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Left Atrial Systolic Force in Hypertensive Patients with Left Ventricular Hypertrophy: A Predictor of Incident Atrial Fibrillation. The LIFE Study

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Abstract

It remains unknown whether left atrial systolic force (LASF), a measure of left atrial function, can be used as a predictor of new-onset atrial fibrillation (NOAF). Furthermore, the effect of the treatment with atenolol and losartan on LASF is unclear. A total of 758 patients without

atrial fibrillation at baseline were enrolled from the Losartan Intervention For Endpoint (LIFE) reduction in hypertension echocardiography sub-study. Participants of the LIFE study were randomized to either atenolol-or losartan-based treatment. The mean follow-up was 59 months. LASF was calculated using the average mitral orifice area and mitral peak. The velocity was obtained by Doppler echocardiography. At baseline, 25% of patients had a LASF ≤ 10.3 kdyn. Compared to other quartiles, this quartile had a higher proportion of men, lower heart rate, body mass index, and age. After controlling for these variables, patients in the first quartile had a lower stroke volume compared to other quartiles. New-onset AF occurred in 29 (8.1/1,000 patient-years of follow-up) patients. In multivariable Cox regression analyses with backward elimination, increasing LASF was associated with a lower risk of NOAF (hazard ratio [HR] = 0.90 [95% confidence interval 0.85-0.96], p = 0.001). Integrated discrimination improvement was 0.054 (p = 0.004) and there was a borderline significant net reclassification improvement of 19.2% (p = 0.075). Over time LASF decreased more in the atenolol-based than the losartan-based treatment group (< 0.001). Low LASF was associated with a higher risk of new-onset AF. Losartan-based treatment was associated with better preservation of LASF compared to atenolol-based treatment.

Keywords
Atrial fibrillation; blood pressure; hypertension; left atrial systolic force; left atrium; left ventricular hypertrophy

1. Introduction

Atrial fibrillation affects 1 to 1.5% of the population in the developed world and is associated with increased morbidity and mortality [1]. Patients with atrial fibrillation have a five-fold increased risk of ischemic stroke [2]. Several anatomical and physiological risk factors of atrial fibrillation, including age, left atrial size, and volume and left ventricular hypertrophy (LVH), have been identified in previous studies [3-5].

Recently, increased left atrial systolic force (LASF) has been associated with LVH in hypertensive patients [6]. Furthermore, impaired left ventricular relaxation is often seen in hypertensive patients [7]. Atrial contribution to ventricular filling is important because of the correlated left ventricular filling impairment [8]. LASF may increase as a compensatory response to preserve a sufficient stroke volume [8, 9], which partly could explain the association between age-related prolonged left ventricular relaxation and increased LASF [10-12]. Reduced left atrial function has also been shown to be associated with poor prognosis in patients with atrial fibrillation [13, 14]. However, it remains unclear whether impaired left atrial function is associated with incident atrial fibrillation, and whether the afterload-reducing treatment with losartan better preserves the left atrial function compared to heart rate-reducing treatment with atenolol.

Therefore, in the present study, as a part of the Losartan Intervention For Endpoint (LIFE) reduction in hypertension [15, 16] echocardiographic sub-study, we determined whether LASF correlated to incident atrial fibrillation and whether the preservation of LASF reduced the risk of incident atrial fibrillation.

2. Materials and Methods

2.1 Patients

A total of 960 patients with stage II-III hypertension were enrolled in the LIFE echocardiography sub-study. Echocardiography was performed at baseline and yearly thereafter [17-20]. In the present analysis, we have used the echocardiograms at baseline and annual clinical visits and endpoints collected during 3,712 patient-years of follow-up. The main LIFE outcome [15], as well as the complete study protocol with study design, organization, clinical measures, endpoint definitions, exclusion criteria basis for the choice of comparative agents, statistical considerations, and baseline characteristics have been previously published [15, 21-24].

