

Joint Association of Albuminuria and Left Ventricular Hypertrophy with Incident Heart Failure in High-Risk Adults with Hypertension: a SPRINT substudy

Short Title: Albuminuria, Left Ventricular Hypertrophy, and Heart Failure

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Abstract

Background: Albuminuria and left ventricular hypertrophy (LVH) are independent predictors of heart failure (HF), however their combined effect on risk of HF has not been explored previously.

Objectives: To examine the joint associations of albuminuria and electrocardiographic (ECG) LVH with incident acute decompensated HF (ADHF), and whether albuminuria/LVH combinations modified the effects of blood pressure control strategy in reducing the risk of ADHF.

Methods: 8,511 participants from the SPRINT (Systolic Blood Pressure Intervention Trial) were included. ECG-LVH was present if any of the following criteria: Cornell voltage, Cornell voltage product, or Sokolow Lyon were present. Albuminuria was defined as urine albumin-creatinine ratio (UACR) ≥ 30 mg/g. ADHF was defined as hospitalization or emergency visit for ADHF. Cox proportional hazard models were used to examine the association of neither LVH, nor albuminuria (reference), either LVH or albuminuria, and both (LVH + albuminuria) with incident ADHF.

Results: Over a median follow-up of 3.2 years, 182 cases of ADHF occurred. In adjusted models, concomitant albuminuria and LVH were associated with higher risk of ADHF than either albuminuria or LVH in isolation (HR (95% CI): 4.95 (3.22-7.62), 2.04 (1.39-3.00), and 1.47 (0.93-2.32), respectively (additive interaction $p=0.01$). The effect of intensive blood pressure in decreasing ADHF attenuated among participants with co-existing albuminuria and LVH without any interaction between treatment group assignment and albuminuria/LVH categories (interaction p -value= 0.26).

Conclusions: Albuminuria and LVH are additive predictors of ADHF. The effect of intensive blood pressure control in decreasing ADHF risk did not vary significantly across albuminuria/LVH combinations.

Keywords: Left ventricular hypertrophy, albuminuria, heart failure, SPRINT

URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01206062

Introduction

Left ventricular hypertrophy (LVH) and albuminuria represent interrelated complications of uncontrolled hypertension¹. Additionally, a complex bidirectional relationship exists between LVH and albuminuria, with each representing a risk factor for the other and vice versa.²⁻⁴ LVH underlies maladaptive cardiac remodeling due to chronic pressure overload, chronic myocardial injury, inflammation, and fibrosis and has strong associations with incident heart failure (HF) and mortality⁵. Albuminuria is a marker of inflammation and endothelial dysfunction and has been strongly associated with incident HF in multiple independent cohort studies^{6,7}. Regression of albuminuria with newer therapies has been associated with clinical benefits such as a reduction in HF hospitalization and mortality^{6,8}. Similarly, regression of LVH with antihypertensive therapies reduced stroke risk, myocardial infarction (MI), HF, and mortality^{9,10}. Given the significant prognostic nature of these markers, an examination of the joint association of LVH and albuminuria with incident HF may identify very high-risk populations. Further, it is also unclear if intensive blood pressure control would modify the joint association of LVH and albuminuria with incident HF. Therefore, we proposed to examine the association and interaction of albuminuria and electrocardiographic LVH (ECG-LVH) with incident acute decompensated HF (ADHF) using data from the Systolic Blood Pressure Intervention Trial (SPRINT) trial.

Methods

Design and Sample

The rationale and design of the SPRINT trial have been previously reported in detail¹¹ and a copy of protocol is available in **Supplement 2**. The CONSORT diagram for the study is shown

