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ORIGINAL RESEARCH

Lipoprotein(a), Oxidized Phospholipids, and Progression to Symptomatic Heart Failure: The CASABLANCA Study

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BACKGROUND: Higher lipoprotein(a) and oxidized phospholipid concentrations are associated with increased risk for coronary artery disease and valvular heart disease. The role of lipoprotein(a) or oxidized phospholipid as a risk factor for incident heart failure (HF) or its complications remains uncertain.

METHODS AND RESULTS: A total of 1251 individuals referred for coronary angiography in the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study were stratified on the basis of universal definition of HF stage; those in stage A/B (N=714) were followed up for an average 3.7 years for incident stage C/D HF or the composite of HF/cardiovascular death. During follow-up, 105 (14.7%) study participants in stage A/B progressed to symptomatic HF and 57 (8.0%) had cardiovascular death. In models adjusted for multiple HF risk factors, including severe coronary artery disease and aortic stenosis, individuals with lipoprotein(a) ≥150 nmol/L were at higher risk for progression to symptomatic HF (hazard ratio [HR], 1.90 [95% CI, 1.15–3.13]; *P*=0.01) or the composite of HF/cardiovascular death (HR, 1.71 [95% CI, 1.10–2.67]; *P*=0.02). These results remained significant after further adjustment of the model to include prior myocardial infarction (HF: HR, 1.89, *P*=0.01; HF/cardiovascular death: HR, 1.68, *P*=0.02). Elevated oxidized phospholipid concentrations were similarly associated with risk, particularly when added to higher lipoprotein(a). In Kaplan-Meier analyses, individuals with stage A/B HF and elevated lipoprotein(a) had shorter time to progression to stage C/D HF or HF/cardiovascular death (both log-rank *P*<0.001).

CONCLUSIONS: Among individuals with stage A or B HF, higher lipoprotein(a) and oxidized phospholipid concentrations are independent risk factors for progression to symptomatic HF or cardiovascular death.

REGISTRATION: URL: https://wwwclinicaltrials.gov; Unique identifier: NCT00842868.

Key Words: heart failure ■ lipoprotein(a) ■ outcomes

Lipoprotein(a) is a lipoprotein that consists of a lipid core and apolipoprotein B-100 (apoB-100) covalently attached to apolipoprotein(a). Apolipoprotein(a) consists of a variable number of repeating units, known as Kringle domains, which have high sequence homology to plasminogen. The combination of proatherogenic oxidized phospholipids (OxPL) present on lipoprotein(a) together with its potential prothrombotic properties is thought to contribute to the unique association between lipoprotein(a) and higher likelihood of atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve disease,[1] a relationship prompting pursuit of lipoprotein(a)-lowering strategies, now underway in large ASCVD outcome trials.

The recent universal definition and classification of heart failure (HF) defines 4 stages of the diagnosis, including those at risk for HF (stage A), those with pre-HF but no symptoms (stage B), and those with

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CLINICAL PERSPECTIVE

What Is New?

- Concentrations of lipoprotein(a) and associated oxidized phospholipids (apolipoprotein B and apolipoprotein[a]) are known to be proatherogenic and a risk for aortic stenosis, but this study reveals an association between lipoprotein(a) and oxidized phospholipid concentrations with risk for incident heart failure.
- Risk for heart failure associated with higher lipoprotein(a) and oxidized phospholipid remained even after adjusting for the presence and severity of coronary artery disease and the presence of valvular heart disease.

What Are the Clinical Implications?

- These results identify lipoprotein(a) and oxidized phospholipids as risk factors for heart failure, further extending the association of lipoprotein(a) and related phospholipids with cardiac damage.
- As therapies specifically lowering lipoprotein(a) are on the horizon, reduction in risk for heart failure may be an important possible benefit from such treatment.

Nonstandard Abbreviations and Acronyms

CASABLANCA	Catheter Sampled Blood Archive in Cardiovascular Diseases
OxPL	oxidized phospholipid

symptomatic HF (stages C/D).[2] For those with presymptomatic HF, although several factors have been suggested to increase the risk of progression to symptomatic HF disease, associations between higher lipoprotein(a) and progression to HF remain less established,[3] and an understanding of how OxPLs modify this risk is not known. In this study, among individuals with stage A/B HF referred for coronary angiography, we investigated the relationship between lipoprotein(a), OxPLs, and the risk of progression to symptomatic stages of HF.

METHODS

The authors declare that all supporting data are available within the article. All study procedures were approved by the Partners Healthcare Institutional Review Board, and all study participants signed informed consent before study enrollment.

Study Population

The design of the CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study has been described previously.[4] Between 2008 and 2011, 1251 patients referred for coronary or peripheral angiography for a variety of indications were enrolled. Two board-certified physicians adjudicated the cases for proper HF classification at baseline, according to the universal definition of HF, as described.[5] Before the angiographic procedure, 15 mL of blood was taken through a vascular access sheath. Study participants were followed up for incident HF events and cardiovascular death for a median of 3.7 years; end points were adjudicated as described.[4]

Lipoprotein(a) and OxPL Measurement

For this study, the measurement of lipoprotein(a) was conducted with a modification to a newly developed and validated isoform-independent immunoassay technique.[6] Instead of using horseradish peroxidase–modified LPA-KIV9, a biotin-modified LPA-KIV9 monoclonal antibody was used. For the purpose of this study, elevated lipoprotein(a) was defined as lipoprotein(a) ≥150 nmol/L (≈70 mg/dL),[7] consistent with the inclusion criteria of an ongoing clinical trial of lipoprotein(a) lowering (NCT04023552).