For the purpose of the present analysis, cases without baseline LASF measurements or electrocardiographic validated atrial fibrillation were excluded. Compared to the ineligible patients, the present study population (n = 758) were younger (66 ±7 vs. 67 ±7 years, $p < 0.01$) at enrollment, had fewer women (42% vs. 55%, $p < 0.01$), and fewer patients with type 2 diabetes (9% vs. 13%, $p = 0.02$). The two groups did not differ in body mass index (BMI), left ventricular mass index, history of cardiovascular diseases, transitory ischemic attack, or systolic and diastolic blood pressure and treatment allocation (data not shown).

The geographic distribution, mean blood pressure, BMI, and prevalence of diabetes and vascular disease resembled those of the entire LIFE population, with the exception of enrolling more men and non-White participants [20]. Screening electrocardiograms were performed before enrollment in the study, and all the selected patients had an electrocardiogram showing LVH by either sex-adjusted Cornell voltage-duration product ≥ 2,440 mV × msec or Sokolow-Lyon voltage criteria > 38 mm [25]. Patients with known left ventricular ejection fraction < 40% and renal function measured by serum creatinine > 160 µmol/L (1.8 mg/dL) were not included. Further exclusion criteria were myocardial infarction or stroke within 6 months, congestive heart failure, or aorta stenosis with a mean gradient > 20 mmHg.

2.2 Ethics Statement

Ethical committees for all participating clinical centers approved the LIFE study. The study was performed in accordance with the Declaration of Helsinki. The protocol was written, the study was chaired by an academic steering committee, and it was overseen by an independent data and safety monitoring board. The LIFE study originally received support from Merck & Co., Inc. The data that support the findings of the present study are available from the corresponding author (RBD) upon reasonable request. The LIFE study was registered at the following URL: https://www.clinicaltrials.gov. It appears with the unique identifier NCT00338260.

2.3 Treatment Regimens

Blinded treatment was initiated and the therapy was up-titrated during the study follow-up visits at 1, 2, 4, 6 months, and semiannually thereafter. Initial treatment was 50 mg of losartan or atenolol up-titrated by adding hydrochlorothiazide 12.5 mg, followed by 100 mg losartan or atenolol aiming at a target blood pressure below 140/90 mmHg. Investigators could further increase hydrochlorothiazide to 25 mg and/or add other antihypertensive medications other than

angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and beta-blocker [25].

2.4 Echocardiographic Methods

Echocardiograms were performed at baseline and yearly thereafter in selected centers in Denmark, Finland, Great Britain, Iceland, Norway, Sweden, and the United States. Training sessions for echo investigators were organized at Ullevaal Hospital in Oslo, and further standardized examinations included two-dimension-guided M-mode echocardiograms and selected two-dimensional and Doppler recordings. The measurements were blinded using computerized review stations and sent to The New York Hospital-Cornell University Medical Center for blind interpretation by experienced technicians and physicians. A detailed description of the echocardiographic procedures for this study has been previously described [17-20].

2.5 Measurement of Left Atrial Systolic Force

Left atrial systolic force (LASF) was measured by the principle: force = mass × acceleration. Mass was defined as the product of the density of blood which is 1.06 g/cm^3, and the volume of blood (v) passing through the mitral orifice area (MOA) during atrial contraction: v = MOA × (peak A × time to peak A)/2. MOA was calculated using Doppler measured stroke volume at the aortic valve and the time velocity integral at the mitral annulus: SV = MOA × TVI (time velocity integral) ↔ MOA = SV/TVI, assuming that in the presence of a non-regurgitant mitral valve the trans-aortic ejected blood volume equals the volume passing through the mitral valve during diastole. Acceleration (a) of blood during atrial systole was measured: a = peak A/time to peak A [6, 26].

