ORIGINAL RESEARCH

Cardiac Biomarkers and Left Ventricular Hypertrophy in Relation to Outcomes in Patients With Atrial Fibrillation: Experiences From the RE-LY Trial

Ziad Hijazi, MD, PhD; Paolo Verdecchia, MD; Jonas Oldgren, MD, PhD; Ulrika Andersson, MSc; Gianpaolo Reboldi, MD, PhD; Giuseppe Di Pasquale, MD; Giovanni Mazzotta, MD; Fabio Angeli, MD; John W. Eikelboom, MD, PhD; Michael D. Ezekowitz, MD; Stuart J. Connolly, MD; Salim Yusuf, MD, PhD; Lars Wallentin, MD, PhD

***Background*—**Cardiac biomarkers and left ventricular hypertrophy (LVH) are related to the risk of stroke and death in patients with atrial fibrillation. We investigated the interrelationship between LVH and cardiac biomarkers and their independent associations with outcomes.

***Methods and Results*—**Plasma samples were obtained at baseline in 5275 patients with atrial fibrillation in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. NT-proBNP (N-terminal pro-B-type natriuretic peptide), cardiac troponin I and T, and growth differentiation factor-15 were determined using high-sensitivity (hs) assays. LVH was defined by ECG. Cox models were adjusted for baseline characteristics, LVH, and biomarkers. LVH was present in 1257 patients. During a median follow-up of 2.0 years, 165 patients developed a stroke and 370 died. LVH was significantly (P<0.0001) associated with higher levels of all biomarkers in linear regression analyses adjusting for baseline characteristics. Geometric mean ratios (95% CIs) were as follows: NT-proBNP, 1.32 (1.25–1.38); hs cardiac troponin I, 1.67 (1.57–1.78); hs troponin T, 1.38 (1.32–1.44); and growth differentiation factor-15, 1.09 (1.05–1.12). For stroke, the hazard ratios (95% CIs) per 50% increase were as follows: NT-proBNP, 1.09 (1.00–1.19); hs cardiac troponin I, 1.09 (1.03–1.15); hs troponin T, 1.14 (1.06–1.24); and growth differentiation factor-15, 1.22 (1.08–1.38) (all P<0.05). For death, hazard ratios (95% CIs) were as follows: NT-proBNP, 1.24 (1.17–1.31); hs cardiac troponin I, 1.13 (1.10–1.17); hs troponin T, 1.28 (1.23–1.34); and growth differentiation factor-15, 1.31 (1.22–1.42) (all P<0.0001). LVH was not significantly associated with stroke or death after adjustment for biomarkers.

***Conclusions*—**Cardiac biomarkers are significantly associated with LVH. The prognostic value of biomarkers for stroke and death is not affected by LVH. The prognostic information of LVH is attenuated in the presence of cardiac biomarkers.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00262600. **(*J Am Heart Assoc*. 2019;8: e010107. DOI: 10.1161/JAHA.118.010107.)**

Key Words: atrial fibrillation • biomarker • left ventricular hypertrophy • risk prediction

Atrial fibrillation (AF), the most common sustained arrhythmia, substantially increases the risk of stroke and mortality.[1,2] Left ventricular hypertrophy (LVH) is a recognized risk factor for cardiovascular disease and mortality.[3] Recently, LVH diagnosed by ECG was also confirmed to be a predictor in patients with AF for risk of stroke and death.[4] Similarly, cardiac biomarkers are well-known predictors of cardiovascular risk and their independent association with stroke and mortality outcomes in AF has consistently been demonstrated.[5–9] Several factors influence the concentrations of cardiac biomarkers, including the presence of LVH.[10–13] To date, there are limited data on

From the Department of Medical Sciences, Cardiology (Z.H., J.O., L.W.), and Uppsala Clinical Research Center (Z.H., J.O., U.A., L.W.), Uppsala University, Uppsala, Sweden; Department of Medicine, Hospital of Assisi, Italy (P.V., G.M.); Department of Medicine (G.R.) and Cardiology and Cardiovascular Pathophysiology (F.A.), University of Perugia, Perugia, Italy; Department of Cardiology, Maggiore Hospital, Bologna, Italy (G.D.P.); Thomas Jefferson Medical College and the Heart Center, Wynnewood, PA (M.D.E.); and Population Health Research Institute, Hamilton, Ontario, Canada (S.J.C., S.Y.).

Accompanying Figure S1 and Tables S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010107

Correspondence to: Ziad Hijazi, MD, PhD, Uppsala Clinical Research Center, Dag Hammarskjölds Väg 38, SE-751 85 Uppsala, Sweden. E-mail: ziad.hijazi@ucr.uu.se

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Clinical Perspective

What Is New?

- The prognostic value of cardiovascular biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide], growth differentiation factor-15, and troponin) for stroke, death, and major bleeding is not affected by left ventricular hypertrophy in patients with atrial fibrillation.

What Are the Clinical Implications?

- Cardiac biomarkers are able to further identify patients with lower or higher risk both in the presence and in the absence of left ventricular hypertrophy by ECG.

the association of cardiac biomarkers with LVH in patients with AF, neither on the combination of these 2 indicators, to further increase the understanding of and improve the risk stratification in AF.

In the present RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)[14] trial, we investigated the relationship between cardiovascular biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide], high-sensitivity cardiac troponin I [hs-cTnI] and T [hs-cTnT], and growth differentiation factor-15 [GDF-15]) and LVH diagnosed by ECG and their individual independent associations with outcomes in 5275 anticoagulated patients with AF using baseline plasma samples.

Methods

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population and Trial Design

The study organization, trial design, patient characteristics, and outcomes of the RE-LY trial have been published previously.[14,15] Patients were recruited from 967 centers in 44 countries between November 2005 and December 2007. A total of 18 113 patients with AF, with at least 1 additional risk factor for stroke, were randomized in a 1:1:1 manner to receive either fixed doses of dabigatran (110 or 150 mg twice daily) in a blinded manner or adjusted-dose warfarin (target international normalized ratio, 2.0–3.0) in an unblinded manner for a median of 2 years.[15] All patients were centrally randomized through an interactive voice response system located at the Coordinating Centre at Population Health Research Institute (Hamilton, Ontario, Canada). Estimated glomerular filtration rate <30 mL/min, according to Cockcroft-Gault, was an exclusion criterion. The primary efficacy outcome was fatal and nonfatal stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism. The main safety outcome was major bleeding, defined as (1) a reduction in hemoglobin level of at least 20 g/L, (2) transfusion of at least 2 units of blood, or (3) symptomatic bleeding in a critical area or organ. Approval by the appropriate ethics committees was obtained at all sites. All patients provided written informed consent.