OxPLs associated with apoB-100 and apolipoprotein(a) were quantified via immunoassay, as described.[8,9] Units are reports as nmol/L of phosphocholine equivalents of phosphocholine-containing oxidized phospholipids. The median split for each OxPL was used for analyses.

Statistical Analysis

Continuous variables are presented as mean (SD) and median (quartile 1–quartile 3), and counted categorical variables are presented as count (frequency). For statistical comparisons, we used the χ^2 test for categorical variables, the Wilcoxon rank-sum test for nonnormally distributed continuous variables, and the *t*-test for normally distributed continuous variables. These comparison tests were used to assess the differences in baseline characteristics between patients with normal lipoprotein(a) levels and those with elevated lipoprotein(a) levels.

To better understand prognostic associations between lipoprotein(a) and outcomes, cubic spline curves were assembled showing the unadjusted association between continuous $\log_{(2)}$ lipoprotein(a) level with incident HF and incident HF/cardiovascular death. Furthermore, adjusted Cox proportional hazards regression was used to assess the association between elevated lipoprotein(a) concentrations and risk of HF and HF/cardiovascular death during

follow-up. Covariates incorporated included age, sex, hypertension, diabetes, smoking, prevalent atrial fibrillation/flutter, chronic kidney disease, total cholesterol/high-density lipoprotein ratio, concentrations of high-sensitivity CRP (C-reactive protein), and presence of severe ASCVD, defined by angiographic severity at the time of index angiogram. Sensitivity analyses were performed, incorporating history of myocardial infarction into the models, and exclusion of those with severe aortic valve disease. Hazard ratios (HRs) and 95% CIs were reported to predict risk for events in those with a lipoprotein(a) ≥150 nmol/L and in those with OxPL greater than median concentration. Last, Kaplan-Meier survival plots were constructed to evaluate time to first HF event and time to first HF event or cardiovascular death in those with lipoprotein(a) ≥150 nmol/L or OxPLs greater than median versus lower concentrations and compared using the log-rank test.

All *P* values reported were 2 sided, and $P<0.05$ was considered statistically significant. We conducted all statistical analyses using R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

RESULTS

Study Population

After excluding patients without lipoprotein(a) measurement (n=153) and those with already established stage C/D HF (n=384), the final study cohort for this analysis consisted of 714 patients with stage A/B HF. Notably, the median (quartile 1–quartile 3) lipoprotein(a) was slightly higher in those with stage C/D HF compared with those with stage A/B HF (30.5 [13.6–98.7] versus 24.9 [10.8–79.9] nmol/L; *P*=0.04). In contrast, there was no difference between stages C/D versus A/B in terms of OxPL apoB-100 (3.99 [2.79–9.14] versus 3.72 [2.68–8.03] nmol/L; *P*=0.14) or OxPL apolipoprotein(a) (11.85 [4.86–39.99] versus 11.49 [4.42–36.00] nmol/L; *P*=0.27). There were also no other significant differences in other baseline lipid measurements between those with and without overt HF.

Among the 714 individuals with stage A/B HF included in this study, 506 (70.9%) were men, and most were White race (92.3%; Table). The mean±SD age of study participants was 65±11 years. Individuals with lipoprotein(a) levels ≥150 nmol/L had several differences at baseline indicating more extensive ASCVD and previous revascularization, but they were not more likely to have severe aortic valve disease. Notably, most study participants were receiving lipid lowering in the form of a statin, with a slightly higher percentage of those with elevated lipoprotein(a) receiving such therapy; the median (quartile 1–quartile 3) low-density lipoprotein (LDL) cholesterol in those with and without elevated lipoprotein(a) was accordingly suppressed, at 79 (interquartile range, 61–101) and 82 (interquartile range, 66–104) mg/dL, respectively.

Outcomes

Over a median follow-up of 3.7 years, 105 individuals (14.7%) progressed to symptomatic HF. In cubic spline analyses (Figure 1), a continuous risk was present between lipoprotein(a) and risk for HF events, such that in parallel with more elevated $\log_2$ concentrations of lipoprotein(a), risk for progression to adjudicated stage C/D HF or the composite of HF/cardiovascular death also increased. In a similar manner, higher concentrations of OxPL apoB-100 and OxPL apolipoprotein(a) were associated with more elevated risk for HF events (Figure 2).

Among the 105 individuals progressing to symptomatic HF, 22 (21%) had a lipoprotein(a) ≥150 nmol/L. Using this lipoprotein(a) cut point (Figure 3) in multivariable models (adjusted for age, sex, hypertension, diabetes, smoking, atrial fibrillation, chronic kidney disease, prevalent ASCVD at index angiogram, total cholesterol/high-density lipoprotein cholesterol ratio, severe aortic valve stenosis, and high sensitivity CRP), study participants in stage A/B with lipoprotein(a) ≥150 nmol/L were at higher risk of new-onset symptomatic HF (HR, 1.90 [95% CI, 1.15–3.13]; *P*=0.01) or the composite of HF hospitalization/cardiovascular death (HR, 1.71 [95% CI, 1.10–2.67]; *P*=0.02). These results remained significant after further expanding the model to control for prior myocardial infarction (new-onset HF: HR, 1.89, *P*=0.01; new-onset HF/cardiovascular death: HR, 1.68, *P*=0.02), adding LDL cholesterol and triglycerides (new-onset HF: HR, 1.99, *P*=0.03; new-onset HF/cardiovascular death: HR, 1.76, *P*=0.04), or adding prevalent statin use at baseline (new-onset HF: HR, 1.87, *P*=0.02; new-onset HF/cardiovascular death: HR, 1.67, *P*=0.02). Similarly, excluding those with severe aortic stenosis did not materially change the HRs for either outcome (HR, 1.93 and 1.73, respectively).