in **Supplemental Figure 1**. Briefly, SPRINT was a randomized, controlled, open-label trial in which 9361 participants ≥ 50 years of age with systolic blood pressure (SBP) ≥ 130 -180 mmHg and at high risk for or with CVD were randomized to achieve either an SBP target of < 140 mmHg (standard treatment group) or < 120 mmHg (intensive treatment group). SPRINT aimed to test whether intensive SBP control to < 120 mmHg results in the reduction of a composite of CVD events. High CVD risk was defined as ≥ 1 of the following: clinical or subclinical CVD; chronic kidney disease (CKD); 10-year risk of CVD $\geq 15\%$ by Framingham risk score; or age ≥ 75 years. Clinical CVD was defined as the following: 1) prior myocardial infarction (MI), coronary artery bypass grafting, carotid endarterectomy, or carotid stenting; peripheral arterial disease with revascularization; 2) acute coronary syndrome with or without resting ECG change, ECG changes on an exercise test or positive cardiac imaging study; 3) at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery; or abdominal aortic aneurysm ≥ 5 cm with or without repair. Subclinical CVD was defined as the following: 1) coronary artery calcium (CAC) score ≥ 400 Agatston units; b) ankle-brachial index (ABI) ≤ 0.90 ; 2) LVH by ECG, echocardiogram report, or other cardiac imaging procedure. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m² using the four-variable Modification of Diet in Renal Disease (MDRD) equation¹². Participants with a known LV ejection fraction of $< 35\%$, any symptomatic HF within 6 months, diabetes mellitus, prior transient ischemic attack or stroke, polycystic kidney disease, dementia, non-adherence to medication, and eGFR < 20 mL/min/1.73 m² were excluded. The SPRINT study was approved by the Institutional Review Board at each participating study site, and all participants provided written informed consent. The initial trial was registered at ClinicalTrials.gov (NCT01206062).

For the purpose of this analysis, we included 8,511 SPRINT participants with a baseline standard 12-lead ECG and baseline measures of urine albumin creatinine ratio (UACR). We excluded participants with missing ECG or uninterpretable baseline ECG or missing UACR values or a history of atrial fibrillation (AF). A limited de-identified dataset was obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center after the study was approved by the institutional review board at the Medical College of Wisconsin.

Electrocardiographic Data

LVH was detected using standard 12-lead ECGs obtained at baseline. Digital ECGs were recorded using a GE MAC 1200 electrocardiograph at 10 mm/mV calibration and a speed of 25 mm/s. ECGs were read centrally at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, North Carolina. All ECG tracings were inspected visually for technical errors and inadequate quality before being automatically processed using GE 12-SL Marquette version 2001. LVH was present if met any of the following criteria; Cornell voltage criteria (R_{aVL} amplitude + SV_3 amplitude) with sex-specific thresholds of $\geq 2,200$ μV in women and $\geq 2,800$ μV in men, or Sokolow-Lyon (SV_1 amplitude + RV_5/V_6 amplitude) LVH criteria or Cornell voltage product ($[R_{aVL}$ amplitude + SV_3 amplitude] \times QRS duration)¹³.

Albuminuria

Albuminuria was estimated by a random urine albumin-creatinine ratio (UACR). Serum creatinine and urine creatinine were measured using an enzymatic method (Roche, Indianapolis, IN) at the SPRINT central laboratory at the University of Minnesota¹⁴. Albuminuria was defined as UACR ≥ 30 mg/g.

Heart Failure Events

Data about potential outcomes were assessed every 3 months in both arms using a standardized protocol with centralized monitoring by the coordinating center. To minimize any ascertainment bias, a structured interview was used to obtain self-reported CVD outcomes¹¹. All ADHF events were new or incident HF events and included both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). ADHF events were adjudicated by a Morbidity and Mortality committee using the standardized Atherosclerosis Risk in Communities (ARIC) study adjudication system¹⁵. Adjudicators were blinded to treatment assignment. ADHF was defined as a hospitalization or emergency (ED) visit for a clinical syndrome with multiple symptoms and signs consistent with cardiac decompensation and inadequate cardiac pump function requiring treatment with diuretics or inotropic agents. Symptoms supporting the diagnosis of ADHF included evidence of new or increasing shortness of breath, peripheral edema, orthopnea, or paroxysmal nocturnal dyspnea. Positive signs supporting the diagnosis of ADHF included hypoxia, pulmonary rales on clinical examination, pulmonary vascular congestion on chest X-ray, the elevation of B-type natriuretic peptide (BNP) or pro-N-terminal BNP (NTpro-BNP) above the diagnostic threshold, reduced left ventricular ejection fraction or diastolic dysfunction, new or increased treatment with intravenous loop diuretic or inotrope for ADHF, documented response to therapy or evidence in treating physician's notes that the primary reason for the hospitalization or ED visit was ADHF. Chronic stable HF, right-sided HF, low EF without symptoms of HF, or HF related to volume overload due to inadequate dialysis with end-stage renal disease and new outpatient HF were not included as ADHF endpoints.