Of the 18 113 patients included in the RE-LY trial, LVH data by ECG were available in 10 372. Of these, 5275 patients also had baseline measurements available for at least 1 of the cardiovascular biomarkers (NT-proBNP, hs-cTnI, hs-cTnT, and GDF-15). The data set for this study was accordingly 5275 patients. A flowchart is presented in Figure S1.

ECG Procedure and LVH Definition

The ECG procedure has been described in detail previously.[4] Briefly, a 25-mm/s 12-lead ECG obtained at study entry was examined by an expert reader (G.M.), blinded to the patients' features and randomized treatment. Electrographic LVH was defined according to the Cornell voltage criteria (R wave in aVL+S wave in V3 >2.0 mV in women or >2.4 mV in men) or by presence of strain pattern (ST-segment depression of at least 0.5 mm and inverted T wave in at least 1 of the leads in I, II, aVL, or V4 to V6). LVH diagnosis by electrocardiography was thus a binary variable (yes/no). This definition of electrographic LVH is considered simple and applicable in large populations and has been validated in large studies.[4,16,17] In a large validation study in hypertensive patients, this definition yielded 34% sensitivity and 91% specificity with echocardiographic LVH as reference, performed better than traditional ECG criteria of LVH, and identified subjects at higher risk of cardiovascular outcomes.[17]

Laboratory Methods

Venous blood was drawn at randomization, before initiation of study treatment, using a 21/22-gauge needle into vacutainer tubes containing EDTA. The blood was centrifuged within 30 minutes at 2000*g* for 10 minutes. The tubes were thereafter immediately frozen at −20°C or colder. Aliquots were stored at −70°C to allow for central batch analysis.

Plasma concentration of GDF-15 was determined by Elecsys GDF-15 precommercial assay kit P03 with the same standardization as the recently introduced routine reagent (Roche Diagnostics).[9,18] cTnI concentrations were measured on Architect i1000SR (Abbott Diagnostics) using hs assays. cTnT and NT-proBNP were analyzed with high-sensitivity assays on Cobas Analytics e601 and c501 Immunoanalyzer (Roche Diagnostics). These biochemical analyses were performed centrally at Uppsala Clinical Research Center

laboratory (Uppsala, Sweden), according to the instructions of the manufacturer. Details about the characteristics of these assays have been reported previously.[19,20]

Statistical Analyses

The numbers of patients with available GDF-15, NT-proBNP, hs-cTnI, and hs-cTnT were 4850, 5239, 4948, and 4892, respectively. There were relatively few missing data (<1%) on other covariates, and a complete case analysis was therefore implemented. In a univariate analysis comparing baseline characteristics of patients between categories of LVH, continuous variables were reported with median and first and third quartiles and compared by Wilcoxon rank sum test. Categorical variables were reported as number and column percentage and compared by χ^2 tests.

Continuous biomarker levels were log transformed and used as outcome in linear regression models, including LVH category (no/yes), age, sex, body mass index, current smoking, heart failure, hypertension, prior myocardial infarction, diabetes mellitus, systolic blood pressure, permanent AF, creatinine clearance, digoxin use, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker as explanatory variables, on the basis of clinical importance. The results are presented as model adjusted geometric mean ratios of biomarker levels between LVH categories, with nominal CIs and *P* values. Observed marginal distributions were used in the model adjustment.

The impact of biomarkers at baseline on the association between LVH and outcomes was analyzed by adding biomarkers (continuous, log-transformed values) to Cox regression models, including LVH category, randomized treatment, CHA_2DS_2-VASc score, permanent AF at entry, smoking, digoxin use, and creatinine clearance. Biomarkers were added individually to the model, as well as simultaneously in prespecified combinations. The interactions between LVH category and biomarkers were analyzed by Cox regression models, including LVH category, biomarker, and interaction between LVH category and biomarker. The biomarkers were included as continuous, log transformed, and fitted using restricted cubic splines with 4 knots, located at the 5th, 35th, 65th, and 95th percentiles. Plots of estimated probability of event at 1 year against biomarker values for each LVH category were constructed. The *P* values for the tests of interactions are reported.

The impact of LVH on the association between biomarkers and outcomes was analyzed by adding LVH to Cox regression models, including 1 biomarker (continuous, log transformed) and randomized treatment, CHA_2DS_2-VASc score, permanent AF at entry, smoking, digoxin use, and creatinine clearance.

All statistical tests were 2 tailed and performed at the 0.05 significance level. Because the analyses were exploratory, no adjustments for multiple comparisons were made. The proportional hazards assumption was evaluated by plotting Schoenfeld residuals against rank time and fitting a smooth curve. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Baseline Data and Clinical Characteristics According to Presence of LVH

The median age was 72.0 years, and 3431 patients (65%) were men. LVH was present in 1257 patients (23.8%). Baseline characteristics and comorbidities according to presence of LVH are shown in Table 1.

All the cardiovascular biomarkers and several clinical characteristics were significantly associated with presence of LVH. Patients with AF and LVH more often had heart failure, poor renal function, diabetes mellitus, hypertension, permanent AF, and vascular disease. They had also more commonly been prescribed digoxin, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blocker treatment, but less commonly statins. A slightly larger proportion of patients with both AF and LVH were naïve to oral anticoagulation therapy. In linear regression analyses adjusting for baseline characteristics, LVH was significantly ($P<0.0001$) associated with higher levels of all analyzed biomarkers (Table 2).

The baseline characteristics of the present cohort with available data on both biomarkers and LVH were similar to the larger cohort with available LVH data (Table S1).

Prognostic Value of LVH and Cardiac Biomarker Levels

During a median follow-up of 2.0 years, 165 patients developed a stroke, 370 died, and 258 had a major bleeding event. For stroke, the hazard ratios (95% CIs) per 50% increase after adjustment for clinical risk factors and LVH were as follows: NT-proBNP, 1.09 (1.00–1.19); hs-cTnI, 1.09 (1.03–1.15); hs-cTnT, 1.14 (1.06–1.24); and GDF-15, 1.22 (1.08–1.38) (all $P<0.05$) (Figure 1). For death, the hazard ratios (95% CIs) per 50% increase were as follows: NT-proBNP, 1.24 (1.17–1.31); hs-cTnI, 1.13 (1.10–1.17); hs-cTnT, 1.28 (1.23–1.34); and GDF-15, 1.31 (1.22–1.42) (all $P<0.0001$) (Figure 1). Elevated biomarker levels were consistently associated with poorer prognosis in patients with AF, regardless of LVH (Figure 2). Results were similar for the association between biomarker levels and major bleeding (Figure 1).