The median OxPL apoB-100 was 3.63 (2.66–6.90) nmol/L, whereas the median OxPL apolipoprotein(a) was 9.81 (3.97–36.34) nmol/L. Among those progressing to HF events, concentrations were above the median for OxPL apoB-100 in 25.7%, and for OxPL apolipoprotein(a) in 24.8%. Adding supramedian results for each OxPL to the fully adjusted model resulted in increase of the HR for lipoprotein(a) to predict HF (when elevated OxPL apoB-100 added: 3.97 [95% CI, 1.63–9.64], *P*=0.002; when elevated OxPL apolipoprotein(a) added: 2.90 [95% CI, 1.28–6.54], *P*=0.01) and for HF/cardiovascular death (when elevated OxPL apoB-100 added: 3.03 [95% CI, 1.44–6.36], *P*=0.004;

Table. Baseline Characteristics of Study Population With Stage A/B HF Stratified by Lipoprotein(a) Level

Characteristic	Lipoprotein(a) <150 nmol/L (N=616)	Lipoprotein(a) ≥150 nmol/L (N=98)	*P* value
Age, mean±SD, y	64.8±11.2	65.6±11.3	0.53
Sex, n (%)			0.99
Male	436 (70.8)	70 (71.4)	
Female	180 (29.2)	28 (28.6)	
Race or ethnicity, n (%)			0.68
White	566 (91.9)	93 (94.9)	
Black	13 (2.1)	3 (3.1)	
Asian	8 (1.3)	0 (0.0)	
Hispanic	16 (2.6)	1 (1.0)	
Native American	1 (0.2)	0 (0.0)	
Others*	12 (1.9)	1 (1.0)	
Medical conditions			
Hypertension, n (%)	445 (72.2)	75 (76.5)	0.45
Diabetes, n (%)	156 (25.3)	24 (24.5)	0.96
Dyslipidemia, n (%)	408 (66.3)	75 (76.5)	0.06
CAD, n (%)	300 (48.7)	57 (58.2)	0.10
CKD, n (%)	63 (10.2)	8 (8.2)	0.65
Smoking, n (%)	111 (18.0)	12 (12.2)	0.21
Atrial fibrillation, n (%)	71 (11.5)	8 (8.2)	0.42
CVA/TIA, n (%)	61 (9.9)	7 (7.1)	0.50
PCI, n (%)	170 (27.6)	33 (33.7)	0.26
CABG, n (%)	91 (14.8)	25 (25.5)	0.01
BMI, mean±SD, kg/m^2	28.86±5.56	29.42±5.57	0.36
Severe AS, n (%)	15 (2.4)	2 (2.0)	0.29
HF stages, n (%)			0.69
Stage A	62 (10.1)	8 (8.2)	
Stage B	554 (89.9)	90 (91.8)	
Medications, n (%)			
ACEi	243 (39.5)	39 (39.8)	1.00
ARB	78 (12.7)	12 (12.2)	1.00
BB	419 (68.1)	69 (70.4)	0.74
AA	18 (2.9)	4 (4.1)	0.77
Loop diuretic	57 (9.3)	9 (9.2)	1.00
Nitrates	110 (17.9)	28 (28.6)	0.02
CCB	162 (26.4)	23 (23.5)	0.63
Aspirin	490 (79.7)	80 (81.6)	0.75
Statin	446 (72.6)	83 (84.7)	0.02
Clopidogrel	161 (26.2)	24 (24.5)	0.82
Extent of atherosclerosis, n (%)			
Angiographic stenosis >70%			
1 Vessel	183 (29.7)	16 (16.3)	<0.001
2 Vessels	94 (15.3)	19 (19.4)	
3 Vessels	52 (8.4)	22 (22.4)	
Lipoprotein(a), median (Q1–Q3), nmol/L	20.4 (9.4–49.0)	216.4 (180.9–270.2)	
Total cholesterol, median (Q1–Q3), mg/dL	150 (126–179)	155 (135–179)	0.26
HDL cholesterol, median (Q1–Q3), mg/dL	42 (34–52)	46 (36–57)	0.01
Total cholesterol/HDL ratio, median (Q1–Q3)	3.4 (2.8–4.4)	3.3 (2.7–4.3)	0.23
Triglycerides, median (Q1–Q3), mg/dL	116 (85–159)	102 (74–145)	0.05

(*Continued*)

Table 1. Continued

Characteristic	Lipoprotein(a) <150 nmol/L (N=616)	Lipoprotein(a) ≥150 nmol/L (N=98)	*P* value
LDL cholesterol, median (Q1–Q3), mg/dL	79 (61–101)	82 (66–104)	0.22
hs-CRP, median (IQR), mg/L	2.4 (1.0–5.2)	2.4 (1.1–5.9)	0.92

An elevated lipoprotein(a) value was ≥150 nmol/L. AA indicates aldosterone antagonist; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; BB, beta blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; CVA, cerebrovascular disease; HDL, high-density lipoprotein; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; Q1, quartile 1; Q3, quartile 3; and TIA, transient ischemic attack.

*Others include Pacific Islander/Alaskan Native.

when elevated OxPL apolipoprotein(a) added: 1.92 [95% CI, 0.98–3.75], *P*=0.06).