Statistical analyses

Four categories were created as follows: neither LVH, nor albuminuria, either LVH or albuminuria, and both (LVH + albuminuria). The baseline characteristics were compared across

LVH/albuminuria categories using analysis of variance for continuous variables, and chi-square test for categorical variables. Continuous variables were reported as mean and standard deviation, median (25%, 75% percentile) for skewed variables, and n (%) for categorical variables.

Incidence rates for ADHF were calculated for each group and Kaplan-Meier plot and the log-rank test were used to compare ADHF-free survival across these groups. We evaluated associations of LVH/albuminuria categories with risk of the ADHF using multivariable Cox proportional hazards models. There was no evidence that the proportional hazards assumptions were violated. Model 1 adjusted for demographics (age, sex, race, randomization site), and model 2 further adjusted for treatment assignment, body mass index, smoking status, prevalent CVD, SBP, eGFR, total cholesterol, statin use, and the number of antihypertensive agents. We tested the additive interaction between LVH and albuminuria and measured additivity by relative excess risk due to interaction (RERI), the proportion of disease attributable to interaction (AP), and synergy index (S)¹⁶. We also tested the multiplicative interaction between LVH and albuminuria for ADHF risk using the likelihood ratio test in a model that included main effects.

ADHF event rates were compared between the intensive SBP and standard SBP arms among participants in each albuminuria/LVH category. The heterogeneity of treatment effect across albuminuria/LVH categories was tested using a likelihood ratio test for multiplicative interaction terms (treatment assignment by albuminuria/LVH category) in models that included main effects.

As the risk of HF exists even at low-grade albuminuria as well⁷, we used a threshold of UACR ≥ 10 mg/g and then examined the association of newly created albuminuria/LVH categories with ADHF adjusting for covariates as mentioned above. We also tested multiplicative and additive interaction between albuminuria (UACR ≥ 10 mg/g) and LVH as described in the main analysis. Additionally, we reported incidence rates of ADHF across UACR categories (<10 mg/g, 10-29.99 mg/g, ≥ 30 mg/g-299.99 mg/g, and ≥ 300 mg/g) stratified by LVH status. Using Cox proportional hazard analysis, we computed HR and 95% of association of these UACR categories with incident ADHF stratified by LVH status.

All data analyses were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC), and two-sided $\alpha=0.05$ was used for hypothesis testing.

Results

Of 9,361 SPRINT participants, 8,511 with complete ECG and UACR data and free of prevalent AF were included in this analysis. The baseline characteristics of the participants stratified by albuminuria/LVH categories are shown in **Table 1**. In addition to predominant demographic factors such as older age, men, and Black individuals, clinical/subclinical CVD and CVD risk factors were also prevalent among participants with concomitant albuminuria and LVH (**Table 1**).

Over a median follow-up of 3.8 years (3.3-4.3), 182 cases of ADHF occurred. 8.7% of participants experienced ADHF events in (LVH + albuminuria) category compared to 1.2% in neither LVH, nor albuminuria category; 3.9% in isolated albuminuria, and 2.2% in the isolated

LVH category. It is further depicted in Kaplan Meier curves, which showed the lowest ADHF survival in (LVH + albuminuria) category (Log-rank rank test $p < 0.001$) **Figure 1**.

In multivariable-adjusted analysis, the presence of LVH vs. absence of LVH and albuminuria vs. no albuminuria were independently associated with ADHF (results not shown). There was a 5-fold higher risk of ADHF in the (+) albuminuria, (+) LVH category compared to (-) albuminuria, (-) LVH category (reference). Further, the (-) albuminuria, (+) LVH category was associated with a statistically non-significant 1.4-fold higher risk of ADHF, while (+) albuminuria, (-) LVH category was associated with a 2-fold higher risk of ADHF. (**Table 2**). There was significant additive interaction between albuminuria and LVH (relative excess risk due to interaction, 2.43; 95% confidence interval (CI): 0.53-4.33; p -value = 0.01). However, there was no significant multiplicative interaction between albuminuria and LVH (p -value for interaction = 0.11).

The effect of intensive blood pressure control on ADHF risk appeared to be attenuated in (+) albuminuria, and (+) LVH category, however, albuminuria/LVH categories did not significantly modify the effects of intensive vs. standard blood pressure control on ADHF risk (p -value for interaction = 0.26) (**Table 3**).