The influence of baseline biomarker levels on the association between LVH and outcomes was analyzed by adding

Table 1. Demographics and Clinical Characteristics According to LVH Category

Baseline Data	No LVH (N=4018)	LVH (N=1257)	*P* Value*
Age, median (quartile 1–quartile 3), y	72.0 (67.0–77.0)	72.0 (66.0–78.0)	0.74
Age ≥75 y, n (%)	1531 (38.1)	503 (40.0)	0.22
Male sex, n (%)	2683 (66.8)	748 (59.5)	<0.0001
Current smoker, n (%)	303 (7.5)	107 (8.5)	0.26
Weight, median (quartile 1–quartile 3), kg	82.0 (71.0–95.0)	78.0 (67.0–90.0)	<0.0001
Body mass index, median (quartile 1–quartile 3), kg/m^2	28.3 (25.3–32.0)	27.6 (24.8–31.0)	<0.0001
Systolic blood pressure, median (quartile 1–quartile 3), mm Hg	130.0 (120.0–140.0)	132.0 (120.0–145.0)	<0.0001
Diastolic blood pressure, median (quartile 1–quartile 3), mm Hg	80.0 (70.0–85.0)	80.0 (70.0–86.0)	0.75
Heart rate, median (quartile 1–quartile 3), bpm	76.0 (68.0–86.0)	76.0 (66.0–87.0)	0.94
Type of atrial fibrillation, n (%)			
Paroxysmal	632 (15.7)	154 (12.3)	0.005
Persistent	1285 (32.0)	397 (31.6)	
Permanent	2099 (52.3)	706 (56.2)	
Heart failure, n (%)	1348 (33.5)	651 (51.8)	<0.0001
Diabetes mellitus, n (%)	837 (20.8)	329 (26.2)	<0.0001
Coronary artery disease, n (%)	896 (22.3)	319 (25.4)	0.0237
Hypertension, n (%)	3105 (77.3)	1010 (80.4)	0.0217
Vascular disease, n (%)†	669 (16.7)	266 (21.2)	0.0003
History of stroke/SEE/TIA, n (%)	872 (21.7)	279 (22.2)	0.71
VKA use class at study entry, n (%)			
Naive	1869 (46.5)	625 (49.7)	0.0469
Statin at baseline, n (%)	1649 (41.0)	474 (37.7)	0.0355
ARB and/or ACEi at baseline, n (%)	2598 (64.7)	938 (74.6)	<0.0001
β Blocker at baseline, n (%)	2558 (63.7)	809 (64.4)	0.65
Digoxin at baseline, n (%)	1209 (30.1)	638 (50.8)	<0.0001
CrCL at baseline, median (quartile 1–quartile 3), mL/min	70.4 (55.6–88.6)	64.3 (50.0–81.1)	<0.0001
CrCL class at baseline, n (%)			
<50 mL/min	639 (16.1)	312 (25.1)	<0.0001
50–<80 mL/min	1929 (48.5)	601 (48.3)	
≥80 mL/min	1412 (35.5)	332 (26.7)	
Left ventricular ejection fraction, n (%)			
≤40%	343 (8.5)	232 (18.5)	NA‡
>40%	1493 (37.2)	424 (33.7)	
Unknown	2182 (54.3)	501 (47.8)	
CHA_2DS_2VASc score, median (quartile 1–quartile 3)	3.0 (2.0–4.0)	4.0 (3.0–5.0)	<0.0001
CHA_2DS_2VASc score category, n (%)			
≤2	1051 (25.3)	239 (19.0)	<0.0001
>2	3003 (74.7)	1018 (81.0)	
NT-proBNP			
Median (quartile 1–quartile 3), ng/L	931 (575–1453)	1354 (775–2277)	<0.0001
n	1250	3989	

Continued

Table 1. Continued

Baseline Data	No LVH (N=4018)	LVH (N=1257)	*P* Value*
Troponin I			
Median (quartile 1–quartile 3), ng/L	6.0 (4.0–10.0)	12.0 (6.6–21.0)	<0.0001
n	1191	3793	
Troponin T			
Median (quartile 1–quartile 3), ng/L	11.2 (7.4–17.2)	17.1 (10.8–27.1)	<0.0001
n	1167	3725	
GDF-15			
Median (quartile 1–quartile 3), ng/L	1472 (1103–2090)	1785 (1271–2601)	<0.0001
n	1159	3691	

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; bpm, beats per minute; CrCL, creatinine clearance; GDF-15, growth differentiation factor-15; LVH, left ventricular hypertrophy; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SEE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

*The *P* value is for the comparison between groups and is based on the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.

†Vascular disease: peripheral artery disease or prior myocardial infarction.

‡Not calculated because of a large proportion with unknown values.

biomarkers (continuous, log transformed) to Cox regression models adjusted for several baseline characteristics (Table 3).

LVH did not remain significantly associated with stroke or death after adjustment for biomarker levels. Similarly, there was no improvement in C-indexes for stroke/systemic embolism, all-cause mortality, or major bleeding events by adding LVH data to risk models containing the cardiovascular biomarkers (Table S2). The biomarkers, however, provided significant improvements when added on top of models containing LVH data.

Discussion

The present study provides new insight into the association between the cardiovascular biomarkers NT-proBNP, troponin, and GDF-15 and LVH in patients with AF. There was an independent association between LVH and increased levels of each biomarker in multiple linear regression analyses, in particular for the cardiac biomarkers (NT-proBNP and troponin). Overall, the biomarkers remained independently associated with cardiovascular outcomes after adjustment for information on LVH status. On the other hand, LVH did not remain an independent predictor for stroke or mortality after adjustment for the cardiac biomarkers NT-proBNP and troponin. Accordingly, in patients with AF, cardiac biomarkers were able to further identify patients with lower or higher risk both in the presence and in the absence of LVH by ECG.

