Measures of left atrial function predict incident heart failure in a low-risk general population
the Copenhagen City Heart Study
Andersen, Ditte Madsen; Sengeløv, Morten; Olsen, Flemming Javier; Marott, Jacob Louis; Jensen, Gorm Boje; Schnohr, Peter; Platz, Elke; Schou, Morten; Mogelvang, Rasmus; Biering-Sørensen, Tor

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2406

Publication date:
2022

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Measures of Left Atrial Function Predicts Incident Heart Failure in a Low Risk General Population: The Copenhagen City Heart Study

Ditte Madsen Andersen, MD; Morten Sengeliøv, MD; Flemming Javier Olsen, MD; Jacob Louis Marott, MSc; Gorm Boje Jensen, MD, DMSc; Peter Schnohr, MD, DMSc; Elke Platz, MD, MS; Morten Schou, MD, PhD; Rasmus Mogelvang, MD, PhD; Tor Biering-Sørensen, MD, PhD, MPH

1) Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
2) The Copenhagen City Heart Study, Frederiksberg Hospital, University of Copenhagen, Denmark
3) Cardiovascular Division, Brigham and Women’s Hospital, Boston, USA
4) Department of Cardiology, Rigshospitalet, University of Copenhagen, Denmark
5) Institute of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
6) Cardiovascular Research Unit, Svendborg, University of Southern Denmark, Denmark.

Conflicts of interest: DMA has received consulting fees from Ambu. EK has received research grants from NIH. Her employer has received support from Novartis for consulting outside the submitted work. She has consulted for scPharmaceuticals outside the submitted work. TBS has received research grants from Sanofi Pasteur and GE healthcare, consulting fees from Amgen, Sanofi Pasteur and lecture fees from Novartis and Sanofi Pasteur.

Correspondence: Ditte Madsen Andersen, MD, Cardiovascular Non-Invasive Imaging Research Laboratory, Department of Cardiology, Herlev & Gentofte Hospital, Gentofte Hospitalsvej 8, Post 835, DK-2900 Hellerup (Denmark), Phone: +45 40375736, Fax: +45 39777381, E-mail: ditte_m_andersen@hotmail.com

Word count: 4,102
Abstract

Aims: This study investigated left atrial (LA) parameters as measured on transthoracic echocardiography as predictors of incident heart failure (HF) in a community cohort.

Methods and Results: In a large general population study (n=2221), participants underwent a health examination with echocardiography. The maximum and minimum LA volumes indexed to body surface area (LAVImax and LAVImin) were measured and the LA emptying fraction (LAEF) and LA expansion index (LAEI) were calculated.

Among 1,951 participants without atrial fibrillation or significant valve disease, the mean age was 59±16 years and 58% were women. At baseline, one percent (n=16) had a LV ejection fraction of less than 50%, 44% had hypertension, and 10% had diabetes. During follow-up (median 15.8 years, IQR: 11.3-16.2 years), 187 (10%) participants were diagnosed with incident HF. Participants who were diagnosed with HF during follow-up had a larger LAVImax and LAVImin and a lower LAEF and LAEI compared to participants without HF.

In unadjusted analysis, LAVImax, LAVImin, LAEF and LAEI were predictors of incident HF. After multivariable adjustment for clinical and echocardiographic parameters, only LAVImin, remained an independent predictors of incident HF (HR per 1 SD increase: 1.22 (1.01-1.47), p=0.038).

Conclusion: In the general population, LAVImin, is an independent predictor of incident HF. LAVImax, currently the only LA measure in a routine echocardiographic examination, was not an independent predictor of incident HF.

Keywords: Echocardiography, Left atrial function, General population, long term outcome, incident HF.
Introduction

Globally, heart failure (HF) is a major cause of cardiovascular mortality and morbidity. The prevalence of HF is approximately 1-2% in the western world and the 5-year mortality rate is as high as 35%\(^1,2\). Being able to detect subclinical signs of HF prior to development of signs of HF could indicate the need for early treatment that potentially could prevent HF.

In HF, the left ventricle (LV) cannot accommodate the cardiac output needed, or can only do so with a significant increase in the LV filling pressure\(^3\). The left atrium (LA) modulates the filling of the LV\(^4\). Changes in the anatomical structure and function of the LA might therefore precede early changes of the LV structure and function. These early changes of the LA and LV might predict future cardiac morbidity, some of which is potentially preventable. Indeed, several studies have demonstrated that LA size as measured on transthoracic echocardiography (TTE) is a strong predictor of atrial fibrillation, ischemic stroke, HF and cardiovascular death, both in the general population and in selected clinical subpopulations\(^5\textsuperscript{–}10\).

Currently, only the LA maximum volume indexed to body surface area (LAVI\(_{\text{max}}\)) is part of a routine echocardiographic examination\(^11\). As mentioned, the relationship between LA anatomical changes and cardiovascular morbidity and mortality is well described, but whether LAVI\(_{\text{max}}\) is the optimal LA parameter to describe the risk of developing cardiovascular disease, including HF, is not as well investigated.

