Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population

Pia R. Kamstrup, MD, PhD,*†‡ | Børge G. Nordestgaard, MD, DMSc,*§

ABSTRACT

OBJECTIVES This study sought to test whether elevated lipoprotein(a) levels and corresponding LPA risk genotypes (low number of kringle IV type 2 repeats, rs3798220 and rs10455872, minor allele carriers) are associated with an increased risk of heart failure (HF).

BACKGROUND Elevated lipoprotein(a) levels represent a genetically determined risk factor for myocardial infarction (MI) and aortic valve stenosis (AVS). It is presently unknown whether elevated lipoprotein(a) levels also cause heart failure (HF).

METHODS We combined 2 general population studies, the Copenhagen City Heart Study (n = 10,855) and the Copenhagen General Population Study (n = 87,242), which totaled 98,097 Danish participants, of whom 4,122 were diagnosed with HF (1976 to 2013). We conducted observational and genetic instrumental variable analyses in a Mendelian randomization study design, assessing evidence of causality, and we performed mediation analyses.

RESULTS Elevated lipoprotein(a) levels were associated with multivariable adjusted hazard ratios for HF of 1.10 (95% CI: 0.97 to 1.25) for the 34th to 66th percentiles (8 to 19 mg/dl), 1.24 (95% CI: 1.08 to 1.42) for the 67th to 90th percentiles (20 to 67 mg/dl), 1.57 (95% CI: 1.32 to 1.87) for the 91st to 99th percentiles (68 to 153 mg/dl), and 1.79 (95% CI: 1.18 to 2.73) for levels >99th percentile (>153 mg/dl) versus levels <34th percentile (<8 mg/dl) (trend, p < 0.001), corresponding to a population-attributable risk of 9%. By combining all LPA risk genotypes, instrumental variable analysis yielded a genetic relative risk for HF of 1.18 (95% CI: 1.04 to 1.34) per 10-fold higher lipoprotein(a) levels, which was comparable to the corresponding observational hazard ratio of 1.22 (95% CI: 1.11 to 1.35). Upon exclusion of participants diagnosed with MI or AVS, risk estimates were attenuated. Accordingly, 63% (95% CI: 45% to 99%) of HF risk was mediated via MI and AVS combined.

CONCLUSIONS Elevated lipoprotein(a) levels and corresponding LPA risk genotypes were associated with an increased risk of HF consistent with a causal association. The association appeared to be partly mediated by MI and AVS.

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Heart failure (HF) affects 1% to 2% of the adult population in developed countries, with the prevalence rising to >10% in individuals aged 70 years or older (1). In ageing populations, HF represents an increasingly common cause of morbidity and mortality despite advances in clinical care (1–3). Risk factors for HF are diverse, reflecting different underlying causes, of which coronary artery disease and myocardial infarction (MI), with contributions from hypertension...
and diabetes, are the most common in Western societies (1,3).

Elevated lipoprotein(a) levels are considered a genetically determined causal risk factor for coronary heart disease (4–9), and as recently shown, for aortic valve stenosis (AVS) (10–12). However, it is unknown whether elevated lipoprotein(a) levels also contribute to the incidence of HF. Clarification of this issue may advance our understanding of the underlying causes of HF and ultimately lead to improved preventive and treatment strategies.

Lipoprotein(a) is a unique lipoprotein consisting of a cholesterol-laden, low-density lipoprotein-like particle bound to a large plasminogen-resembling glycoprotein, apolipoprotein(a) (4). Plasma levels of lipoprotein(a) are primarily genetically determined by polymorphisms in the LPA gene coding for apolipoprotein(a). The kringle IV type 2 (KIV-2) repeat polymorphism is particularly important; it determines apolipoprotein(a) size that correlates inversely with plasma lipoprotein(a) levels (4–6). In addition, a number of single nucleotide polymorphisms (SNPs) partly tracking the KIV-2 polymorphism are also strongly associated with plasma lipoprotein(a) levels (5,7,8).