LVH is a strong marker for adverse outcomes in several populations ranging from the general population to those with cardiovascular diseases,[3,17,21,22] but is not included among the traditional risk factors for stroke or death in AF.[1,2] LVH according to either ECG or echocardiography was recently shown to be a marker of increased risk for adverse outcomes also in patients with AF.[4,23] Similarly, the cardiovascular biomarkers NT-proBNP,[5,8,24–26] troponin,[6,7,11,27,28] and GDF-15[9,29–31] are powerful risk markers for cardiovascular outcomes in both the general population and in patients with cardiovascular diseases, including AF.[32] In the present study, we confirmed the significant independent associations between the levels of these cardiovascular

Table 2. Linear Regression Analysis of Biomarker Level According to LVH Category

Biomarker	Without LVH	With LVH	Ratio	*P* Value
NT-proBNP, ng/L	924 (903–946)	1220 (1169–1273)	1.32 (1.26–1.39)	<0.0001
Troponin I, ng/L	7.1 (6.9–7.3)	11.8 (11.2–12.5)	1.67 (1.57–1.78)	<0.0001
Troponin T, ng/L	11.6 (11.4–11.9)	16.2 (15.6–16.9)	1.40 (1.34–1.46)	<0.0001
GDF-15, ng/L	1589 (1567–1612)	1735 (1690–1780)	1.09 (1.06–1.12)	<0.0001

Data are given as geometric mean (95% CI). Multiple linear regression analyses with log-transformed continuous biomarker levels as outcome in models including LVH category (no/yes), age, sex, body mass index, current smoking, heart failure, hypertension, prior myocardial infarction, diabetes mellitus, systolic blood pressure, permanent atrial fibrillation, creatinine clearance, digoxin use, and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker as explanatory variables. GDF-15 indicates growth differentiation factor-15; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Outcome/Biomarker	No of patients	Events (%/year)	Model	HR 50% increase (95% CI)	p-value effect of biomarker
Stroke or SEE					
NT-proBNP	5239	165 (1.57)	Without LVH	1.10 (1.01-1.19)	0.0290
NT-proBNP			With LVH	1.09 (1.00-1.19)	0.0363
Troponin I	4984	151 (1.53)	Without LVH	1.09 (1.04-1.15)	0.0020
Troponin I			With LVH	1.09 (1.03-1.15)	0.0029
Troponin T	4892	150 (1.54)	Without LVH	1.14 (1.06-1.24)	0.0017
Troponin T			With LVH	1.14 (1.06-1.24)	0.0021
GDF-15	4850	150 (1.56)	Without LVH	1.23 (1.09-1.38)	0.0012
GDF-15			With LVH	1.22 (1.08-1.38)	0.0014
Death					
NT-proBNP	5239	365 (3.48)	Without LVH	1.25 (1.18-1.32)	<.0001
NT-proBNP			With LVH	1.24 (1.17-1.31)	<.0001
Troponin I	4984	339 (3.44)	Without LVH	1.14 (1.11-1.18)	<.0001
Troponin I			With LVH	1.13 (1.10-1.17)	<.0001
Troponin T	4892	332 (3.41)	Without LVH	1.29 (1.24-1.35)	<.0001
Troponin T			With LVH	1.28 (1.23-1.34)	<.0001
GDF-15	4850	334 (3.47)	Without LVH	1.32 (1.22-1.43)	<.0001
GDF-15			With LVH	1.31 (1.22-1.42)	<.0001
Major bleed					
NT-proBNP	5239	254 (2.42)	Without LVH	1.07 (1.00-1.15)	0.0371
NT-proBNP			With LVH	1.07 (1.00-1.14)	0.0619
Troponin I	4984	242 (2.46)	Without LVH	1.09 (1.05-1.14)	0.0001
Troponin I			With LVH	1.09 (1.04-1.13)	0.0005
Troponin T	4892	228 (2.34)	Without LVH	1.18 (1.11-1.25)	<.0001
Troponin T			With LVH	1.17 (1.10-1.25)	<.0001
GDF-15	4850	226 (2.35)	Without LVH	1.40 (1.28-1.54)	<.0001
GDF-15			With LVH	1.40 (1.28-1.53)	<.0001

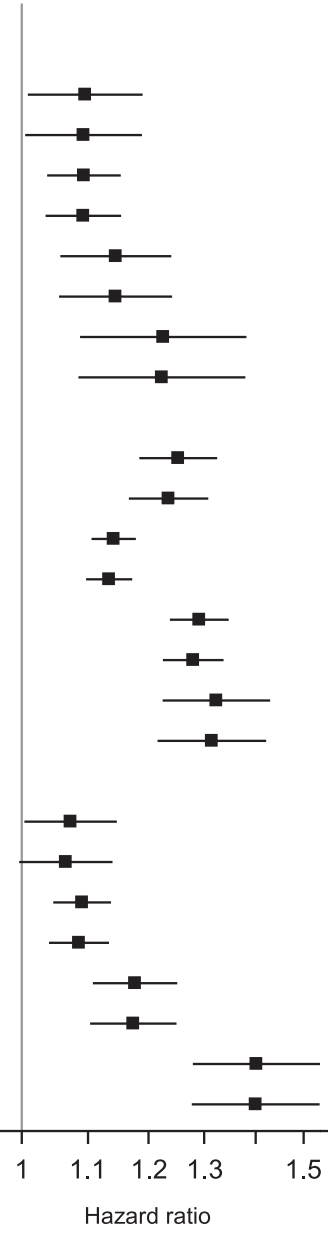

Figure 1. Impact of left ventricular hypertrophy (LVH) on the association between baseline biomarkers and stroke or systemic embolism (SEE), all-cause mortality, and major bleeding outcomes. GDF-15 indicates growth differentiation factor-15; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

biomarkers and adverse outcomes in patients with AF, even after adjustment for LVH by ECG. Biomarkers thus remained significant predictors for cardiovascular outcomes both in the presence as well as in the absence of LVH. In contrast, the association between LVH and outcomes did not remain after adjustment for biomarker levels. Previous studies on the prognostic impact of these biomarkers in other cohorts have accounted for the presence of LVH to a varying degree. This issue was recently investigated comprehensively in a general population in the DHS (Dallas Heart Study) cohort, which confirmed the prognostic value of the cardiac biomarkers.[13] In the present study, we extended these observations and showed a prognostic value of the levels of the cardiovascular biomarkers beyond information on LVH also in patients with AF.