When albuminuria was defined as UACR ≥ 10 mg/g, similar results of a stronger association of the concomitant presence of albuminuria and LVH with incident ADHF than albuminuria and LVH in isolation was observed. (Additive and multiplicative interaction p -value between albuminuria (≥ 10 mg/g) and LVH = 0.01 and 0.048 respectively. (**Supplemental Table 1**). The incidence rate of ADHF increased linearly across these UACR categories with a higher incidence rate in the presence of LVH **Figure 2**.

In the multivariable-adjusted model compared to the reference group (UACR<10 mg/g and no LVH), the association between increasing UACR categories and incident ADHF was stronger in the presence of LVH than in the absence of LVH (**Table 4**).

Supplemental Tables 2, 3, and 4 show multivariable-adjusted models of the association of LVH/albuminuria combinations with ADHF using Cornell Voltage, Sokolow Lyon, and Cornell product criteria respectively. Similar, higher incidence and relative risk of ADHF was observed with (+) LVH, (+) albuminuria combination compared to (-) LVH, (-) albuminuria (reference).

Discussion

In this post-hoc analysis from the SPRINT trial, we evaluated the independent and joint association of LVH and albuminuria with incident HF. The main finding of our analysis from this trial was that LVH and albuminuria were independent and additive predictors of HF risk with significant interaction between these predictors. The combination of LVH and albuminuria posed the highest risk of ADHF than LVH or albuminuria in isolation and the risk increased with increasing levels of albuminuria. Additionally, the effect of intensive blood pressure control in decreasing ADHF risk did not vary significantly across albuminuria/LVH combinations. Taken together, these findings suggest that LVH and albuminuria even at low-grade levels are strong additive predictors of future ADHF and therefore, the concomitant presence of these markers may identify high-risk individuals in need of intensive surveillance and neurohormonal modification with potential newer therapies.

Albuminuria is prevalent in high-risk populations such as those with obesity, diabetes mellitus, and hypertension and is increasingly being recognized as an important predictor of HF^{6,17}.

Albuminuria reflects structural damage to the filtration barrier and is linked to CVD through

multifactorial mechanisms such as endothelial damage, systemic inflammation, presence of comorbid conditions, and neurohormonal activation, including activation of the renin-angiotensin-aldosterone system (RAAS)¹⁸. Systemic inflammation and neurohormonal activation via the heightened activity of RAAS promote oxidative stress and more systemic vascular injury. These pathophysiological processes may promote volume overload via an increase in sodium and water retention and cardiac filling pressures due to increased reabsorption, thereby promoting the development and progression of HF⁶. The resulting venous congestion may promote renal venous congestion, resulting in a decline in effective perfusion pressure and eGFR which may lead to further activation of compensatory mechanisms such as RASS and thus creating a bidirectional progressive cardiorenal injury¹⁹. Therefore, albuminuria is not only a predictor of future HF in otherwise healthy participants but among patients with HF, albuminuria is an independent predictor of exacerbation of HF and increased mortality risk²⁰⁻²². Similarly, LVH is an established risk for HF and despite the low sensitivity of ECG to detect LV mass, ECG-LVH is still a strong predictor of HF²³. Individuals with asymptomatic LVH who were later transitioned to HF are hypothesized to have maladaptive cardiac remodeling due to myocardial injury, inflammation, and fibrosis^{23,24} and albuminuria is one of the pathophysiological links between LVH and inflammation²⁵. On the other hand, albuminuria is associated with eccentric and concentric LVH, and this abnormal LV geometry may mediate the association of albuminuria with CVD events^{26,27}. Analysis of data from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that both LVH and albuminuria independently increased the risk of CVD events and mortality.²⁸ Additionally, the risk of CVD outcomes with albuminuria appeared to occur at much lower levels of UACR among participants with hypertension and LVH.²⁹ Thus, both albuminuria and LVH which represent long-term

consequences of uncontrolled hypertension are strongly interrelated in a complex and bidirectional relationship and may modify/amplify the effect of each other in predicting CVD outcomes as observed in our study.

In this study, we did not find evidence that baseline albuminuria and LVH modified the effects of intensive systolic BP lowering on HF incidence. The effect of intensive systolic blood pressure lowering on the reduction of HF incidence was attenuated among participants with concomitant LVH and albuminuria. Notably, a prior post-hoc analysis from SPRINT trial also reported that albuminuria did not modify the absolute benefits and risks of intensive systolic BP lowering.³⁰ Long-term follow-up data is needed to draw further conclusions on the long-term effect of intensive systolic BP lowering on the risk of HF among participants with concomitant LVH and albuminuria.