Therefore:

$$\text{LASF} = \text{Blood viscosity} \times v \times a$$

$$\text{LASF} = 1.06\ \text{g/cm}^3 \times \text{MOA} \times (\text{peak A} \times \text{time to peak A}/2) \times (\text{peak A}/\text{time to peak A})$$

$$\leftrightarrow$$

$$\text{LASF} = 0.53 \times \text{MOA} \times (\text{peak A velocity})^2$$

LASF was measured at baseline and at annual follow-up. The criteria for present LVH were left ventricle mass index > 116 g/m^2 for men and > 104 g/m^2 for women [27] and was calculated with an anatomical validated formula using echocardiographic end-diastolic left ventricular dimensions. This method correlates with necropsy findings by r = 0.90. Left atrial diameter was measured in the left ventricular end-systole in long-axis views from the trailing edge of the posterior aortic-anterior left atrial complex [28]. Aortic and mitral regurgitations were assessed by Doppler using a 4-point grading system [29, 30]. The aortic annular diameter and pulsed-wave Doppler recording of blood velocity at the annular level were used in the LIFE study according to the original publication by Ihlen et al. [31], which validated stroke volume assessment by Doppler to invasive measurements.

2.6 Study Endpoints

Incident atrial fibrillation was identified from annual in-study electrocardiograms that underwent

Minnesota coding for atrial fibrillation at the electrocardiographic Core Center in Gothenburg [25]. Treatment of patients with incident atrial fibrillation was up to the discretion of local investigators. Information regarding prevalent coronary, cerebral, or peripheral vascular disease and smoking habits were reported by patients and investigators and source-verified by monitors who did not have insight into the echo protocol.

All endpoints were analyzed using the intention to treat approach. All randomized patients with baseline LASF measurements were included in their randomized treatment group, and all available follow-ups were included from randomization until the study termination date.

2.7 Statistical Analyses

The IBM SPSS statistics software version 20.0 (SPSS Inc., Chicago, IL, USA) and SAS statistical software package version 9.2 (SAS Institute Inc., Cary, NC, USA) were used by investigators to perform data management and statistical analyses. All variables were controlled for normal distribution and log transformation was applied when needed. Results are expressed as mean ± standard deviation (SD) or frequencies expressed as percentages. Independent Student's *t*-test was used for statistical comparison of continuous variables between the excluded and the included patient group while one-way analysis of variance was used to compare the baseline data in four quartile groups. Chi-square test was used to compare categorical variables. Aortic or mitral regurgitation was dichotomized as either no, discrete, or ≥ grade 1. Aortic valvular stenosis was dichotomized as either none or as ≥ mild aortic stenosis.

Significant baseline clinical and laboratory data were assessed for the association with incident atrial fibrillation using Cox proportional hazard analysis to estimate hazards ratios (HR) and confidence interval (CI). Important conventional risk factors for incident atrial fibrillation were determined by identifying significant univariate predictors in the Cox regression analysis: age, sex, heart rate, left ventricular ejection fraction, systolic and diastolic blood pressures, left ventricular mass index, left atrial diameter, and LASF. A final model was developed using backward elimination of the identified univariate predictors (a p-value > 0.05 resulted in deletion). The final model included age, heart rate, left atrial diameter, and LASF. Differences of risk of new-onset AF between the quartiles of LASF were also assessed using a comparison of the fourth quartile to the other quartiles in Cox regression analysis. To evaluate how much new information was obtained by, including LASF as a predictor of atrial fibrillation, models, including the significant conventional risk factors with and without LASF were compared. The p-value for the likelihood ratio and c-index for the models were compared [32]. Finally, we tested these models in the integrated discrimination improvement (IDI) and net reclassification improvement (NRI). IDI and NRI are based on the difference between the two models to correctly classify the patients. In this study, we used the method to compare a model with conventional risk factors with a model, including LASF to classify the patients into risk groups. The IDI considers the change in the estimated prediction probabilities as a continuous variable, whereas the NRI considers how large a proportion of the patients is correctly classified, subtracting the proportion of incorrectly reclassified patients from the proportion of correctly reclassified patients [32]. For atrial fibrillation, we used risk category thresholds of <5%, 5 to 15%, and ≥15% as proposed for the Framingham prediction model [33]. Cumulative incidence curves were made for incident atrial fibrillation according to LASF quartiles adjusted for significant conventional factors (i.e., age, sex, left atrial size, and heart rate).