We hypothesized that measures of LA function may reflect the relationship between the LA and LV better than the LAVI\(_{\text{max}}\), and thus be superior in predicting incident HF. Therefore, we aimed to investigate whether LAVI\(_{\text{min}}\), LAEF, and LAEI are stronger predictors of incident HF than LAVI\(_{\text{max}}\) in a low risk general population. Additionally, we aimed to investigate whether LAVI\(_{\text{min}}\), LAEF, and LAEI provided valuable prognostic information beyond an established clinical risk score for HF.
Methods

Study population: The study population consisted of the echocardiographic subpopulation of the 4th Copenhagen City Heart Study (CCHS), which is a longitudinal cohort study of cardiovascular risk factors and disease\textsuperscript{12,13} (ClinicalTrials.gov Unique Identifier: NCT02993172). The 4th CCHS ran from 2001 to 2003. It was independent of the participants’ risk factors and health status whether they were invited for an echocardiography as part of the 4\textsuperscript{th} CCHS. All examinations were performed on the same day. All participants who had an echocardiographic examination, including color tissue Doppler imaging (TDI), were included in this substudy (n=2,221)\textsuperscript{13–18}. None of the participants had significant valvular stenosis or regurgitation. Participants with prevalent HF (n=22), atrial fibrillation (n=43), and inadequate quality of the echocardiographic examination (n=205) were excluded. After exclusion, LA measures were available in a total of 1,951 participants aged 20 to 93 years. The study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee. All participants gave written informed consent.

Health Examination: All participants underwent physical examinations and answered a self-administered questionnaire. Methods for blood samples and ECG recording, and the definitions of hypertension, diabetes mellitus, and ischemic heart disease (IHD) at baseline have been described elsewhere\textsuperscript{17}.

HF at baseline was defined by previous outpatient visit or hospital admissions for HF, according to the Danish National Patient Registry, using International Classification of Diseases (ICD)-10 codes (DI500-DI509 and DJ819).

Echocardiography: Three experienced sonographers performed echocardiography, using Vivid 5 ultrasound systems (GE Healthcare, Horten, Norway) with a 2.5-MHz transducer. All
Echocardiograms were conducted as a conventional two-dimensional echocardiography and color TDI and were stored on magneto-optical disks and an external FireWire hard drive (LaCie, France). Echocardiograms were analyzed offline with commercially available software (EchoPac, GE Medical, Horten, Norway).

**Conventional echocardiography:** The LV ejection fraction (LVEF) was determined by 1 observer by an evaluation of the regional LV function as evaluated by the 16 standard segments model, as suggested by the American Society of Echocardiography [11]. LV systolic dysfunction was defined as an LVEF below 50% [15,16]. LV mass index (LVMI) was calculated as the anatomic mass divided by body surface area. LV hypertrophy (LVH) was defined as LVMI ≥ 96 g/m^2^ for women and ≥ 116 g/m^2^ for men [11]. LV dilatation was defined as an LV internal diameter at end-diastole (LVIDd) divided by height ≥ 3.3 cm/m [11]. Global mitral annular plane systolic excursion (global MAPSE) was measured by TDI in the apical 4-, 2- and 3-chamber views. A sample volume was placed at the annular site and MAPSE was then measured by tracking the tissue from the start of the systolic ejection period to the aortic valve closure. Global MAPSE was averaged from all six annular sites. Aortic valve opening and closure were measured by placing a curved M-mode through the mitral leaflet in the color TDI.

Mitral inflow velocity curves, including peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave (DT) were measured by placing a pulsed-wave Doppler sample at the top of the mitral leaflet. E/A-ratio was calculated.

In the 4-chamber view, color TDI was used to measure the septal and lateral peak early diastolic longitudinal mitral annular velocity (e’). The average e’ was calculated from the septal and lateral e’ and used to calculate E/e’.

**LA measures:** LA volume was measured using the biplane area-length method in the 2-chamber and
4-chamber apical views. If a 2-chamber apical view could not be visualized, the LA size was traced in a 3-chamber apical view. LA volume index was calculated as volume divided by body surface area (BSA). The maximum LA volume indexed to BSA (LAVI\text{max}) was traced at the end of ventricular systole, when the chamber was at its largest. Minimum LA volume indexed to BSA (LAVI\text{min}) was traced at the end of the ventricular diastole, when the chamber was at its smallest. The LA emptying fraction (LAEF) was calculated using the formula: LAEF = (LAVI\text{max}-LAVI\text{min})/LAVI\text{max}. The LA expansion index (LAEI) was calculated as LAEI = (LAVI\text{max}-LAVI\text{min})/LAVI\text{min}. A normal LA volume was defined as LAVI\text{max} < 34 mL/m\text{^2}.

All echocardiographic analyses were performed by one investigator, who was blinded to all other information.

**Follow-up and outcome:** The examinations took place between 2001 and 2003, and participants were followed until outcome data extraction in April 2018 or time of event. Follow-up was 100%. The primary endpoint was defined as time to a hospital contact due to incident HF. Follow-up data on incident HF was obtained from the Danish National Patient Registry, using ICD-10 codes (DI500-DI509 and DJ819). Follow-up data on mortality was obtained from the Danish Civil Registration System.