In Kaplan-Meier analyses, study participants with stage A/B HF and elevated lipoprotein(a) had shorter time to progression to symptomatic stage C/D HF over 3.7 years of follow-up and shorter time to HF events or cardiovascular death (both log-rank *P*<0.001; Figure 4). Notably, Kaplan-Meier curves for these events continued to separate over time. Despite association between greater risk in those with higher lipoprotein(a), when analyzed as a stand-alone risk predictor, supramedian concentrations of OxPLs were not associated with shorter time to first events (Figure 5).

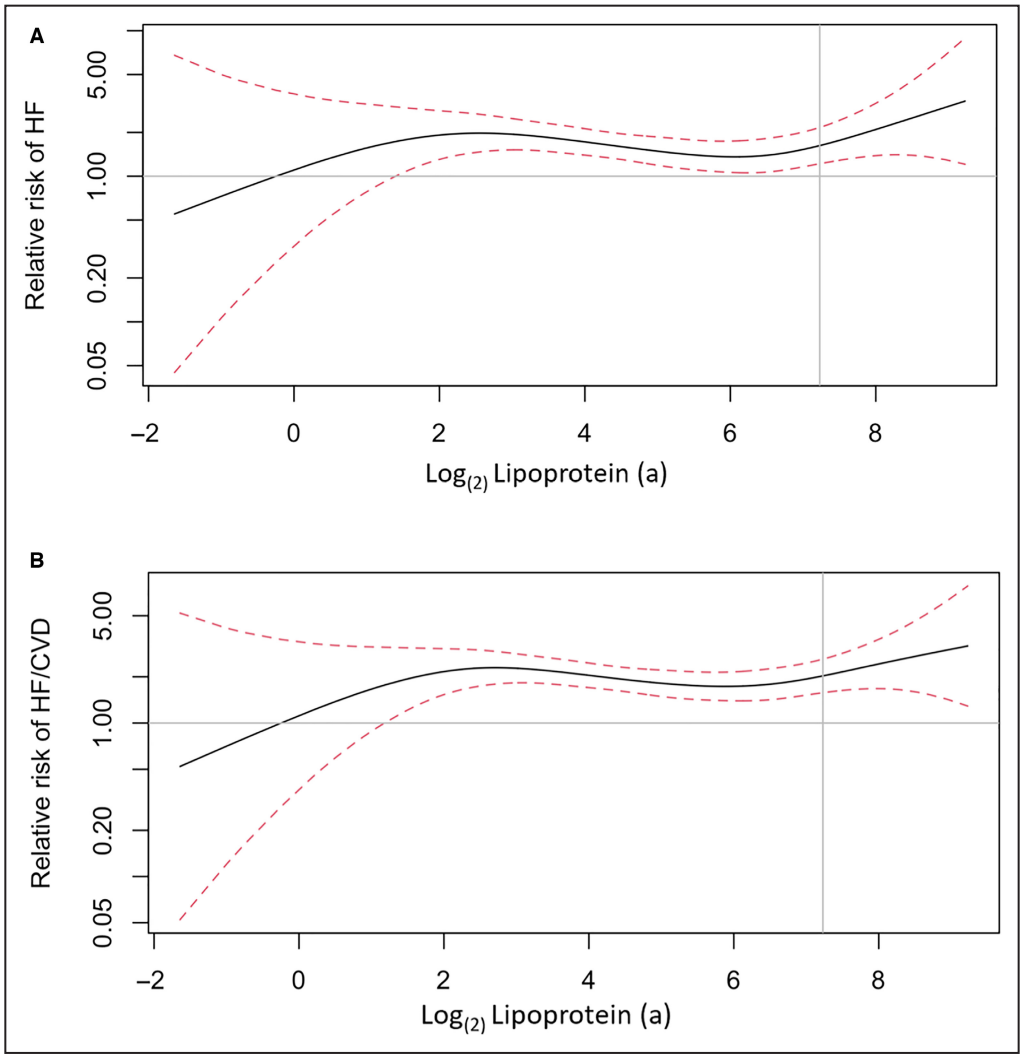

Figure 1. Cubic spline modeling analysis showed a nonlinear association between Lp(a) and risk of incident HF (A) or incident HF/CVD death (B).
Study participants with higher Lp(a) concentrations had higher relative risk for HF-related events. The gray line indicates the concentration of Lp(a) ≥150 nmol/L. CVD indicates cardiovascular disease; HF, heart failure; and Lp(a), lipoprotein(a).