Analyses of repeated measures were performed using a general linear model applying treatment randomization as between-subject effects and LASF measurements at baseline, 12, 24, 36, and 48 months as within-subject effects. In case of a missing LASF value, the time-varying analysis used the most recent measurement before the event. Because Mauchly´s test of sphericity was violated, the Greenhouse-Geisser correction was applied to the within-subject effect. Two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1 Quartile of Patients with Lowest Left Atrial Systolic Force

The first quartile of patients with the lowest LASF consisted of more men (71%) compared to the other groups (Table 1, Table 2). They had lower heart rate, stroke volume, and BMI, and higher creatinine compared to the other quartiles. The average age was 65 years in the first quartile, which was lower than 67 years in the fourth quartile. The blood pressure and the percentage of patients with echocardiographic LVH were, on average, higher in the fourth quartile.

Table 1 Baseline data according to quartiles of left atrial systolic force (LASH).

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***p* (ANOVA)**
LASF (kdyn)	≤10.3	>10.3 and ≤14.6	>14.6 and ≤19.2	>19.2	
Sex (women)	29%	42%	48%	49%	<0.001
Race (% Black)	17%	15%	13%	10%	0.403
Age (years)	65 ±7	65 ±7	66 ±7	67 ±7	0.024
Systolic BP (mmHg)	173 ±20	170 ±21	173 ±21	179 ±22	0.001
Diastolic BP (mmHg)	95 ±11	95 ±11	94 ±12	97 ±12	0.112
Heart rate (beats/min)	63 ±11	65 ±10	68 ±10	74 ±13	<0.001
Body mass index (kg/m^2)	26.4 ±4.0	26.8 ±4.0	28.4 ±4.9	27.8 ±4.4	<0.001
Hemoglobin (mmol/L)	143 ±12	142 ±14	142 ±12	141 ±13	0.593
Creatinine (µmol/L)	94 ±23	88 ±20	89 ±23	86 ±19	0.001

Abbreviation: BP: blood pressure.

Table 2 Echocardiographic data according to quartiles of left atrial systolic force (LASF).

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***p****
LASF (kdyn)	≤10.3	>10.3 and ≤14.6	>14.6 and ≤19.2	>19.2	
LA systolic diameter (cm)	3.9 ±0.5	3.9 ±0.6	3.9 ±0.5	4.0 ±0.5	0.053
Ejection fraction (%)	60 ±8	61 ±8	61 ±9	62 ±8	0.204
LV mass index (g/m^2)	123 ±25	119 ±27	124 ±28	125 ±21	0.031
Stroke volume (mL)	69 ±16	75 ±15	83 ±16	84 ±17	<0.001
LV internal diameter in diastole (cm)	5.3 ±0.5	5.2 ±0.6	5.3 ±0.6	5.3 ±0.6	0.003
LV hypertrophy	68%	62%	70%	82%	<0.001

Aortic regurgitation†	17%	13%	13%	20%	0.686
Aortic stenosis†	11%	11%	3%	15%	0.149
Mitral regurgitation†	27%	30%	32%	30%	0.675

Abbreviation: LA = left atrial; LV = left ventricular.

*Adjusted for age, systolic blood pressure, heart rate, body mass index, creatinine, and sex.

†Indicates grade 1 or more.

3.2 Lowest Left Atrial Systolic Force and Development of Incident Atrial Fibrillation

In our study, 29 patients (8.1/1,000 patient-years of follow-up) developed incident atrial fibrillation. Twelve (41%) patients with incident atrial fibrillation had a LASF in the lowest quartile, at a baseline LASF ≤ 10.3 kdyn.

The fourth quartile showed no difference in the risk of incident atrial fibrillation compared to the second and third quartiles, but the first quartile had an increased rate of incident atrial fibrillation (HR = 1.90 [0.71-5.08], p = 0.201). However, HR was not significant before adjusting for sex, heart rate, and left atrial diameter that showed a significantly increased incident atrial fibrillation risk (HR = 6.11 [2.03-18.39], p = 0.001) (Figure 1). This increased risk of incident atrial fibrillation for patients in the first quartile is also shown in the cumulative incidence curves according to the quartiles (Figure 2). Multivariate Cox regression with backward elimination identified age, heart rate, and left atrial diameter as predictors of incident atrial fibrillation in a final model (Table 3), whereas sex, systolic and diastolic blood pressures, left ventricle ejection fraction, and left ventricle mass index were eliminated from the model.