**Statistical analyses:** Baseline characteristics for participants were stratified according to the primary endpoint (incident HF) and compared with student t-test for continuous Gaussian distributed variables, by a Wilcoxon rank-sum test for continuous non-Gaussian distributed variables, and by Pearson’s chi-squared test for proportions and displayed in Table 1. Gaussian-distributed continuous variables are expressed as means ± the standard deviation (SD). Non-
Gaussian distributed continuous variables are expressed as medians (interquartile range). Categorical values are expressed as number (percentage).

Intraobserver and interobserver variability for LAVI_{max}, LAVI_{min}, and LAEF was examined in 19 randomly selected participants from this cohort. We calculated coefficients of variation (CVs) and bias coefficients (mean difference ± SD)\textsuperscript{20}.

Tests were performed to assess whether clinical variables like age, sex and BMI modified the association between measures of LA structure and function and incident HF.

Linear regression analyses were conducted, and standardized b-coefficients were calculated to estimate the association between the natural logarithmic value of pro b-type natriuretic peptide (log(proBNP)) and LA measures (LAVI_{max}, LAVI_{min}, LAEF and LAEI). Restricted cubic spline curves were constructed using linear regression to illustrate the association between log(proBNP) and LA measures and displayed in Figure 1. Number of knots were chosen based on the lowest Akaike Information Criterion.

Hazard ratios (HR) were calculated by Cox proportional hazards regression analyses and displayed in Tables 2 and 3. Harrell’s C-statistic was obtained from univariable Cox proportional hazards regression models in order to test the prognostic performance of LA volumes for predicting the endpoint. Missing variables were not imputed. LVEF was included in the multivariable Cox regression models as a dichotomous variable, with the cut-off for normality of LVEF\geq 50\%. In sensitivity analyses, Cox regression models with participants with LVEF \geq 50\% and LAVI_{max}< 34 mL/m\textsuperscript{2}, were performed. ProBNP was transformed using the natural logarithmic value before being included in the multivariable Cox regression models. The assumptions of proportional hazards in the models were tested based on the Schoenfeld residuals.
Restricted cubic spline curves were constructed using a Poisson model to estimate incidence rates and number of knots were chosen based on the Akaike Information Criterion and displayed in Figure 2.

The cumulative incidence function stratified according to tertiles of the explanatory variable were computed, calculating the absolute risk of HF by time from baseline, with death as a competing risk, and displayed in Figure 3.

The Framingham “Probability of Congestive Heart Failure Within 4 Years for Men Aged 45 to 94 Years”-score and the “Probability of Congestive Heart Failure Within 4 Years for Women Aged 45 to 94 Years”-score were calculated for men and women, respectively21, with a higher score indicating a higher probability for HF. The score includes age, systolic blood pressure, heart rate, LVH on electrocardiogram, and presence of coronary heart disease, valve disease and diabetes mellitus. For women, it also includes the body mass index (BMI)21. If participants were below the age of 45 years, they were considered to be the same age as a 45-year-old which constituted 0 points. LVH on electrocardiogram was obtained from Minnesota codes 3.1 and 3.3. LAVI\textsubscript{max}, LAVI\textsubscript{min}, LAEF and LAEI was added to the Framingham HF probability score and the net reclassification index (NRI) was calculated by a statistical package in STATA\textsuperscript{22} to see whether the parameters added prognostic value to the score. The NRI is displayed in Figure 4.

A p-value ≤ 0.05 in 2-sided test was considered statistically significant.

All analyses were performed with STATA Statistics/Data analysis for Mac, SE 14.0 (StataCorp, Texas, USA).
Results

Among 1,951 participants, the mean age was 59 ± 16 years and 58% were women. One percent (n=16) had a LVEF of less than 50% at baseline, 44% had hypertension, and 10% had diabetes mellitus.

Median follow-up time was 15.8 years (IQR: 11.3-16.2 years). During follow-up, 187 (10%) participants were diagnosed with incident HF.

Table 1 shows the baseline characteristics of the study population stratified according to whether they experienced an incident HF event during follow-up or not.

Participants who developed HF were older, a higher proportion were men, and they had higher BMI. Likewise, participants who developed HF had higher systolic blood pressure, higher heart rate, higher proBNP, lower estimated glomerular filtration rate (eGFR) and a higher proportion had hypertension, diabetes mellitus, previous hospital visits for chronic obstructive pulmonary disease (COPD), and ischemic heart disease (IHD). Regarding the echocardiographic parameters, patients suffering from a HF event during follow-up had lower LVEF, higher LVMI, lower global MAPSE, higher A wave, lower E wave, lower E/A ratio, lower e´, higher E/e´, longer DT, larger LAVImax and LAVImin, lower LAEF and LAEI (Table 1).