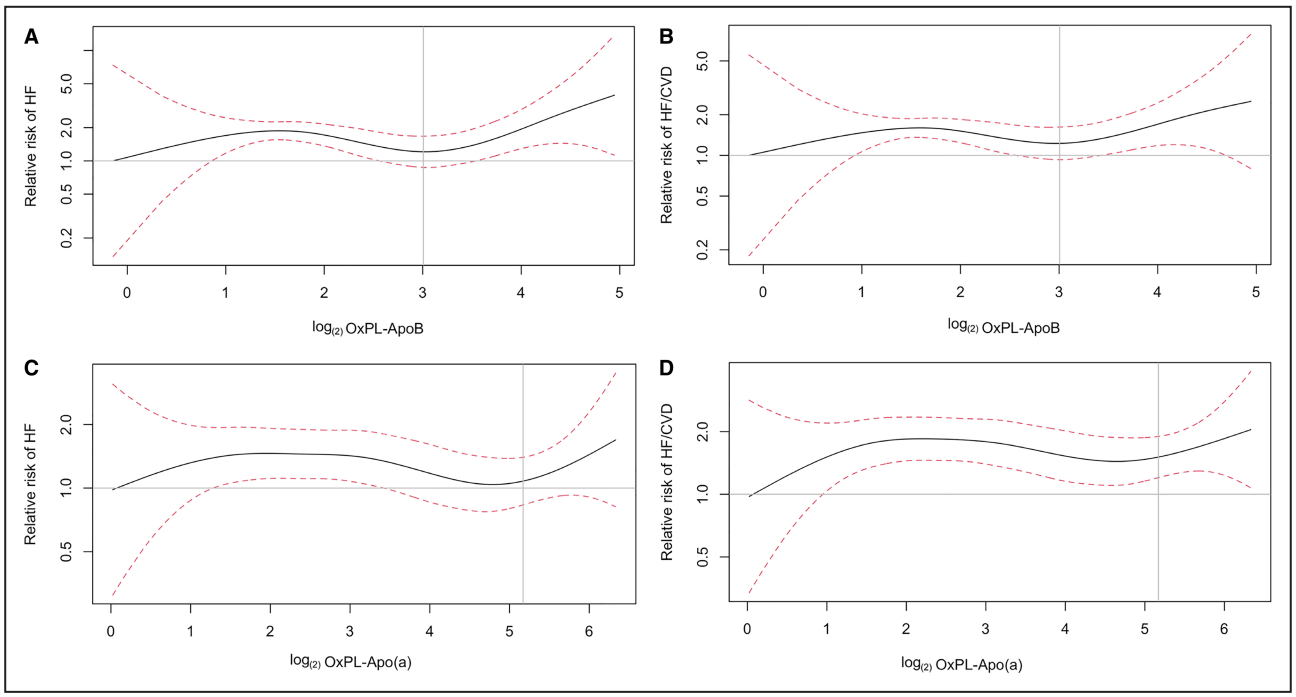

Figure 2. Cubic spline modeling analysis showed a nonlinear association between OxPLs and risk of incident HF or incident HF/CV death.

A and **B**, OxPL ApoB. **C** and **D**, OxPL Apo(a). Study participants with higher OxPL concentrations had generally higher relative risk for HF-related events. The gray line indicates the concentration corresponding to the median split for each OxPL. Apo(a) indicates apolipoprotein(a); ApoB, apolipoprotein B-100; CV, cardiovascular; HF, heart failure; and OxPLs, oxidized phospholipids.

DISCUSSION

In this study of people with prevalent ASCVD who underwent angiographic procedures prospectively followed up for a median of 3.7 years and evaluated with formal adjudication, study participants in HF stage A/B with elevated lipoprotein(a) or OxPLs associated with apoB-100 or apolipoprotein(a) remained at higher risk of progression to stage C/D HF or HF hospitalization/cardiovascular death after adjustment for conventional HF risk factors over an average of 4 years of follow-up. These findings suggest that there may be an important role of elevated lipoprotein(a) and related OxPLs in development of HF and its complications.

Limited data exist on the association between lipoprotein(a) and related OxPLs with risk for onset of HF. In this study, spline analyses suggest the risk for HF increases with even modest elevation of lipoprotein(a), although higher risk for HF events clearly existed at more elevated concentrations. Kamstrup and Nordestgaard[3] showed that higher lipoprotein(a) concentrations were independently associated with higher risk of developing new-onset HF; in that study, a lipoprotein(a) concentration >68 mg/dL was associated with similar HR for HF complications as a lipoprotein(a) of ≥150 nmol/L (corresponding to ≈70 mg/dL) in the present study. This threshold also corresponds to the concentration used for inclusion in trials of therapeutic lipoprotein(a) lowering.[10] Nonetheless, as it appears to be a continuous risk marker, lower lipoprotein(a) values may be associated with incident HF risk; indeed, although the risk was considerably higher at more elevated values, nearly 80% of study participants proceeding to overt HF had lipoprotein(a) values <150 nmol/L. Understanding optimal thresholds for lipoprotein(a)-based HF prediction will be important as therapeutic interventions for lipoprotein(a) lowering may have direct benefits to lower HF risk.

The higher risk associated with lipoprotein(a) in the context of elevated OxPLs is entirely novel. The OxPL apoB-100 and OxPL apolipoprotein(a) values in this study are typical of patients with cardiovascular diseases, as documented in multiple studies.[11] It is striking to note the higher HRs when combining elevation of either OxPL together with elevated lipoprotein(a). Whether this suggests additive risk in those with higher concentrations of both particles remains uncertain but bears further evaluation. What is noteworthy is that elevated OxPL alone did not have discrimination for events, suggesting the combination of higher lipoprotein(a) with elevated OxPLs is necessary to drive risk for HF events.

Mechanistically, links between lipoprotein(a) and related OxPLs with progression to symptomatic HF may