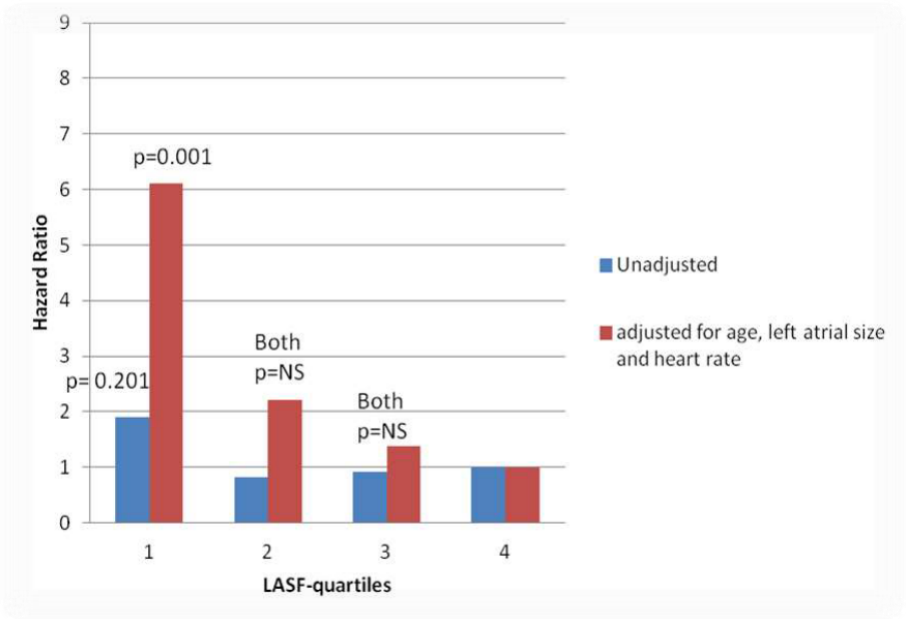

Figure 1 Hazard ratio for new-onset atrial fibrillation according to quartiles of left atrial systolic force. The quartiles are compared to the fourth quartile. First quartile ≤ 10.3 kdyn, second quartile > 10.3 and ≤ 14.6, third quartile > 14.6 and ≤ 19.2, fourth quartile >19.2.

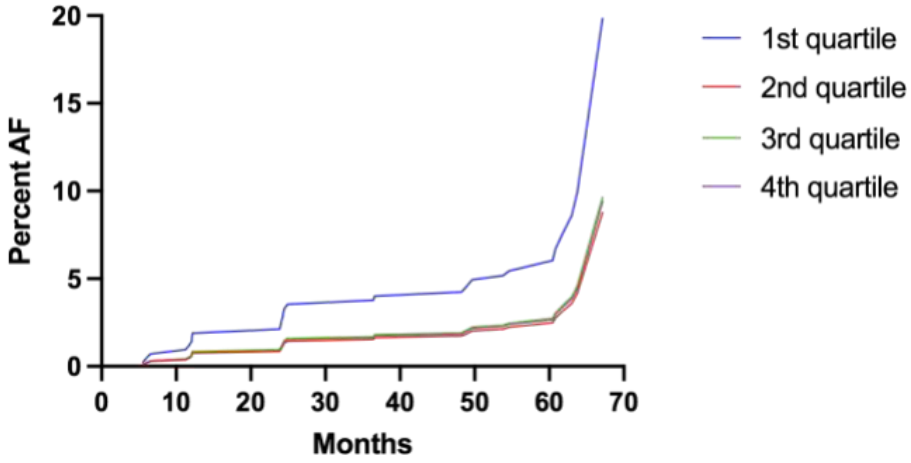

Figure 2 Adjusted cumulative incidence curves for new-onset atrial fibrillation according to the quartiles of left atrial systolic force. First quartile ≤ 10.3 kdyn, second quartile > 10.3 and ≤ 14.6, third quartile > 14.6 and ≤ 19.2, fourth quartile > 19.2. Adjusted for age, sex, heart rate, and left atrial size.