In intraobserver analysis, LAVImax and LAVImin both had a CV = 10.7%. LAEF had the lowest intraobserver variability (CV = 9.0%). In interobserver analysis, we found that LAVImax had a lower variability (CV = 24.6%) than LAVImin (CV = 29.3%), with LAEF showing the lowest variability (CV = 19.9%). The bias coefficients were: LAVImax intraobserver: −1.85 ± 4.01 ml/m²; LAVImax interobserver: 1.41 ± 8.79 ml/m²; LAVImin intraobserver: 0.26 ± 1.89 ml/m²; LAVImin interobserver: 0.76 ± 5.12 ml/m²; LAEF intraobserver: −3.25 ± 4.75%; LAEF interobserver: 0.25 ± 10.16%²⁰.
Age and sex did not modify the association between LA measures and HF. BMI significantly modified the association between LAVI\textsubscript{max} and HF (p=0.007) as well as LAVI\textsubscript{min} and HF (p=0.002) but not the association between LAEF and HF (p=0.13) or LAEI and HF (p=0.13). BMI was divided into a low BMI below 25 and a high BMI equal to or above 25 (p-value for interaction 0.003 and 0.006 for LAVI\textsubscript{max} and LAVI\textsubscript{min}, respectively). For LAVI\textsubscript{max} and LAVI\textsubscript{min} the risk for developing HF was significantly higher for a low BMI than a high BMI in univariable Cox regression analyses (LAVI\textsubscript{max}: HR 1.10, 95% CI 1.06-1.14, p<0.001 vs. HR 1.03, 95% CI 1.01-1.06, p=0.011, for low and high BMI, respectively; LAVI\textsubscript{min}: HR 1.18, 95% CI 1.13-1.23, p<0.001 vs. HR 1.10, 95% CI 1.06-1.14, p<0.001, for low and high BMI, respectively).

Figure 1 illustrates the associations between log(proBNP) and LAVI\textsubscript{max}, LAVI\textsubscript{min}, LAEF and LAEI. The association between log(proBNP) and LA parameters was strongest for LAVI\textsubscript{min} but significant for all LA parameters (p<0.001). Increasing proBNP was associated with increasing LAVI\textsubscript{max} and LAVI\textsubscript{min} and decreasing LAEF and LAEI.

**Left atrial function as a predictor of incident heart failure in the general population**

In unadjusted Cox regression analysis, LAVI\textsubscript{max}, LAVI\textsubscript{min}, LAEF and LAEI were all predictors of incident HF (Table 2). After multivariable adjustment for age and sex (Table 2, model 1) and age, sex, BMI, eGFR, heart rate, systolic and diastolic blood pressure, cholesterol, log(proBNP), hypertension, diabetes mellitus, smoking status, ischemic heart disease, COPD, ischemic stroke, (Table 2, model 2), all four measures remained independent predictors of incident HF.

After multivariable adjustment for the aforementioned clinical parameters as well as echocardiographic parameters (LVEF<50%, global MAPSE, LVMI, E/e’, DT, and E/A ratio), only LAVI\textsubscript{min}, remained an independent predictor of incident HF (Table 2, model 3).
In sensitivity analysis, we restricted the population to only include participants with a normal LVEF, defined as LVEF $\geq 50\%$ and a normal LA volume, defined as LAVI max $< 34 \text{ mL/m}^2$. Sixteen participants had a LVEF under 50%, 52 participants had a LAVI max above or equal to 34 mL/m2, one person had both low LVEF and a dilated LA, leaving 1884 participants for this analysis. Similar results were found as for the overall population, with the exception that LAVI max was not a significant predictor of HF in any of the adjusted models (Table 3, Supplementals). The continuous associations between LA measures and risk of HF are shown in Figure 2. For LAVI max, only an increase in LA size beyond 20mL/m2 was associated with an increased risk of HF, whereas any increase in LAVI min posed an increased risk of HF. Decreasing LAEF and LAEI were also associated with a higher risk of HF. The highest incidence rates (IR) for incident HF for LA measures were found in the highest tertile of LAVI min (IR 13.1 per 1000 person years), the lowest tertile of LAEF (IR 11.8 per 1000 person years), the lowest tertile of LAEI (IR 11.8 per 1000 person years) and the highest tertile of LAVI max (IR 10.6 per 1000 person years), $p<0.001$ for all comparisons between highest and lowest tertile of each LA measure. The cumulative incidence of HF by these tertiles, while accounting for death as a competing event (n=522), are shown in Figure 3.

When adding LAVI min, LAEF and LAEI to the Framingham score “Probability of Congestive Heart Failure Within 4 Years for Men Aged 45 to 94 Years” and “Probability of Congestive Heart Failure Within 4 Years for Women Aged 45 to 94 Years”21 for men and women, respectively, the net reclassification index (NRI) was significantly improved by 0.10 for LAVI min ($p=0.023$), 0.13 for LAEF ($p=0.002$) and 0.092 for LAEI ($p=0.030$). When LAVI max and LAVI min was added together to the Framingham score, the NRI was improved by 0.11 ($p=0.011$). The NRI was not significantly improved by LAVI max ($p=0.18$), (Figure 4).
Discussion

In this large prospective study of participants from the general population (n=1,951) undergoing transthoracic echocardiography, including an assessment of LA size and function, we found that the LAVImin, and measures of left atrial function, LAEF and LAEI, were independent predictors of incident HF after adjustment for clinical parameters. Only LAVImin continued to be a predictor of incident HF after adjustment for clinical and echocardiographic parameters. When restricting the analysis to only include individuals with a normal conventional echocardiography (normal LVEF and LAVImax), LAVImin, LAEF and LAEI were all independent predictors of incident HF.