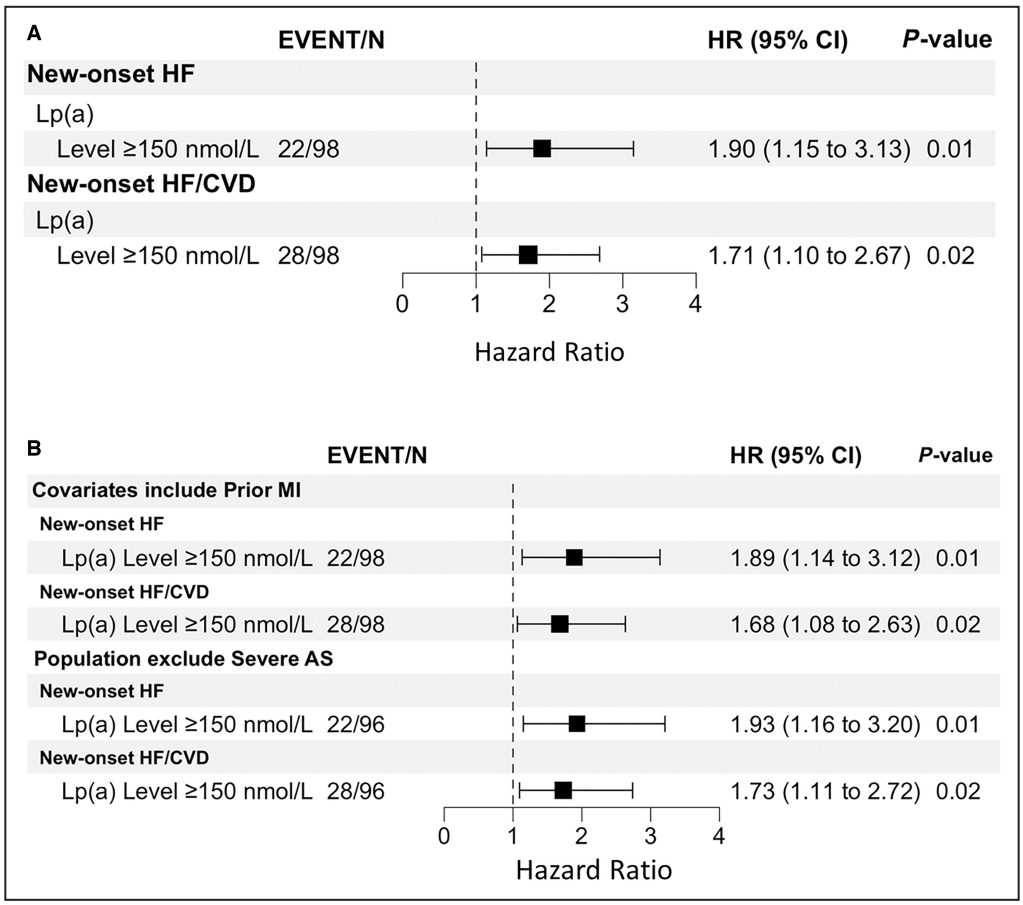

Figure 3. Forest plot indicating adjusted risk associated with elevated Lp(a) concentrations.
A, In models adjusted for relevant covariates, an Lp(a) ≥150 nmol/L was independently associated with progression from stage A/B HF to symptomatic stages, and was similarly prognostic for HF/CVD death. **B**, In sensitivity analyses, an elevated Lp(a) remained prognostic even when including both severe coronary artery disease and prior myocardial infarction in the model or when excluding those with severe AS at baseline. HR indicates hazard ratio. AS indicates aortic stenosis; CVD, cardiovascular disease; HF, heart failure; and Lp(a), lipoprotein(a).

derive from advancing coronary artery or valvular heart disease, with lipoprotein(a) implicated in both these processes.[1] Importantly, an association between lipoprotein(a) and severe aortic valve disease at baseline was not evident in this study, which may involve the specific population enrolled herein. This cohort did have significant associations between lipoprotein(a), OxPLs, and likelihood for severe coronary artery disease as well as risk for major adverse cardiovascular events (coronary revascularization, nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), as we have previously reported.[6] Among those with higher lipoprotein(a) in this cohort of individuals with stage A/B HF, there was more extensive coronary artery disease and a higher likelihood for prior surgical revascularization, although the association between higher lipoprotein(a) and HF events here persisted even after adjusting for coronary artery disease presence/severity, prior ischemic events, and known valve disease. This raises the possibility of direct effect of elevated lipoprotein(a) or OxPLs on the myocardium.

Recent data have implicated higher lipoprotein(a) concentrations as a cause of subclinical interstitial and replacement myocardial fibrosis, along with left atrial and left ventricular cardiac remodeling; these findings were independent of age, sex, race, ethnicity, or traditional risk factors, including presence/severity of coronary atherosclerosis.[12] Supporting this, Fasolo and colleagues recently reported that elevated concentrations of lipoprotein(a) stimulate production of a long noncoding RNA with profibrotic effects in numerous organs, including the heart[13]; interestingly, this effect was driven by the content of OxPL, which was documented by using apolipoprotein(a) constructs lacking OxPL that did not elicit myocardial infarction associated transcript upregulation. OxPLs are proinflammatory[11] and may induce fibrosis in several organs. Such fibrosis was ameliorated in transgenic mice that