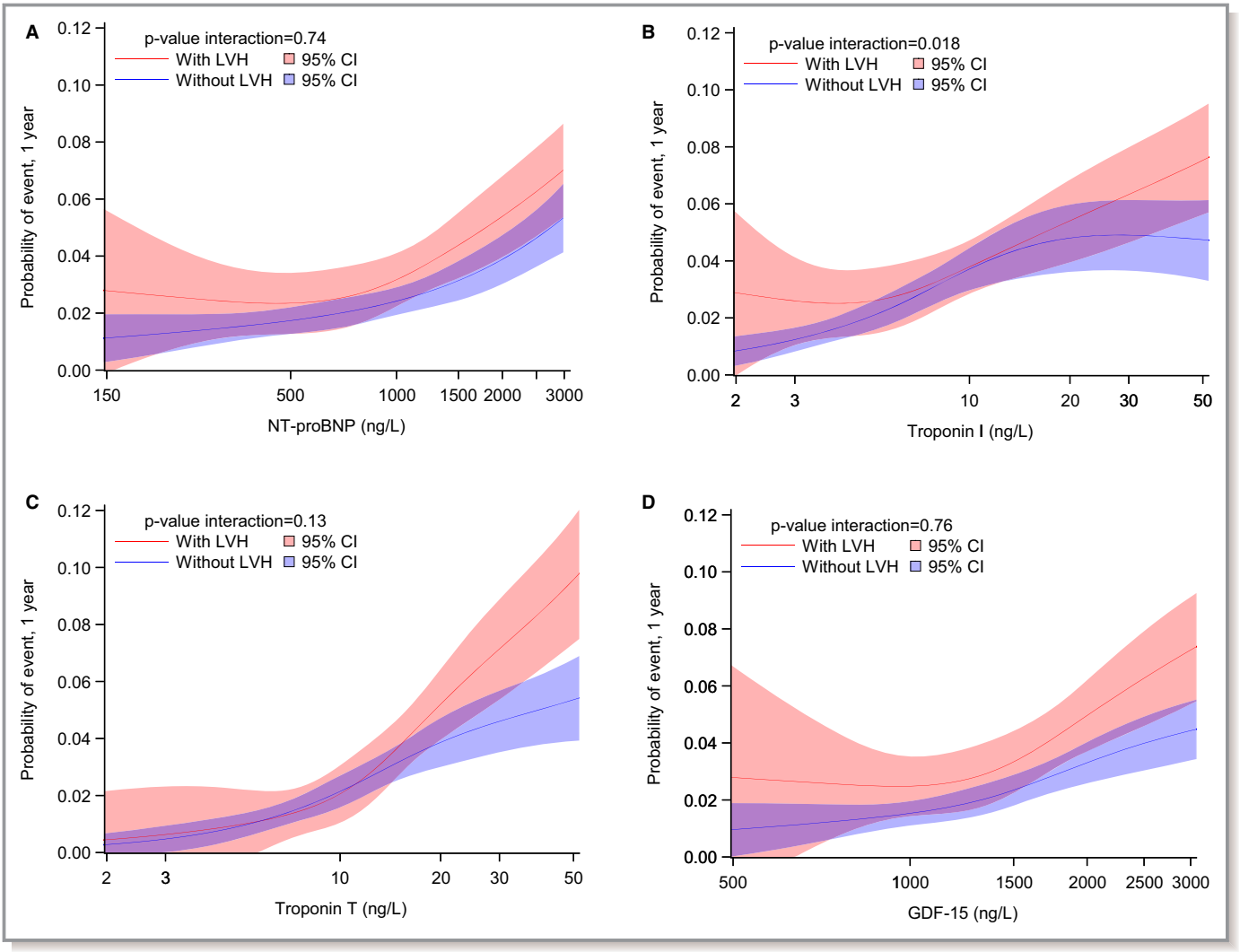

Figure 2. One-year risk for all-cause mortality by left ventricular hypertrophy (LVH) category according to levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide; **A**), troponin I (**B**), troponin T (**C**), and growth differentiation factor-15 (GDF-15; **D**). The biomarkers were included as continuous, log transformed, and fitted using restricted cubic splines with 4 knots, located at the 5th, 35th, 65th, and 95th percentiles.

Causes of LVH mainly include hemodynamic states with increased afterload, such as hypertension and aortic valvular disease, besides specific genetic myocardial diseases, such as hypertrophic cardiomyopathies.[33,34] In addition, the levels of troponin, natriuretic peptides, and GDF-15 have been shown to increase with progression of LVH.[11–13,35] LVH and elevated levels of cardiac biomarkers thus seem to have several causes in common. On the other hand, biomarker levels not only reflect *structural* abnormalities in the heart, but are also related to cardiac and vascular function.[11,12,36] Besides the positive interaction between these variables, the reasons that cardiovascular biomarkers are stronger risk markers than LVH may be because of the fact that they also indicate underlying potentially clinically silent cardiovascular disease processes or dysfunctions that are also related to cardiovascular outcomes.[7–9,37] For example, the levels of cardiac biomarkers seem to signal adverse remodeling in patients with LVH, indicating a transition from structural LVH to clinical heart failure.[13] This transition was recently termed "malignant LVH" and confers a state of even poorer prognosis.[38] There are thus several reasons that cardiovascular biomarkers provide additional dimensions of information on risk of cardiovascular events that also seem to include the signal provided by LVH in patients with AF. This notion is also supported in the current findings, which show no added prognostic value of LVH by ECG in predictive models already containing the plasma biomarkers.