LAVImax, although currently the only LA parameter included in a standard echocardiographic examination\(^\text{11}\), was not an independent predictor after adjustment for clinical and echocardiographic parameters. Additionally, LAVImin, LAEF and LAEI provided incremental prognostic information to an established risk score used to predict incident HF in the general population, as indicated by significant increases in the NRI.

BMI significantly modified the association between LAVImax, LAVImin and HF. The risk for developing HF was significantly higher for a low BMI than a high BMI for both LAVImax and LAVImin. Previous studies have shown that the indexed LA size was overcorrected by the BSA in obese patients, why an allometric correction could be considered instead\(^\text{23}\).

Our hypothesis was that LAVImin, LAEF and LAEI reflect the relationship between the LA and LV better than LAVImax. In diastole, when the mitral valve is open, the LA is directly exposed to the LV. According to the Frank-Starling law, if the LV end-diastolic pressure (LVEDP) is continuously increased, secondary changes in the LA will develop\(^\text{24}\). In a general population, hypertension and other cardiac risk factors such as ischemic heart disease (IHD), diabetes mellitus, atrial fibrillation, obesity, and dyslipidemia, contribute to an increasingly stiffness in the LV which increases LVEDP and thus display changes in the LA, firstly seen as an increased LAVImin.\(^\text{25}\)
While the LAVImin is directly affected by the LVEDP, the LAVImax is affected by LV systolic function and mean LA pressure. Since the mean LA pressure increases later than the LVEDP, changes in LAVImax is seen later than changes in LAVImin\textsuperscript{26}.

ProBNP is released from the heart in response to cardiac wall stress when the myocytes stretch\textsuperscript{27}. In our study we found that proBNP was more closely associated with LAVImin than LAVImax, indicating that LAVImin might reflect the endocrine function of the LA more closely than LAVImax.

These factors may explain the superior prognostic abilities of LAVImin in this study compared to LAVImax.

Recent studies have proposed how intrinsic factors in the LA, such as atrial remodeling, can contribute to the development of HF. Atrial remodeling include chamber enlargement, fibrosis, and arrhythmias (as a sign of electrical remodeling). Especially the development of atrial fibrosis results in LA stiffness\textsuperscript{28,29}. LA stiffness was associated with low LAEF in a study examining patients with HF with right heart catheterization. Low LAEF due to LA stiffness was associated with pulmonary vascular disease and right sided HF\textsuperscript{30}, that might present with symptoms such as dyspnea and peripheral edema. This could explain how LA dysfunction in itself could result in symptoms of HF.

LAEI was not reported in the previous study, but as LA stiffness was associated with a decrease in LA diastolic function (during LV systole)\textsuperscript{30}, and LAEI displays the reservoir function, which is part of LA diastole\textsuperscript{4}, one could speculate that LA stiffness and LAEI were associated with each other.

These factors may contribute to the explanation of the prognostic capabilities of LAEF and LAEI. As LAEF and LAEI can be derived mathematically from each other, it is questionable whether one is superior to the other, and as this study suggests, it seems more important to consider LAVImin than LAEF and LAEI.
To our knowledge, this is the largest study in a general population examining whether LA functional measures, as measured by TTE, are predictors of incident HF. Our results are in accordance with other echocardiographic studies: A community-based study (n=740) found that LAEF was an independent predictor of a composite outcome, consisting of cardiovascular death, hospitalization for ischemic heart disease, HF, or stroke. LAVImin was a predictor of the composite outcome in an adjusted model with clinical parameters, but not when echocardiographic parameters were added. LAVImax was not a predictor of the outcome in any of the adjusted models. The study had a shorter follow-up time than ours (median 4.9 years)\(^{31}\). In a population with stable IHD (n=938) followed for a mean 7 years, 147 participants were hospitalized due to HF. For a composite endpoint consisting of hospitalizations in a mean follow-up time of 7.3 years, it was shown that LAVImin was a better predictor of HF hospitalizations cardiovascular outcomes than LAVImax. Also, a composite endpoint of HF hospitalizations, MI, stroke, and heart disease death and an all-cause mortality endpoint was studied. LAVImin was a better predictor of all three endpoints than LAVImax\(^{32}\). A study consisting of a population with underlying heart disease (n=439), showed a significant better prediction for LAVImin than LAVImax of a composite outcome consisting of cardiac death, myocardial infarction, stroke, and admission due to HF, both for 2-dimensional and 3-dimensional echocardiography\(^{33}\). A MESA substudy of LA sizes and function measured by magnetic resonance imaging (MRI), also revealed that LAVImin and LAEF were better predictors of incident HF than LAVImax\(^{34}\).