Albuminuria and LVH are both potentially modifiable risk factors and regression of these markers has been associated with a reduction of subsequent CVD events^{10,31}. For example, in addition to RAAS blockade, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and nonsteroidal mineralocorticoid receptor antagonists (MRAs) have been proven effective in reducing the progression of albuminuria, with resultant reduction in the progression of chronic kidney disease (CKD) and HF hospitalization^{8,32,33}. Similarly, regression of LVH by ECG or imaging with antihypertensive medications has been associated with a reduced risk of CVD events including HF^{10,34}. Although universal screening for LVH is not recommended due to the paucity of data on the value of ECG in assessing CVD risk³⁵, our findings suggest that wider availability of ECG may render it as an effective tool that can be employed for surveillance in high-risk populations such as those with albuminuria to identify participants in need of aggressive risk factor control. On the other hand, screening for albuminuria also represents a

scalable and cost-effective method to detect and prevent CVD but despite a promising marker for risk stratification, testing for spot albuminuria remains suboptimal in routine clinical care³⁶.

Therefore, regular screening of albuminuria especially in participants with diabetes mellitus and hypertension may prevent the progression of cardiorenal disease with early interventions³⁷.

Study Limitations and Strengths

Certain limitations of the study are the following: First, we only used baseline measurement of LVH and albuminuria and did not take into account their progression or regression during the follow-up period. Secondly, we lacked imaging data for LVH in SPRINT, accordingly ECG criteria which may be a less sensitive method than echocardiography or cardiac magnetic resonance⁵. However, LVH detected by ECG has similar prognostic value in predicting poor outcomes as LVH detected by imaging³⁸. Thirdly, overall fewer HF events and the exclusion of new outpatient HF as an endpoint event may limit the statistical power of the analysis. Fourthly, our results may not be generalizable to other populations who did not meet eligibility criteria for SPRINT such as individuals with diabetes mellitus, individuals with low CVD risk, prior stroke, <50 years old, and individuals residing in nursing homes or assisted living facilities. The strengths of our study include a large sample size from the well-designed clinical trial of a diverse population at high risk of CVD. The data variables were collected using standardized procedures in the context of a clinical trial with the central reading of ECGs blinded to the treatment assignment. Since ADHF was a component of the primary composite outcome, robust protocol-driven procedures were employed to ensure the validity of ADHF events in SPRINT.

Conclusion

In SPRINT, albuminuria and LVH are independent and additive predictors of ADHF, and the incidence and relative risk of ADHF increases with increasing levels of albuminuria, with the

highest risk in the presence of LVH than in the absence of it. The concomitant presence of LVH and albuminuria can potentially identify participants who need intensive disease management to prevent HF.

Clinical Perspective

Albuminuria and LVH are independent and additive predictors of ADHF and the relative risk of ADHF is progressively higher with increasing levels of albuminuria with a higher risk in the presence of LVH than in the absence of it. Albuminuria and LVH are both potentially modifiable risk factors as regression of these markers have been associated with reduced risk of future CVD including HF. Whether intensive blood pressure control and modification of neurohormonal activation with newly approved therapies would reduce the risk of ADHF among participants with concomitant albuminuria and LVH need to be tested in large clinical trials with longer-follow up.

Novelty And Relevance

What is New?

This is the first study to directly examine the interaction between albuminuria and LVH on ADHF outcome in participants with hypertension.

What is Relevant?

Albuminuria and LVH are additive predictors of ADHF, and the risk increases with increasing levels of albuminuria especially in those with concomitant LVH.

Clinical/Pathophysiological Implication?

Both albuminuria and LVH are potentially modifiable risk factors and regression of these markers have been associated with reduced risk of CVD outcomes including HF. Individuals

with concomitant albuminuria and LVH may need intensive surveillance and consideration of newer disease modifying therapies.

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Figure 1. Kaplan Meier Curves of Incident ADHF by Albuminuria and Left Ventricular Hypertrophy Status*

*LVH, left ventricular hypertrophy.

Figure 2. Incidence Rate of ADHF across UACR Categories Stratified by Left Ventricular Hypertrophy*

*UACR, urine albumin-creatinine ratio; ADHF, acute decompensated heart failure; LVH, left ventricular hypertrophy.