Table 3 Multivariate Cox proportional hazard with backward elimination for the prediction of incident atrial fibrillation.

Variable	HR	CI 95%	*P*
Age (years)	1.10	1.04-1.17	0.002
Heart rate (beats/min)	1.05	1.02-1.08	0.002
Left atrial systolic diameter (cm)	4.15	2.19-7.84	<0.001
Including left atrial systolic force (LASF) to multivariate Cox proportional hazard with backwards elimination:			
Age (years)	1.11	1.05-1.18	0.001
Heart rate (beats/min)	1.28	1.04-1.11	<0.001
Left atrial systolic diameter (cm)	4.66	2.47-8.79	<0.001
Left atrial systolic force (kdyn)	0.90	0.85-0.96	0.001
Model, including variable indexed by its standard deviation:			
Age (SD 7.0)	2.04	1.34-3.11	0.001
Heart rate (SD 11.6)	2.36	1.62-3.46	<0.001
Left atrial systolic diameter (SD 0.6)	2.31	1.62-3.30	<0.001
Left atrial systolic force (SD 7.4)	0.46	0.29-0.73	0.001

Abbreviations: SD: Standard deviation.

3.3 Including Left Atrial Systolic Force in Multivariate Cox Regression

By including LASF in the multivariate Cox regression, age, heart rate, and left atrial diameter were still significantly associated with incident atrial fibrillation, whereas LASF was reversely associated with incident atrial fibrillation (HR = 0.90 [0.85-0.96], p = 0.001). By calculating the incident atrial fibrillation risk using SD in multiple Cox regression, including age, heart rate, left atrial diameter, and LASF, the HR of incident atrial fibrillation for 1 SD decrease in LASF was 2.17 (HR per increase = 0.46

[0.29-0.73], $p = 0.001$).

There was a significant improvement in the integrated discrimination improvement (IDI) of 0.054 ($p = 0.004$) and a borderline significant improvement in the net reclassification improvement (NRI) of 19.2% ($p = 0.075$). The likelihood ratio was significantly larger for LASF ($p < 0.001$); however, the c-index only improved 0.003 when LASF was added to conventional factors (Table 4).

Table 4 Discrimination and risk category reclassification using left atrial systolic force.

	Log-likelihood	*c*-Statistic	IDI	NRI
Conventional risk factors	-	0.797	-	-
Conventional risk factors	10.17 (p<0.001)	0.800	0.054 (p = 0.004)	19.2% ($p = 0.075$)

Shown are measures of discrimination and reclassification for models with conventional risk factors only and models with the addition of left atrial systolic force to conventional risk factors for new-onset atrial fibrillation. Abbreviations: IDI: integrated discrimination improvement statistics, NRI: net reclassification improvement, the proportion of individuals correctly reclassified minus the proportion of individuals incorrectly reclassified.

3.4 Left Atrial Function in the Randomized Groups

Left atrial function decreased for both randomization groups during the study time. The baseline mean LASF value was 15.7 kdyn and decreased to 13.7 kdyn at the fourth year of follow-up ($p < 0.001$). The decrease in the atrial function was more pronounced in the group of patients treated with atenolol. General linear model with repeated measures showed that the mean LASF decreased by 2.6 kdyn (baseline LASF = 15.2 kdyn, fourth-year follow-up LASF = 12.6 kdyn) compared to a decrease of 1.3 kdyn in the losartan-treated patient group (baseline LASF = 16.1 kdyn, fourth-year follow-up LASF = 14.8 kdyn, $p < 0.001$) (Figure 3).

