81 (0.71–0.93)</td>
<td>0.83 (0.74–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In-treatment DBP</td>
<td>0.82 (0.70–0.95)</td>
<td>0.84 (0.73–0.95)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline MAP</td>
<td>1.24 (1.14–1.35)</td>
<td>1.39 (1.22–1.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In-treatment PP</td>
<td>1.21 (1.11–1.33)</td>
<td>1.33 (1.17–1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline MAP</td>
<td>0.98 (0.87–1.11)</td>
<td>0.99 (0.89–1.09)</td>
<td>0.77</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.

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).
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 prespecified 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 substudy was partially funded by a grant from South-Eastern Norway Regional Health Authority.

Disclosures
Drs Gjesdal, Olsen, Devereux, Kjeldsen, 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, and Wachtell have received occasional speaker honoraria from Merck & Co, Inc.

References
Larstorp et al

Pulse Pressure and Risk of Atrial Fibrillation 353


23. Molloy TJ, O’kin PM, Devereux RB, Kligﬁeld P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. J Am Coll Cardiol. 1999;20:1180–1186.


Novelty and Signiﬁcance

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_. 2012;60:347-353; originally published online July 2, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.195032
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
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/60/2/347

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>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 (≤67.0 mm Hg) n=2334</th>
<th>Q2 (67.5-77.0 mm Hg) n=2189</th>
<th>Q3 (77.5-87.0 mm Hg) n=2139</th>
<th>Q4 (≥87.5 mm Hg) n=2148</th>
<th>P</th>
</tr>
</thead>
<tbody>
<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 S2. Cox Proportional Hazards Model for Baseline PP and In-Treatment PP as Independent Predictors of New-Onset AF in Patients with Hypertension and ECG-LVH

<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.