Table 1: Baseline Characteristics of Study Participants by Albuminuria and LVH Status

Characteristics	Albuminuria and LVH Status				p-value!
	(-) Albuminuria (-) LVH	(+) Albuminuria (-) LVH	(-) Albuminuria (+) LVH	(+) Albuminuria (+) LVH	
	(n= 5638)	(n= 1202)	(n= 1257)	(n= 414)	
Age (Years)	67± 9	67± 10	70± 10	69± 10	<.001
Women (%)	1851(32.8%)	359(29.8%)	616(49.0%)	196(47.3%)	<.001
Race (%)					<.001
<i>White</i>	3421(60.6%)	733(60.6%)	520(41.3%)	180(43.4%)	
<i>Black</i>	1476(26.1%)	339(28.2%)	606(48.2%)	192(46.3%)	
<i>Hispanic</i>	629(11.1%)	113(9.4%)	116(9.2%)	33(7.9%)	
<i>Other</i>	112(1.9%)	17(1.4%)	15(1.1%)	9(2.1%)	
Body mass index (kg/m²)	30.0± 5.7	29.9± 6.0	29.6± 5.9	29.2± 6.2	0.01
Systolic Blood Pressure (mm Hg)	137.8± 14.6	142.3± 15.8	142.8± 16.3	148.3± 19.0	<.001
Diastolic Blood Pressure (mm Hg)	77.8± 11.3	77.8± 13.0	78.9± 12.8	80.1± 14.1	<.001
Total Cholesterol (mg/dl)	190.6± 40.4	186.2± 41.7	193.8± 41.6	187.4± 45.2	<.001
Ever Smokers (%)	3136(55.6%)	711(59.1%)	665(52.9%)	235(56.7%)	0.01
Prevalent CVD (%)	1000(17.7%)	258(21.4%)	312(24.8%)	126(30.4%)	<.001
Number of BP Medications	1.7± 0.99	2.0± 1.0	2.0± 1.0	2.1± 1.1	<.001
Statin Therapy (%)	2446(43.6%)	581(48.6%)	491(39.4%)	191(46.5%)	<.001
Estimated GFR (ml/min/1.73 m²)	73.4± 19.0	63.7± 23.1	74.7 ±20.5	62.7± 24.8	<.001
Cornell Voltage Index μV	1358.5± 478.5	1382.9± 495.4	2301.0± 726.7	2474.0± 879	<.001
Sokolow-Lyon μV	2003.2± 622.7	2051.7± 630.1	2805.2± 1086.6	2876.6± 1102.0	<.001
Cornell voltage product mV*ms	147.3± 49.6	147.6± 50.2	287.2± 112.3	312.5± 135.0	<.001
UACR mg/g*	7.4 (5.0-12.2)	69 (41-157)	8.4 (5.4-13.9)	68.6 (41.8-158.9)	<.001
Intensive BP Arm (%)	2824 (50.0%)	606 (50.4%)	619 (49.2%)	203 (49.0%)	0.91

Continuous variables are presented as mean (standard deviation) and categorical variables as count (percentage).

¶p-value by ANOVA for continuous variable or chi-square for categorical variables

*UACR reported as median and 25-75th percentile.

ECG-LVG, electrocardiographic left ventricular hypertrophy; GFR, glomerular filtration rate; UACR, urine albumin creatinine ratio.

Table 2. Association of Albuminuria and LVH Categories with Incident ADHF

Albuminuria and LVH Categories	Events/Total	Model 1!	p-value	Model 2]	p-value
	n (%)	HR (95% CI)		HR (95%CI)	
(-) Albuminuria (-) LVH	70/5638 (1.2%)	<i>Ref</i>	-	<i>Ref</i>	-
(+) Albuminuria (-) LVH	48/1202 (3.9%)	2.50 (1.72-3.63)	<.001	2.04 (1.39-3.00)	<.001
(-) Albuminuria (+) LVH	28/1257 (2.2%)	1.78 (1.14-2.78)	0.01	1.47 (0.93-2.32)	0.09
(+) Albuminuria (+) LVH	36/414 (8.7%)	6.80 (4.51-10.2)	<.001	4.95 (3.22-7.62)	<.001

! Model 1 adjusted for age, sex, race, and randomization site.