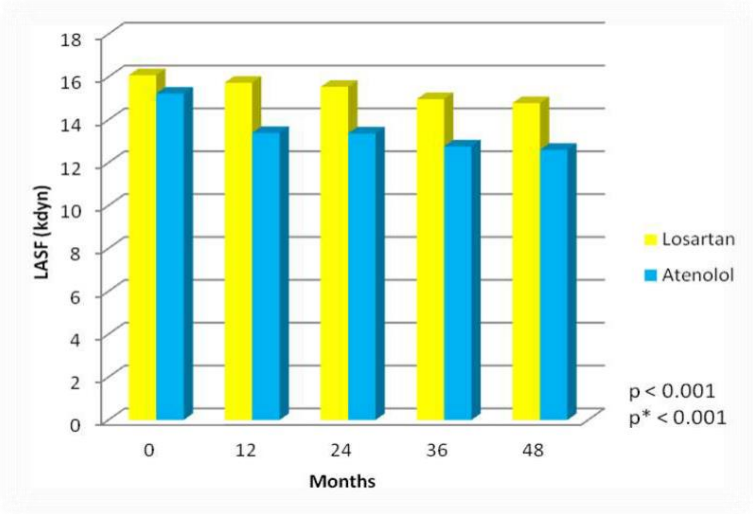

Figure 3 Development of left atrial systolic force during follow-up. Comparison between the two randomization groups using a general linear model with repeated measures. A general linear model was calculated with treatment randomization as a between-subject effect. *Adjusted for age, sex, left atrial size, and left ventricular mass index.

4. Discussion

This study has three new observations. First, the low baseline LASF was associated with an increased risk of new-onset atrial fibrillation. Second, LASF, on average, decreased over time in all patients, and third that the afterload-reducing losartan-based antihypertensive treatment preserved the left atrial function better than the heart rate-reducing atenolol-based treatment.

Decreased left atrial function in patients with atrial fibrillation has previously been associated with poor outcomes [34], but to our knowledge, our study is the first to show an association between LASF in hypertensive patients and the risk of developing atrial fibrillation. Our study showed that decreased LASF was associated with a greater risk of incident atrial fibrillation when adjusted for age, left atrial size, and left ventricular mass. Compared to the other quartiles, almost twice as many patients in the first quartile developed atrial fibrillation, with no significant differences among the other quartiles. Previous publications showed evidence that LASF increases with age in healthy people and is attributed to a compensatory mechanism to maintain cardiac output when left ventricular diastolic function is reduced [11, 12]. LASF is likewise found initially increased in patients with left ventricular dysfunction, but LASF gradually decreases over time with the progression of left ventricular dysfunction [9]. We have previously published data from the LIFE study showing an association between increased LASF and pronounced LVH following increased preload and filling pressure [35]. The present study shows that low LASF is associated with an increased risk of incident atrial fibrillation. In these high-risk patients, low LASF, therefore, is likely to indicate progressed atrial dysfunction and poor prognosis. Our results complement prior observations by Abhayaratna et al. [36], who reported an association between low left atrial reservoir function and increased risk of incident atrial fibrillation in elderly people.

4.1 Association between Age, Left Atrial Size, and Incident Atrial Fibrillation

We also found an association between age and left atrial size and the risk of incident atrial fibrillation, which complements the previously published data [37-40]. Surprisingly, the baseline data showed that patients in the first quartile having the highest risk of incident atrial fibrillation were on average younger, did not have larger left atrial dimension nor higher left ventricular mass index than patients in the other quartiles, suggesting that using only age and left atrial size could underestimate the risk of incident atrial fibrillation. Our study shows that the use of LASF as an additional predictor (in addition to age, left atrial size, and heart rate) in risk stratification of the hypertensive patients improved the accuracy of predicting incident atrial fibrillation.

Looking at the total follow-up period, the mean LASF decreased over time, which could be explained by the patient population using their atrial reserves, had increased prevalence of mitral regurgitation, as well as some increased incidence of depressed left ventricular systolic function due to clinical or silent myocardial infarction [41].