In the clinical setting, ECG recording is fundamental in the management of patients with AF to obtain information on heart rhythm and heart rate.[1,2] It therefore provides easy accessible screening of other possible abnormalities, such as LVH, and may aid in the decision about rate or rhythm control strategies and/or the selection of antiarrhythmic drugs.[1,2,39] For risk stratification, electrographic LVH data may still

Table 3. Association Between LVH and Outcomes According to Adjustment for Biomarkers

Outcome	Biomarker Added in Model	Events, %/Year		Adjusted Cox Model	
		Without LVH (N=3616)	With LVH (N=1136)	HR (95% CI)	*P* Value*
Stroke or systemic embolism	LVH without biomarkers in model	105 (1.46)	43 (1.94)	1.14 (0.79–1.64)	0.49
	Troponin I			1.02 (0.70–1.50)	0.91
	Troponin T			1.03 (0.71–1.49)	0.89
	NT-proBNP			1.06 (0.73–1.54)	0.75
	GDF-15			1.10 (0.77–1.59)	0.60
	Troponin T+NT-proBNP			0.99 (0.68–1.44)	0.95
	Troponin T+NT-proBNP+GDF-15			1.00 (0.69–1.46)	0.99
All-cause mortality	LVH without biomarkers in model	204 (2.83)	119 (5.38)	1.60 (1.27–2.02)	0.0001
	Troponin I			1.33 (1.04–1.70)	0.0249
	Troponin T			1.28 (1.01–1.63)	0.0408
	NT-proBNP			1.35 (1.07–1.72)	0.0143
	GDF-15			1.53 (1.21–1.93)	0.0005
	Troponin T+NT-proBNP			1.17 (0.92–1.49)	0.21
	Troponin T+NT-proBNP+GDF-15			1.19 (0.93–1.51)	0.16
Major bleed	LVH without biomarkers in model	155 (2.15)	67 (3.03)	1.27 (0.95–1.70)	0.12
	Troponin I			1.20 (0.88–1.63)	0.25
	Troponin T			1.12 (0.83–1.51)	0.47
	NT-proBNP			1.24 (0.92–1.68)	0.16
	GDF-15			1.22 (0.91–1.64)	0.19
	Troponin T+NT-proBNP			1.12 (0.83–1.51)	0.47
	Troponin T+NT-proBNP+GDF-15			1.18 (0.87–1.59)	0.30

Biomarkers included as continuous, log-transformed, variables. Patients with no missing data for clinical risk factors, troponin T, GDF-15, and NT-proBNP were included in the analysis. GDF-15 indicates growth differentiation factor-15; HR, hazard ratio; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
**P* value for effect of LVH.

provide practical prognostic information for cardiovascular events in AF. However, if plasma biomarker measurements are available, they can improve risk prediction in patients with AF both in the presence or absence of LVH.[4,40,41] Measurement of the cardiac biomarkers NT-proBNP and troponin would thus probably be useful as part of the routine evaluation of a patient with AF.

Limitations

The present study was a post hoc analysis based on a subgroup of participants in the RE-LY trial with ECGs suitable for LVH analysis and biomarker measurements at baseline available. Generalizability of our results may thus be limited. Although baseline characteristics in patients with available biomarker measurements were almost identical to the total cohort with available LVH data, the annual event rate was somewhat lower in those with available biomarker measurements. This may have influenced the results on the association of LVH with outcomes in presence of biomarkers.[4] LVH was assessed by ECG and not magnetic resonance imaging or echocardiography. ECG assessment of LVH traditionally indicates the presence or absence of LVH, not the actual severity. However, a validated definition for electrographic LVH was applied in the analysis, which also encompassed ECG strain patterns in addition to traditional voltage criteria, thereby providing additional prognostic information because strain pattern is associated with higher left ventricular mass indexes.[21] Moreover, ECG screening is often used in large-scale screening programs for practical reasons.

Conclusions

Levels of cardiac biomarkers are significantly associated with LVH. The prognostic value of biomarkers on stroke, death, and major bleeding is not affected by LVH. The association of LVH with outcomes is attenuated in the presence of cardiac biomarkers.

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Disclosures

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References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
2. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
3. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
4. Verdecchia P, Reboldi G, Di Pasquale G, Mazzotta G, Ambrosio G, Yang S, Pogue J, Wallentin L, Ezekowitz MD, Connolly SJ, Yusuf S; Re-Ly Study Investigators. Prognostic usefulness of left ventricular hypertrophy by electrocardiography in patients with atrial fibrillation (from the Randomized Evaluation of Long-Term Anticoagulant Therapy Study). *Am J Cardiol*. 2014;113:669–675.
5. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation*. 2012;125:1605–1616.
6. Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, Gersh BJ, Mohan P, Harjola VP, Horowitz J, Husted S, Hylek EM, Lopes RD, McMurray JJ, Wallentin L; Aristotle Investigators. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;129:625–634.
7. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Alexander JH, Atar D, Gersh BJ, Hanna M, Harjola VP, Horowitz JD, Husted S, Hylek EM, Lopes RD, McMurray JJ, Granger CB; Aristotle Investigators. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *J Am Coll Cardiol*. 2014;63:52–61.
8. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, Gersh BJ, Hanna M, Hohnloser S, Horowitz J, Huber K, Hylek EM, Lopes RD, McMurray JJ, Granger CB. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61:2274–2284.
9. Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, Horowitz JD, Hylek EM, Lopes RD, Asberg S, Granger CB, Siegbahn A; Aristotle Investigators. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;130:1847–1858.
10. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. 2010;304:2494–2502.
11. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503–2512.
12. Lind L, Wallentin L, Kempf T, Tapken H, Quint A, Lindahl B, Olofsson S, Venge P, Larsson A, Hulthe J, Elmgren A, Wollert KC. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. *Eur Heart J*. 2009;30:2346–2353.
13. Neeland IJ, Drazner MH, Berry JD, Ayers CR, deFilippi C, Seliger SL, Nambi V, McGuire DK, Omland T, de Lemos JA. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. *J Am Coll Cardiol*. 2013;61:187–195.
14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; Re-Ly Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
15. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009;157:805–810, 810.e1-2.
16. Verdecchia P, Sleight P, Mancia G, Fagard R, Trimarco B, Schmieder RE, Kim JH, Jennings G, Jansky P, Chen JH, Liu L, Gao P, Probstfield J, Teo K, Yusuf S; Ontarget Transcend Investigators. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. *Circulation*. 2009;120:1380–1389.
17. Verdecchia P, Angeli F, Reboldi G, Carluccio E, Benemio G, Gattobigio R, Borgioni C, Bentivoglio M, Porcellati C, Ambrosio G. Improved cardiovascular risk stratification by a simple ECG index in hypertension. *Am J Hypertens*. 2003;16:646–652.
18. Kempf T, Horn-Wichmann R, Brabant G, Peter T, Allhoff T, Klein G, Drexler H, Johnston N, Wallentin L, Wollert KC. Circulating concentrations of growth-differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. *Clin Chem*. 2007;53:284–291.
19. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Yusuf S, Siegbahn A, Wallentin L. Growth-differentiation factor 15 and risk of major bleeding in atrial fibrillation: insights from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Am Heart J*. 2017;190:94–103.
20. Hijazi Z, Siegbahn A, Andersson U, Lindahl B, Granger CB, Alexander JH, Atar D, Gersh BJ, Hanna M, Harjola VP, Horowitz J, Husted S, Hylek EM, Lopes RD, McMurray JJ, Wallentin L. Comparison of cardiac troponins I and T measured

with high-sensitivity methods for evaluation of prognosis in atrial fibrillation: an ARISTOTLE substudy. *Clin Chem*. 2015;61:368–378.