]Model 2 adjusted for smoking, body mass index, systolic blood pressure, total cholesterol, prevalent clinical/subclinical CVD, statin use, number of antihypertensive agents, eGFR, treatment assignment.

Additive interaction p-value= 0.01. Relative excess risk due to interaction, 2.43; 95% confidence interval (CI): 0.53-4.33; p=0.01).

Proportion of disease attributable to interaction (AP)= 0.49 (95% CI: 0.23-0.74)

Synergy index (S)= 2.60 (95% CI: 1.26-5.33)

Multiplicative interaction p-value =0.11

Table 3. Effect of Intensive Blood Pressure Lowering on ADHF Stratified by Albuminuria and LVH combinations.

Albuminuria and LVH Categories	Standard SBP	Intensive SBP	HR (95% CI)	Interaction
	n (%)	n (%)	Intensive vs. Standard	p-value*
(-) Albuminuria (-) LVH	39/2814 (1.3%)	31/2824 (1.1%)	0.79 (0.49-1.26)	0.26
(+) Albuminuria (-) LVH	26/596 (4.3%)	22/606 (3.6%)	0.81 (0.45-1.43)	
(-) Albuminuria (+) LVH	20/638 (3.1%)	8/619 (1.3%)	0.39 (0.17-0.90)	
(+) Albuminuria (+) LVH	17/211 (8.0%)	19/203 (9.3%)	1.13 (0.59-2.18)	

*The p-value reflects the interaction between albuminuria/LVH combinations and intensive systolic blood pressure lowering on ADHF.

Table 4. Risk of ADHF by UACR Levels and LVH Groups

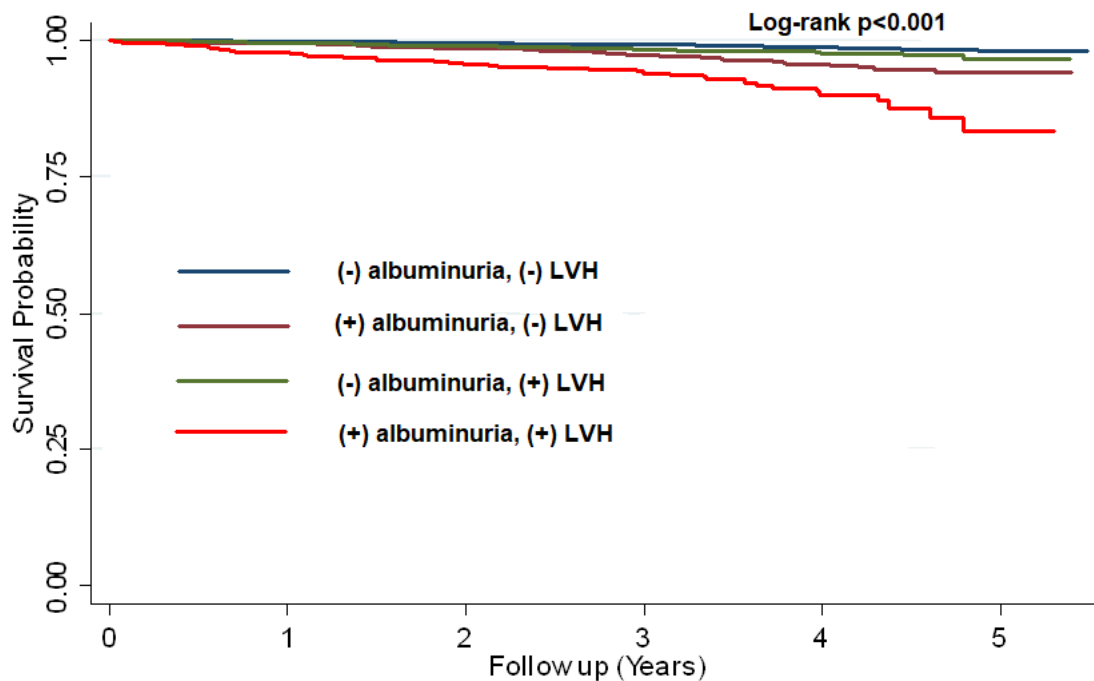
UACR and LVH Categories	Event/Total n (%)	Model 1! HR (95% CI)	p-value	Model 2 [‡] HR (95%CI)	p-value
UACR <10 mg/g and (-) LVH	35/3723 (0.94%)	<i>Ref</i>	-	<i>Ref</i>	-
UACR <10 mg/g and (+) LVH	35/1915 (1.8%)	1.64 (1.02-2.64)	0.03	1.53 (0.95-2.46)	0.07
UACR 10-29.9 mg/g and (-) LVH	8/739 (1.0%)	1.14 (0.52-2.47)	0.73	0.96 (0.44-2.08)	0.91
UACR 10-29.9 mg/g and (+) LVH	20/518 (3.8%)	3.63 (2.07-6.36)	<0.01	2.90 (1.63-5.16)	0.001
UACR 30-299.9 mg/g and (-) LVH	40/1037 (3.8%)	2.99 (1.89-4.75)	<.001	2.55 (1.59-4.09)	<.001
UACR 30-299.9 mg/g and (+) LVH	25/365 (7.0%)	6.65 (3.95-11.20)	<.001	4.92 (2.87-8.43)	<.001
UACR ≥300 mg/g and (-) LVH	8/165 (4.8%)	4.09 (1.89-8.85)	0.01	2.58 (1.12-5.95)	0.02
UACR ≥300 mg/g and (+) LVH	11/58 (18.9%)	24.8 (12.4-49.3)	<.001	17.9 (8.59-37.3)	<.001