4.2 Effect of Losartan vs. Atenolol on Atrial Function

Though left atrial function, in general, decreased with time, we found a significant difference between the two treatment groups. Patients treated with losartan preserved their atrial function better than patients treated with atenolol although both treatment groups, on average, had a similar decrease in blood pressure. This suggests that left atrial function is better preserved by the

afterload-reducing properties of losartan than the heart rate-reducing properties of atenolol. The fact that losartan was better in preserving LASF is also complemented by another sub-study of LIFE, showing a relative decrease in atrial natriuretic peptide when treated with losartan compared to atenolol [42]. Altogether, these studies complement the finding from the overall LIFE study where a significantly lower incidence of atrial fibrillation appeared in patients treated with losartan-based treatment [16].

4.3 Influence of Diuretic Treatment and Low Serum Potassium on Incident Atrial Fibrillation

Up-titrating medication with hydrochlorothiazide (HCTZ) was part of the protocol to control blood pressure in the LIFE study. Following blinded study drug 50 mg investigators should add 12.5 mg HCTZ; then up-titrate blinded study drug to 100 mg before HCTZ should be up-titrate to 25 mg. This led to the same use of HCTZ in the two randomized arms [43]. Serum electrolytes were measured at all study visits, and data on serum potassium were included in the main LIFE publication [15] without any significant difference between the study arms. However, despite the use of equal doses of HCTZ and minimal changes in serum potassium, low serum potassium may be a variable involved in causing atrial fibrillation in the LIFE population. Of the patients who developed atrial fibrillation, patients on atenolol had a small but significant change in potassium [16]. Further, in the pre-specified subgroup of patients with isolated systolic hypertension [44], potassium was slightly lower in patients with atrial fibrillation (p = 0.02), and serum potassium was a significant predictor of new-onset atrial fibrillation (HR = 0.39, 95% CIs: 0.18-0.86, p = 0.019).

4.4 Limitations

Our study results should be interpreted with caution outside the study population. In our study, incident atrial fibrillation was monitored by an annual electrocardiogram. Patients with paroxysmal atrial fibrillation may not have been identified. However, most likely, data available from LIFE may be a conservative estimate of the total burden of atrial fibrillation with reduced power to see a biological signal. In our study, we only included patients without atrial fibrillation, and we excluded all patients without baseline LASF measurements. Left atrial volumes were not measured; hence data on left atrial ejection fraction, another measure of left atrial systolic function, were unavailable.

5. Conclusions

These considerations lead to the conclusion that in hypertensive patients with left ventricle hypertrophy, low LASF identifies a patient group with progressed left atrial dysfunction and with a high risk of incident atrial fibrillation. Because of the preserving effect of losartan on the function and structure of the left atrium, treating hypertensive patients with left ventricular hypertrophy with losartan might decrease their risk of incident atrial fibrillation.

Our findings suggest that low left atrial systolic force in hypertensive patients with left ventricular hypertrophy is associated with a higher risk of incident atrial fibrillation. Left atrial function diminishes in these patients, and losartan is superior to atenolol in preserving the left atrial function.

Author Contributions

Professor Richard B. Devereux, MD was responsible for the echocardiographic protocol and the echocardiographic reading center. Professor Peter M. Okin, MD was responsible for the EKG protocol. Professor Sverre E. Kjeldsen, MD, Dr. med. and Professor Stevo Julius, MD, Dr. Sci. were coordinators of the LIFE study and responsible for patient inclusions and follow-up in Scandinavia and in USA, respectively. Professor Eva Gerdts, MD, Dr. med. was responsible for coordinating the echo sub-study in Norway. Kristian Wachtell, MD, Dr. med. was international secretary of the echocardiographic sub-study. Lotte Gerholt, MD and Casper N. Bang, MD, PhD were responsible for the present data analyses and drafting the first version of Ms. Assoc. Professor Anne Cecilie Larstorp, MD, PhD was responsible for study technical issues throughout the course of the LIFE Study. All authors were responsible for reading and approving the final manuscript.

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Competing Interests

Lotte Gerholt, MD has subsequently been employed by Novo Nordisk A/S. Professor Sverre E. Kjeldsen, MD, Dr. med. has received lecture honoraria within the past 3 years from Getz Pharma, Merck Healthcare KGaA, Sanofi-Aventis and Vector-Intas. The other authors have declared that no competing interests exist.

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