Previous studies have shown that LAVImax is a predictor of incident HF\(^{6,8-10}\). In this study, we did not find LAVImax to be a predictor of incident HF after adjusting for multiple clinical and echocardiographic parameters. Our study compared to previous studies\(^{6,9,10}\) is larger in size, has more events, has longer follow up time, and accounted for more confounding factors, including clinical, biochemical and echocardiographic parameters. A large general population study (n=851)
with 255 cases of incident HF in people above 65 years, found that LAVI\textsubscript{max} was a predictor of incident HF, but it did not investigate LAVI\textsubscript{min}. Also, the study had a shorter follow up time (3-4 years)\textsuperscript{8}.

In an aging population with increasing numbers of incident HF\textsuperscript{2}, it is important to be able to detect early signs of HF before structural and functional changes in the heart turn into fulminant disease. Being able to detect early signs of HF could implement new study designs for preventive treatment strategies and stratify the prognosis. TTE is an inexpensive, noninvasive, and non-ionizing procedure and can be used among other imaging modalities to measure LA size and function. Based on our findings, we suggest that LAVI\textsubscript{min} should be included alongside LAVI\textsubscript{max} in routine echocardiographic examinations. Newer echocardiographic fully automated software automatically quantifies LAVI\textsubscript{min} and LAVI\textsubscript{max} and is expected to limit time spent on measuring size and function and improve the reproducibility of the measurements\textsuperscript{35}. Another LA parameter of interest, is LA strain that represents a more novel technique that can directly assess LA reservoir function and has also shown a potential for predicting cardiovascular outcomes in the general population\textsuperscript{36}. Future studies should aim at comparing volumetric measures of LA structure and function with LA strain to determine whether LA strain adds clinical information beyond volumetric measures of LA structure and function for the prediction of HF, similar to what has recently been reported for AF\textsuperscript{37}.

**Strengths and limitations**

The large number of participants from a community cohort, and the long follow-up with the resulting high number of incident HF events makes the results found in the present study strong. Due to the prospective design, we were able to collect data on important confounders. Limitations include that LVEF and LA size were not measured by the Simpson biplane method. As for LA size, the area-length method overestimates the LA volume compared to the Simpson biplane
method\textsuperscript{38}, however, this method was used to obtain both LAVI_{max} and LAVI_{min}, and would therefore not affect the associations found with incident HF.

As the echocardiograms and analyses were done before GLS was widely used, the images were not optimized for strain analysis by speckle tracking. We were not able to estimate GLS for 39% (n=752) of the participants and because of that, we did not have enough HF events to include GLS in the Cox regression model with echocardiographic data. Instead, we included global MAPSE, which like GLS is a measure of the longitudinal LV function.

The information about HF was obtained from Danish nationwide registries and registered as ICD10-codes. The diagnosis has previously been validated with a positive predictive value of 100% (95% CI 92.9-100), nevertheless using ICD-10 codes are obviously not as precise as adjudicated events\textsuperscript{39}. The HF diagnosis is not specified as either HF with reduced ejection fraction or HF with preserved ejection fraction.

In sensitivity analysis, the Cox regression model 2 and 3 is on the brink of being overfitted which should be taken into account when interpreted. This can be accepted though, as the focus is not on building prediction models but controlling for confounders\textsuperscript{40}.

**Conclusion**

The minimum LA volume (LAVI_{min}) is an independent predictor of incident heart failure in a general population. The maximum LA volume, currently the only LA measurement included in a standard clinical echocardiographic report, was not an independent predictor after adjustment for clinical and echocardiographic parameters. LAVI_{min}, LAEF and LAEI provided incremental prognostic information to an established risk score for prediction of incident HF in the general population.
Funding Sources

This work was supported by Herlev & Gentofte Hospital’s internal funds (grant received by DMA). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Acknowledgements

The authors would like to sincerely thank our late Professor Jan Skov Jensen, MD, PhD, DMSc for his immense contribution to The Copenhagen City Heart Study.

Conflicts of interest

DMA has received consulting fees from Ambu. TBS has received research grants from Sanofi Pasteur and GE healthcare, consulting fees from Amgen, Sanofi Pasteur and lecture fees from Novartis and Sanofi Pasteur.

References

**Figure legends**

Figure 1: Title: The association between log(proBNP) and LA measures.

Caption: Displaying the association (solid line) between log(proBNP) (natural logarithmic value of pro b-type natriuretic peptide) and left atrial measures (left atrial maximum volume indexed to body surface area, left atrial minimum volume indexed to body surface area, left atrial emptying fraction, and left atrial expansion index) with 95% confidence intervals (dotted lines).

Abbreviations: LAVI_{max} = left atrial maximum volume, LAVI_{min} = left atrial minimum volume, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index. Log(proBNP) = natural logarithmic value of pro b-type natriuretic peptide. β = Standardized β-coefficients from linear regression. Shown with p-value.

Figure 2. Title: Incidence rate of heart failure per 1,000 person years according to LA measures.

Histogram: The distribution of LA measures in the population.