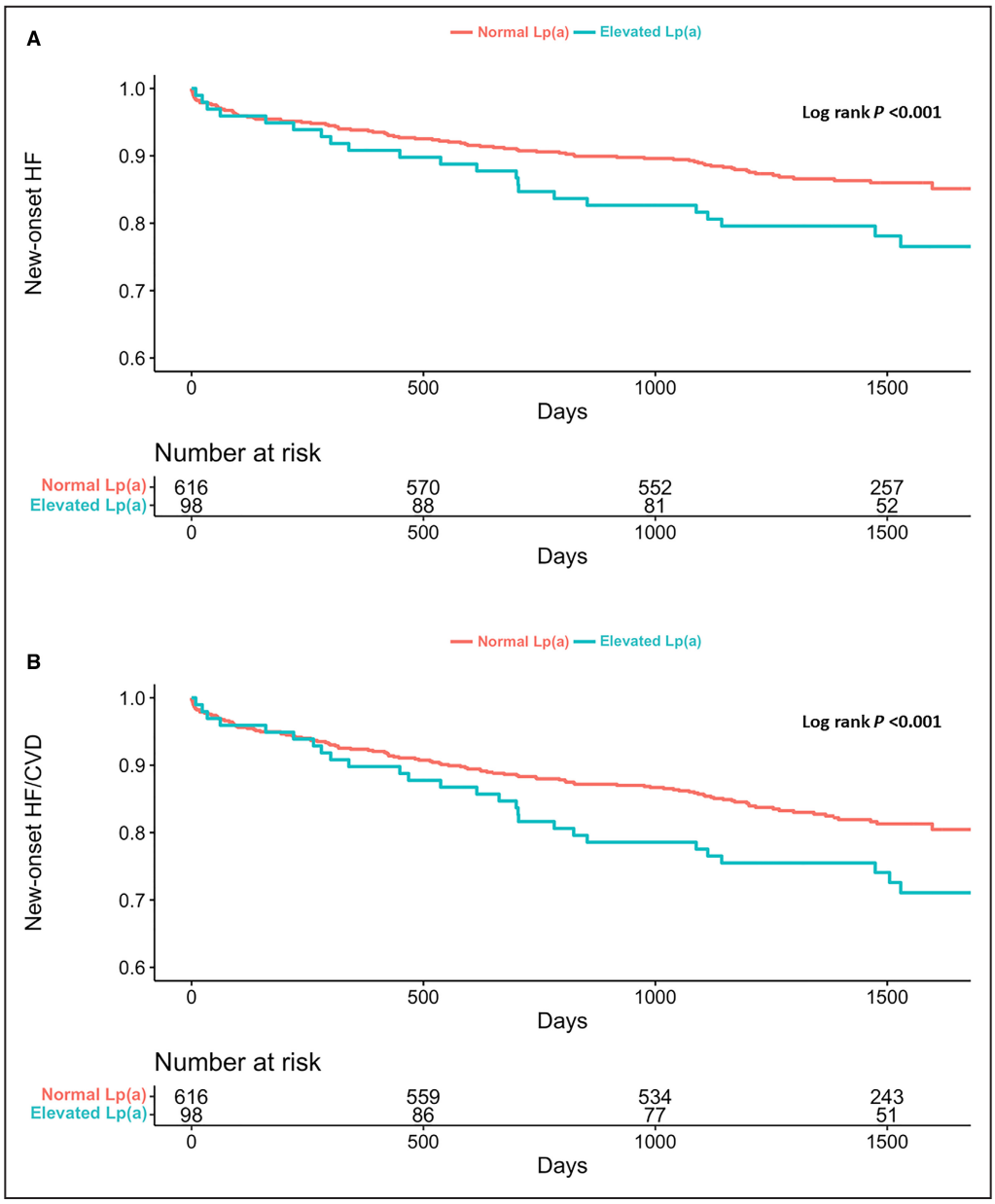

Figure 4. Kaplan-Meier curves demonstrating time to onset of symptomatic HF (A) or onset of symptomatic HF/CVD death (B) during follow-up in those as a function of elevated Lp(a) (150 nmol/L).
CVD indicates cardiovascular disease; HF, heart failure; and Lp(a), lipoprotein(a).

express the natural murine monoclonal antibody that binds a variety of OxPLs or by AV8-induced expression of scFv-E06.[14] Clinically, OxPLs may be delivered to the myocardium on lipoprotein(a), or they may be additionally generated in other lipoproteins, apoptotic cells, and microparticles with consequent diffusion into the myocardium. Generation of OxPLs in the context of myocardial ischemia is also a potential mechanism as OxPLs are also generated within cardiomyocytes during ischemia/reperfusion.[15] Taken together, it is reasonable to suggest lipoprotein(a) as a unique risk factor for tissue damage involving not just the vasculature through acceleration of atherosclerosis but also via direct tissue damage in the heart valves and myocardium; this may be mediated by OxPL concentrations associated with lipoprotein(a); however, this bears further scrutiny.

The results of this analysis extend the potential value from therapies to lower lipoprotein(a) and may help inform results from ongoing clinical trials targeting lipoprotein(a). PCSK9 (proprotein convertase subtilisin/kexin type 9) indirectly lowers lipoprotein(a) through