21. Shah AS, Chin CW, Vassiliou V, Cowell SJ, Doris M, Kwok TC, Semple S, Zamvar V, White AC, McKillop G, Boon NA, Prasad SK, Mills NL, Newby DE, Dweck MR. Left ventricular hypertrophy with strain and aortic stenosis. *Circulation*. 2014;130:1607–1616.
22. Westerhout CM, Lauer MS, James S, Fu Y, Wallentin L, Armstrong PW; Gusto IV ACS Investigators. Electrocardiographic left ventricular hypertrophy in GUSTO IV ACS: an important risk marker of mortality in women. *Eur Heart J*. 2007;28:2064–2069.
23. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Left ventricular geometry and outcomes in patients with atrial fibrillation: the AFFIRM Trial. *Int J Cardiol*. 2014;170:303–308.
24. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275–281.
25. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, Sugimoto Y, Kinoshita M. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*. 1997;96:509–516.
26. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350:655–663.
27. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*. 2007;116:1242–1249.
28. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538–2547.
29. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H, Wollert KC. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation*. 2010;122:1387–1395.
30. Daniels LB, Clopton P, Laughlin GA, Maisel AS, Barrett-Connor E. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo Study. *Circulation*. 2011;123:2101–2110.
31. Kempf T, von Haehling S, Peter T, Allhoff T, Cicoira M, Doehner W, Ponikowski P, Filippatos GS, Rozentryt P, Drexler H, Anker SD, Wollert KC. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol*. 2007;50:1054–1060.
32. Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of biomarkers for risk stratification in patients with atrial fibrillation. *Clin Chem*. 2017;63:152–164.
33. Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, Fauad-Tarazi F, Horan MJ, Marcus M, Massie B. The heart in hypertension. *N Engl J Med*. 1992;327:998–1008.
34. Authors/Task Force Members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.
35. Chin CW, Shah AS, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, Strachan FE, Hunter AL, Maria Choy A, Lang CC, Walker S, Boon NA, Newby DE, Mills NL, Dweck MR. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J*. 2014;35:2312–2321.
36. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation*. 2004;109:3176–3181.
37. Nadir MA, Rekhraj S, Wei L, Lim TK, Davidson J, MacDonald TM, Lang CC, Dow E, Struthers AD. Improving the primary prevention of cardiovascular events by using biomarkers to identify individuals with silent heart disease. *J Am Coll Cardiol*. 2012;60:960–968.
38. Peters MN, Seliger SL, Christenson RH, Hong-Zohlman SN, Daniels LB, Lima JAC, de Lemos JA, Neeland IJ, deFilippi CR. "Malignant" left ventricular hypertrophy identifies subjects at high risk for progression to asymptomatic left ventricular dysfunction, heart failure, and death: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Heart Assoc*. 2018;7:e006619. DOI: 10.1161/JAHA.117.006619.
39. Badheka AO, Shah N, Grover PM, Patel NJ, Chothani A, Mehta K, Singh V, Deshmukh A, Savani GT, Rathod A, Panaich SS, Patel N, Arora S, Bhalara V, Coffey JO, Mitrani RD, Halperin JL, Viles-Gonzalez JF. Outcomes in atrial fibrillation patients with and without left ventricular hypertrophy when treated with a lenient rate-control or rhythm-control strategy. *Am J Cardiol*. 2014;113:1159–1165.
40. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L; Aristotle and Stability Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J*. 2016;37:1582–1590.
41. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L; Aristotle, Re-Ly Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet*. 2016;387:2302–2311.

Supplemental Material

Figure S1. Flowchart.