Caption: A) Displaying the unadjusted incidence rate of incident heart failure (solid line) per 1000 person years for the population with 95% confidence intervals (dotted lines), according to left atrial measures (left atrial maximum volume indexed to body surface area, left atrial minimum volume indexed to body surface area, left atrial emptying fraction, and left atrial expansion index). B) Histogram displaying the distribution of left atrial measures in the population.

Abbreviations: LAVI_{max} = left atrial maximum volume, LAVI_{min} = left atrial minimum volume, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index.

Figure 3. Title: Cumulative incidence of heart failure according to tertiles of LA measures with death as a competing risk.
Caption: Displaying the absolute risk of heart failure with 95% confidence intervals according to tertiles of left atrial measures (left atrial maximum volume indexed to body surface area, left atrial minimum volume indexed to body surface area, left atrial emptying fraction, and left atrial expansion index) by time from baseline, with death as a competing risk.

Abbreviations: LAVI_{max} = left atrial maximum volume, LAVI_{min} = left atrial minimum volume, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index.

Figure 4: Title: Addition of LA measures to the Framingham heart failure probability score: Improvement of the net reclassification index. Caption: Displaying the improvement in the net reclassification index in percentages after adding left atrial measures (left atrial maximum volume indexed to body surface area, left atrial minimum volume indexed to body surface area, left atrial emptying fraction, and left atrial expansion index) to the "Probability of Congestive Heart Failure Within 4 Years for Men Aged 45 to 94 Years" and "Probability of Congestive Heart Failure Within 4 Years for Women Aged 45 to 94 Years" for men and women, respectively. Abbreviations: LAVI_{max} = left atrial maximum volume, LAVI_{min} = left atrial minimum volume, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index.
Standardized $\beta$-coefficient = 0.18
$p<0.001$

Standardized $\beta$-coefficient = 0.25
$p<0.001$

Standardized $\beta$-coefficient = -0.16
$p<0.001$

Standardized $\beta$-coefficient = -0.14
$p<0.001$
Net reclassification index improvement

- Framingham + LAVI_{max}: p = 0.18
- Framingham + LAVI_{min}: p = 0.023
- Framingham + LAVI_{max} + LAVI_{min}: p = 0.011
- Framingham + LAEF: p = 0.002
- Framingham + LAEI: p = 0.030
Left atrial function predicts incident heart failure in a general population

Incidences rate of heart failure per 1,000 person years according to left atrial measures.

Histogram: The distribution of left atrial measures in the population.

LAVI\(_{\text{max}}\) = left atrial maximum volume, indexed to body surface area, LAVI\(_{\text{min}}\) = left atrial minimum volume, indexed to body surface area, LAEF = left atrial emptying fraction, LAEI: left atrial expansion index
Permission note

For submission in the European Journal of Heart Failure regarding the article
‘‘Measures of Left Atrial Function Predicts Incident Heart Failure in a Low Risk General Population”.

All submitted material (manuscript, tables and figures) are original to this submission.

On behalf of the authors

[Signature]

Ditte Madsen Andersen (principal author)
Table 1 – Baseline characteristics stratified according to incident heart failure

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All participants</th>
<th>Participants without HF</th>
<th>Participants with HF at follow up*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59 ± 16</td>
<td>58 ± 16</td>
<td>69 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1125 (58%)</td>
<td>1036 (59%)</td>
<td>90 (48%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>All participants</th>
<th>Participants without HF</th>
<th>Participants with HF at follow up*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5 ± 3.9</td>
<td>25.4 ± 3.9</td>
<td>27.0 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>136 ± 23</td>
<td>135 ± 23</td>
<td>145 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78 ± 12</td>
<td>78 ± 12</td>
<td>79 ± 13</td>
<td>0.27</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>67 ± 11</td>
<td>67 ± 11</td>
<td>69 ± 12</td>
<td>0.022</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>838 (44%)</td>
<td>719 (41%)</td>
<td>119 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>189 (10%)</td>
<td>154 (9%)</td>
<td>35 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>40 (2%)</td>
<td>30 (2%)</td>
<td>10 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>109 (6%)</td>
<td>78 (4%)</td>
<td>31 (17%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic stroke, n (%)</td>
<td>30 (2%)</td>
<td>25 (1%)</td>
<td>5 (3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous smoker</td>
<td>Current smoker</td>
<td>Never smoker</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>643 (34%)</td>
<td>570 (33%)</td>
<td>73 (40%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Current smoker</td>
<td>651 (34%)</td>
<td>592 (34%)</td>
<td>59 (32%)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>616 (32%)</td>
<td>567 (33%)</td>
<td>49 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

**Laboratory results**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>77 ± 17</td>
<td>77 ± 17</td>
<td>74 ± 18</td>
<td>0.021</td>
</tr>
<tr>
<td>Plasma ProBNP, pmol/L</td>
<td>17 (8-30)</td>
<td>16 (7-29)</td>
<td>25 (11-45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Plasma Cholesterol, mmol/L</td>
<td>5.6 ± 1.2</td>
<td>5.6 ± 1.2</td>
<td>5.5 ± 1.2</td>
<td>0.66</td>
</tr>
</tbody>
</table>