! Model 1 adjusted for age, sex, race, and randomization site.

‡Model 2 adjusted for smoking, body mass index, systolic blood pressure, total cholesterol, prevalent clinical/subclinical CVD, statin use, number of antihypertensive agents, eGFR, and treatment assignment.

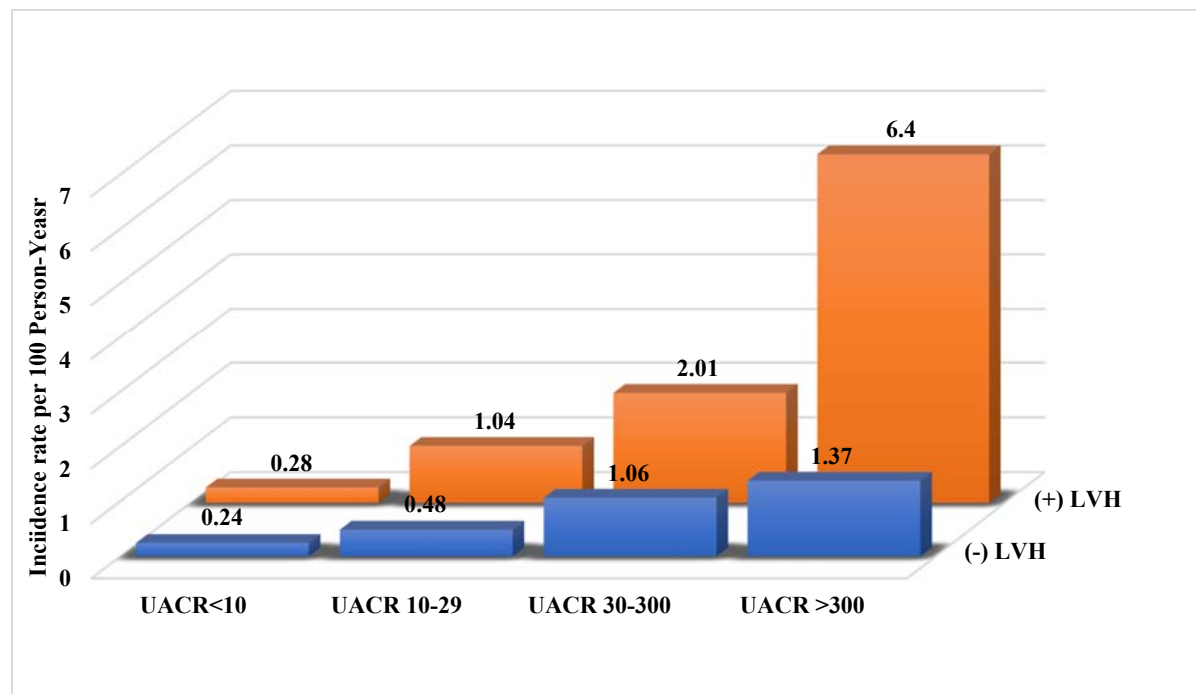
UACR; urine albumin-creatinine ratio; LVH; left ventricular hypertrophy.

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