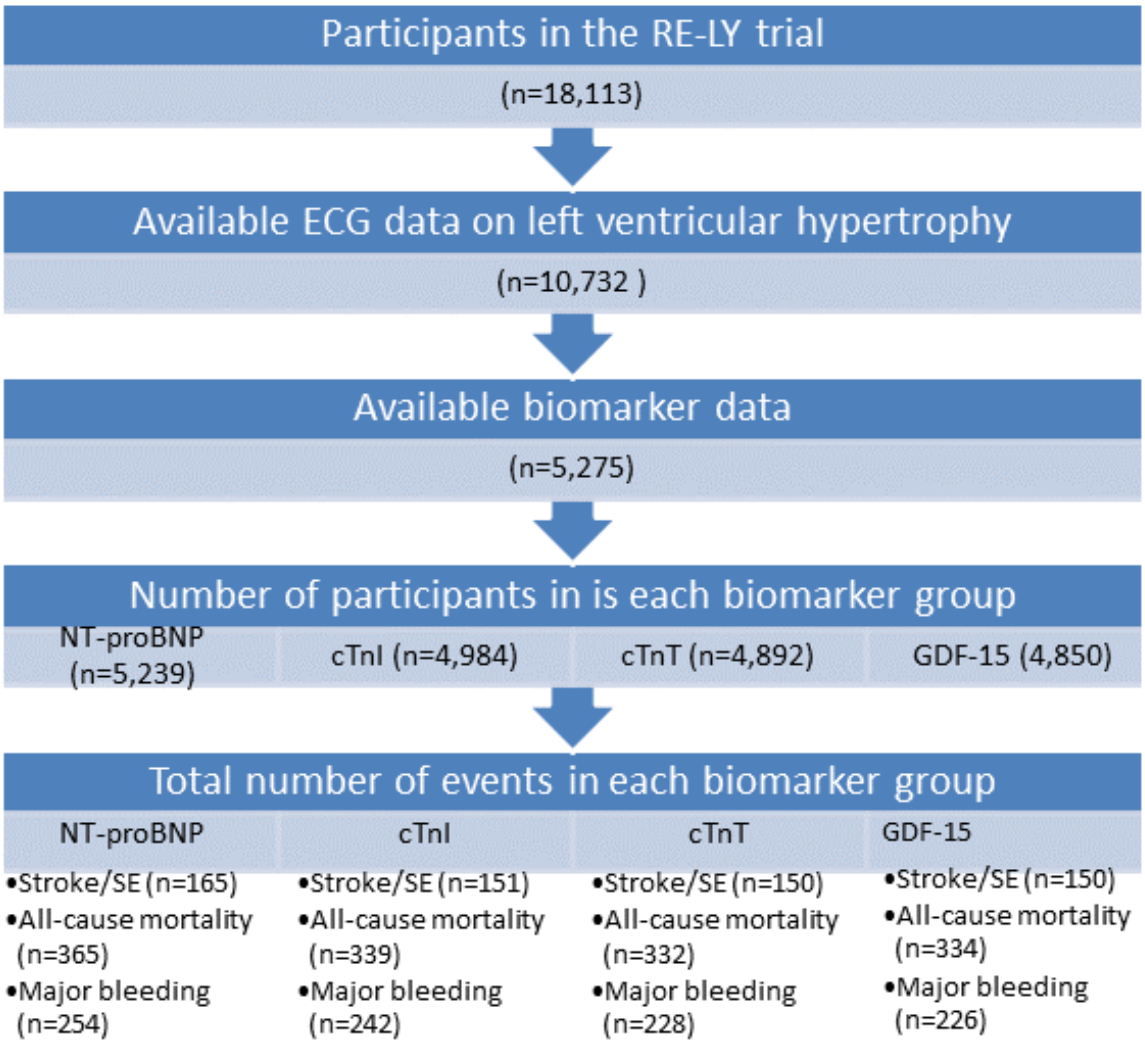

Table S1. Demographics and clinical characteristics for the present subgroup with biomarkers and LVH-data available in comparison to the cohort with LVH-data available.

Baseline data		Biomarkers available N=5275	Total with LVH-data N=10372
Age [years]	Median (Q1, Q3)	72.0 (67.0, 77.0)	72.0 (66.0, 77.0)
Age ≥75 years	n (%)	2034 (38.6%)	4079 (39.3%)
Sex	Male	3431 (65.0%)	6771 (65.3%)
Current smoker	n (%)	410 (7.8%)	789 (7.6%)
Weight [kg]	Median (Q1, Q3)	81.0 (70.0, 93.9)	81.0 (69.9, 94.3)
Body mass index [kg/m2]	Median (Q1, Q3)	28.1 (25.2, 31.7)	28.0 (24.9, 31.8)
Systolic blood pressure (mmHg)	Median (Q1, Q3)	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)
Diastolic blood pressure (mmHg)	Median (Q1, Q3)	80.0 (70.0, 85.0)	80.0 (70.0, 85.0)
Heart rate (bpm)	Median (Q1, Q3)	76.0 (67.0, 86.0)	76.0 (67.0, 85.0)
Type of atrial fibrillation	Paroxysmal	786 (14.9%)	1640 (15.8%)
	Persistent	1682 (31.9%)	4804 (46.3%)
	Permanent	2805 (53.2%)	3926 (37.9%)
Heart failure	n (%)	1999 (37.9%)	3730 (36.0%)
Diabetes mellitus	n (%)	1166 (22.1%)	2405 (23.2%)
Coronary artery disease	n (%)	1215 (23.0%)	2657 (25.6%)
Hypertension	n (%)	4115 (78.0%)	8110 (78.2%)
Vascular disease*	n (%)	935 (17.7%)	1801 (17.4%)
History of stroke/SEE/TIA	n (%)	1151 (21.8%)	2310 (22.3%)
VKA use class at study entry	Naive	2494 (47.3%)	4747 (45.8%)
Statin at baseline	n (%)	2123 (40.2%)	4332 (41.8%)
ARB and/or ACEi at baseline	n (%)	3536 (67.0%)	6797 (65.5%)
Beta blocker at baseline	n (%)	3367 (63.8%)	6455 (62.2%)
Digoxin at baseline	n (%)	1847 (35.0%)	3578 (34.5%)
CrCL [mL/min] at baseline	Median (Q1, Q3)	68.9 (54.0, 87.0)	68.9 (53.8, 87.9)
CrCL class at baseline	<50	912 (18.2%)	1886 (18.9%)

Baseline data		Biomarkers available N=5275	Total with LVH-data N=10372
	50-<80	2432 (48.5%)	4733 (47.5%)
	≥80	1673 (33.3%)	3354 (33.6%)
CHA_2DS_2VASc score	Median (Q1, Q3)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)
CHA_2DS_2VASc score category	≤2	1254 (23.8%)	2477 (23.9%)
	>2	4021 (76.2%)	7895 (76.1%)
LVH	n (%)	1257 (23.8%)	2353 (22.7%)

LVH - left ventricular hypertrophy; SEE - systemic embolism; TIA - transient ischemic attack; VKA - Vitamin K antagonist; ARB - angiotensin II receptor blocker; ACEi - angiotensin converting enzyme inhibitor; CrCl - creatinine clearance.

*Vascular disease - peripheral artery disease or prior myocardial infarction

Table S2. Discriminative ability of models with and without biomarkers and/or left ventricular hypertrophy.

				p-value for comparison with model		
Outcome	Model	Model description	C-index (95% CI)	A	B	C
Stroke or systemic embolism	A	ERF	0.609 (0.564-0.654)	-	-	-
	B	ERF+LVH	0.612 (0.567-0.657)	0.4587	-	-
	C	ERF+Biomarkers	0.639 (0.593-0.685)	0.0016	-	-
	D	ERF+Biomarkers+LVH	0.639 (0.593-0.685)	-	0.0021	0.9999
All-cause mortality	A	ERF	0.618 (0.584-0.651)	-	-	-
	B	ERF+LVH	0.629 (0.597-0.662)	<0.0001	-	-
	C	ERF+Biomarkers	0.712 (0.683-0.741)	<0.0001	-	-
	D	ERF+Biomarkers+LVH	0.711 (0.682-0.740)	-	<0.0001	0.5039
Major bleeding	A	ERF	0.651 (0.613-0.688)	-	-	-
	B	ERF+LVH	0.655 (0.617-0.692)	0.1064	-	-
	C	ERF+Biomarkers	0.693 (0.656-0.730)	<0.0001	-	-
	D	ERF+Biomarkers+LVH	0.693 (0.655-0.730)	-	<0.0001	0.7530

p-values based on likelihood-ratio tests

ERF - model consisting of established risk factors; LVH - left ventricular hypertrophy