**Echocardiographic parameters**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; under 50%, n (%)</td>
<td>16 (1%)</td>
<td>7 (0.4%)</td>
<td>9 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>86 ± 22</td>
<td>85 ± 21</td>
<td>101 ± 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV hypertrophy, n (%)</td>
<td>277 (17%)</td>
<td>225 (15%)</td>
<td>52 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV dilatation, n (%)</td>
<td>91 (5%)</td>
<td>68 (4%)</td>
<td>23 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global MAPSE, mm</td>
<td>10.6 ± 2.2</td>
<td>10.7 ± 2.2</td>
<td>9.5 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E wave, cm/s</td>
<td>7.1 ± 1.6</td>
<td>7.1 ± 1.6</td>
<td>6.7 ± 1.8</td>
<td>0.004</td>
</tr>
<tr>
<td>A wave, cm/s</td>
<td>6.9 ± 1.8</td>
<td>6.9 ± 1.8</td>
<td>7.6 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>1.0 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DT, ms</td>
<td>167 ± 41</td>
<td>166 ± 40</td>
<td>181 ± 49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>e', cm/s</td>
<td>7 ± 3</td>
<td>7 ± 3</td>
<td>5 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>10 (8-13)</td>
<td>10 (8-12)</td>
<td>13 (10-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>LAVImax, mL/m²</td>
<td>19 ± 6</td>
<td>19 ± 6</td>
<td>21 ± 8</td>
<td></td>
</tr>
<tr>
<td>LAVImin, mL/m²</td>
<td>9 ± 4</td>
<td>9 ± 4</td>
<td>12 ± 6</td>
<td></td>
</tr>
<tr>
<td>LAEF, %</td>
<td>51 ± 13</td>
<td>51 ± 13</td>
<td>46 ± 14</td>
<td></td>
</tr>
<tr>
<td>LAEI</td>
<td>1.1 (0.7-1.5)</td>
<td>1.1 (0.8-1.5)</td>
<td>0.9 (0.6-1.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Participants that developed incident heart failure during follow-up.

Values are n, mean ± SD, or median (interquartile range).

COPD = previous hospital visits for chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, Pro-BNP = pro b-type natriuretic peptide, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, LV = left ventricular, Global MAPSE = global mitral annular plane systolic excursion, DT = deceleration time, LAVImax = left atrial maximum volume indexed to body surface area, LAVImin = left atrial minimum volume indexed to body surface area, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index
### Table 2 – Left atrial measures as predictors of incident heart failure in the general population

<table>
<thead>
<tr>
<th></th>
<th>LAVI&lt;sub&gt;max&lt;/sub&gt;</th>
<th>LAVI&lt;sub&gt;min&lt;/sub&gt;</th>
<th>LAEF</th>
<th>LAEI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td></td>
<td>per 1 SD increase</td>
<td>per 1 SD increase</td>
<td>per 5% decrease</td>
<td>per 10% decrease</td>
</tr>
<tr>
<td></td>
<td>(with 95% CI)</td>
<td>(with 95% CI)</td>
<td>(with 95% CI)</td>
<td>(with 95% CI)</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1951)</td>
<td>1.48 (1.30-1.68)</td>
<td>1.70 (1.54-1.89)</td>
<td>1.17 (1.11-1.23)</td>
<td>1.09 (1.05-1.12)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C-stat 0.60</td>
<td>C-stat 0.66</td>
<td>C-stat 0.63</td>
<td>C-stat 0.63</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1928)</td>
<td>1.25 (1.10-1.42)</td>
<td>1.37 (1.22-1.53)</td>
<td>1.09 (1.04-1.15)</td>
<td>1.05 (1.02-1.08)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>C-stat 0.66</td>
<td>C-stat 0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1821)</td>
<td>1.25 (1.09-1.43)</td>
<td>1.36 (1.20-1.55)</td>
<td>1.08 (1.02-1.14)</td>
<td>1.05 (1.01-1.08)</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1390)</td>
<td>1.12 (0.92-1.35)</td>
<td>1.22 (1.01-1.47)</td>
<td>1.07 (1.00-1.15)</td>
<td>1.04 (1.00-1.08)</td>
</tr>
<tr>
<td></td>
<td>0.27</td>
<td>0.038</td>
<td>0.063</td>
<td>0.071</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age and sex.
Model 2: Adjusted for model 1, body mass index, estimated glomerular filtration rate, heart rate, systolic and diastolic blood pressure, cholesterol, log(proBNP), baseline hypertension, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, ischemic stroke and smoking status
Model 3: Adjusted for model 2, LVEF<50%, global MAPSE, LVMI, E/e', DT and E/A ratio.
SD = standard deviation, LAVI_{max} = left atrial maximum volume, LAVI_{min} = left atrial minimum volume, LAEF = left atrial emptying fraction, LAEI = left atrial expansion index. Log(proBNP) = natural logarithmic value of pro b-type natriuretic peptide, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, DT = deceleration time