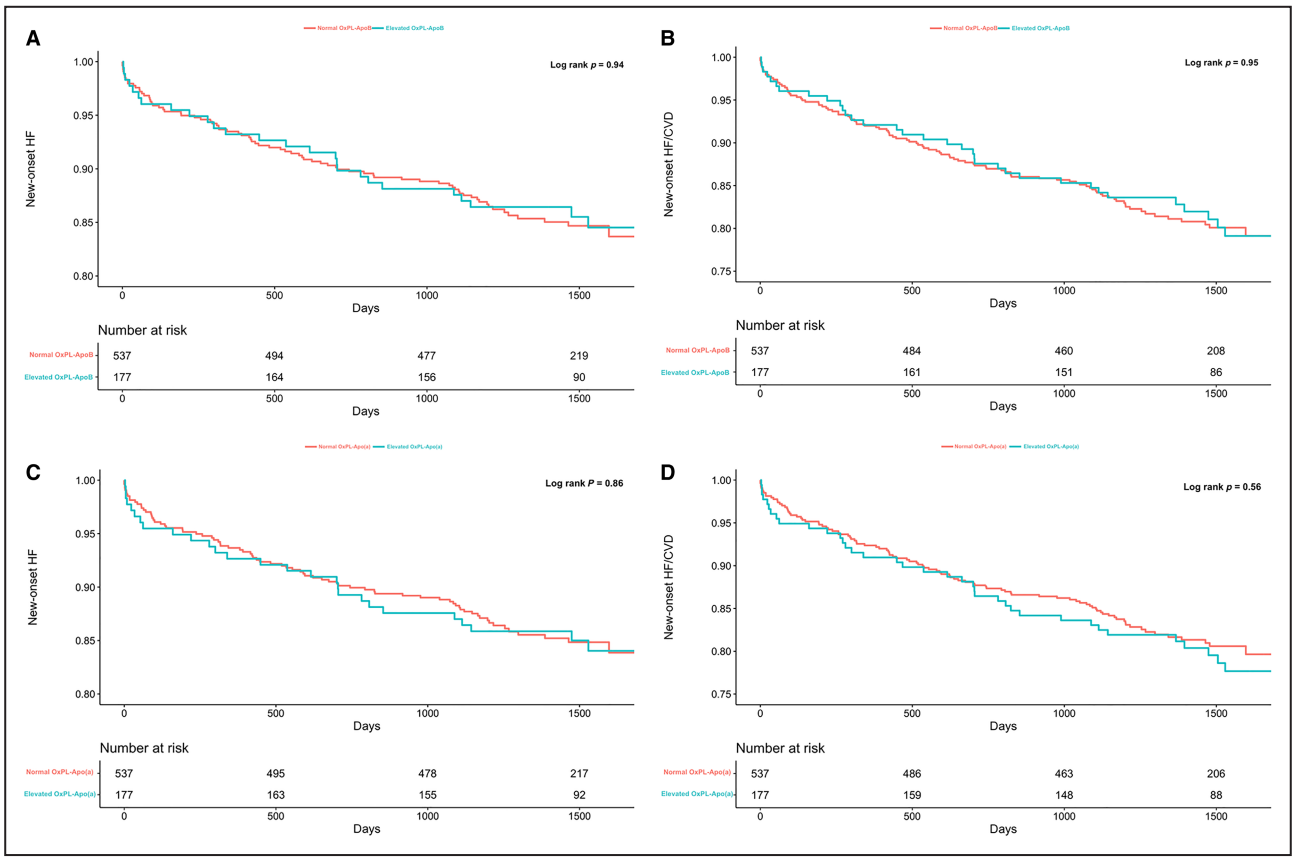

Figure 5. Kaplan-Meier curves demonstrating time to onset of symptomatic HF or symptomatic HF/CVD death during follow-up in those as a function of supramedian concentrations of OxPL ApoB (A and B) or OxPL Apo(a) (C and D).
Apo(a) indicates apolipoprotein(a); ApoB, apolipoprotein B-100; CVD, cardiovascular disease; HF, heart failure; Lp(a), lipoprotein(a); and OxPL, oxidized phospholipid.

profound reduction of LDL cholesterol, typically by ≈20% to 25%. In a post hoc analysis of the large ODYSSEY trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) in individuals with recent acute coronary syndrome and average LDL cholesterol of 70 mg/dL, those treated with alirocumab experienced a modest reduction in lipoprotein(a) when compared with placebo; only those with higher lipoprotein(a) at baseline had a reduction in major adverse cardiovascular events during follow-up.[16] HF was not reported as an outcome in this analysis or the primary ODYSSEY trial report. Although these results support the expectation of reduced cardiovascular events from therapies with even more potent ability to reduce lipoprotein(a),[10] the impact on the risk for HF remains uncertain. The data presented here suggest it is reasonable to hypothesize benefits from potent lowering of lipoprotein(a) might include prevention of progression to HF, whether through an impact on ASCVD events, myocardial changes, or alteration in valvular function. Dedicated studies focused on how lipoprotein(a) lowering might prevent incident HF events are needed, particularly given the high and increasing projected prevalence of HF in upcoming decades.[17] Moreover, given elevated lipoprotein(a) as a genetic, lifelong condition, the potential impact on HF outcomes in those with early stage A/B HF issues, as studied here, may be especially relevant.

Our results should be interpreted in the presence of several limitations. First, most of the CASBLANCA study population was White race. This is important because the concentration of lipoprotein(a) is largely influenced by genetics, with some amount of racial variation.[18] Therefore, our findings may not be applicable to individuals of other races and ethnicities. Furthermore, we do not have serial measures of lipids, lipoprotein(a), or OxPLs over time, including at the time of HF onset. Still, the prevalent use of statins and substantial suppression of LDL cholesterol in this study makes substantial temporal LDL variation less likely. Similarly, lipoprotein(a) has relatively low biological variation over time, with single measurements providing most prognostic information.[19] We provide continuous spline analyses but also analyzed the prognostic

meaning of lipoprotein(a) and OxPLs using dichotomization. Although dichotomy lowers the meaning of values at extremes (low and high), its use provides clinical relevance and identifies cut points to be explored in future studies. Although OxPLs were predictive of events in Cox modeling, in time-to-event analyses, concentrations above the median were not obviously associated with shorter time to first HF event. More data are needed about optimal thresholds for OxPL use. Finally, although the study participants in the CASABLANCA study were exhaustively characterized, it nonetheless remains a small sample size.

In conclusion, among individuals with stage A/B HF, those with elevated lipoprotein(a) and associated OxPLs were at higher risk of progression to symptomatic HF or the composite of HF and cardiovascular death (a joint end point often used in clinical trials of HF therapies). The risk from elevated lipoprotein(a) and elevated OxPL apoB-100 or OxPL apolipoprotein(a) was present even when adjusting for presence of important atherothrombotic risk factors, including extent of coronary artery disease, prior myocardial infarction, valve disease, and other factors associated with HF onset risk. These results suggest an independent role for lipoprotein(a) and related OxPLs for causing heart damage leading to HF. Whether lowering of lipoprotein(a) concentrations might be expected to avert progression to symptomatic HF or its complications requires further study, including clinical trials of lipoprotein(a) lowering in trials evaluating HF outcomes.

ARTICLE INFORMATION

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