METHODS

PARTICIPANTS. The CCHS is a general population study initiated in 1976 to 1978 with follow-up examinations in 1981 to 1983, 1991 to 1994, and 2001 to 2003 (17). Participants were randomly selected to reflect the adult population of Copenhagen. Examinations included a self-administered questionnaire, reviewed by an investigator on the day of attendance, a physical examination, and blood sampling. For the present study, we included all CCHS participants of Danish descent with a lipoprotein(a) measurement and/or LPA genotype as obtained at the 1991 to 1994 or 2001 to 2003 examination (n = 10,855); 96% had both lipoprotein(a) measurements and genotypes (Online Figure 1).

The CGPS is a general population study initiated in 2003 and is still recruiting (18). Participants of Danish descent were randomly selected to reflect the adult population of the greater Copenhagen area. Data collection is almost identical to that of the CCHS. For the present study, we included all participants with an available lipoprotein(a) measurement and/or LPA genotype (total, n = 87,242); lipoprotein(a) measurements were available for 38,719 participants, LPA KIV-2 genotype for 69,706 participants, rs3798220 genotype for 69,182 participants, and rs10455872 genotype for 69,158 participants (Online Figure 1).

We followed all CCHS and CGPS participants from 1977 until the occurrence of the relevant endpoint (HF, n = 4,122; MI, n = 4,221; AVS, n = 1,017), death (n = 8,934), emigration (n = 438), or April 2013, whichever came first. Follow-up was 100% complete; we did not lose track of a single individual during follow-up, and data on all endpoints were available for all 98,097 participants. For the few participants who immigrated, follow-up was terminated on the date of emigration.

Information on diagnoses of HF (International Classification of Diseases-8th edition [ICD-8], codes 427.09, 427.10, 427.11, and 10th edition [ICD-10], codes 150.0, 150.1, 150.9) were ascertained from the national Danish Patient Registry and the national Danish Causes of Death Registry. These are public registers to which all hospitalizations and deaths in Denmark have been reported since 1977 (with

ABBREVIATIONS AND ACRONYMS

AVS = aortic valve stenosis
CI = confidence interval
HDL = high-density lipoprotein
HF = heart failure
MI = myocardial infarction
KIV-2 = kringle IV type 2
SNP = single nucleotide polymorphism
outpatients and emergency treatments included since 1995). Danish national patient registry diagnoses of HF have previously been validated by others (according to European Society of Cardiology HF criteria) and demonstrated a high diagnostic specificity of 99% (19). Similarly, information on diagnoses of MI (ICD-8 code 410 and ICD-10 codes I21-I22) and AVS (ICD-8 codes 424.10, 424.12, 424.18, 424.19, and ICD-10 codes I25.0 and I25.2) were ascertained from these registries for all participants.

The CGPS was approved by Herlev Hospital and by a Danish ethical committee, and was conducted according to the Declaration of Helsinki. Participants gave written informed consent.

**LABORATORY ANALYSES.** Lipoprotein(a) total mass was measured in plasma using mainly fresh or shortly frozen samples and using 3 comparable (Online Figure 2) well-validated, isomorphism-insensitive immunonoturbidimetric assays (an in-house assay and commercial assays by DiaSys, Diagnostic Systems, Holzheim, Germany and Denka Seiken, Tokyo, Japan). Enzymatic assays were used on fresh samples to measure plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. The LPA KIV-2 repeat polymorphism was genotyped by real-time polymerase chain reaction analysis on the ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems, Foster City, California) or the CFX384 Real-time System (Bio-Rad, Copenhagen, Denmark) platform, which yielded comparable (Online Figures 3 and 4) estimates of the sum of repeats on both alleles (6). The LPA rs3798220 and rs10455872 SNPs were TaqMan genotyped in Hardy-Weinberg equilibrium. SNP carriers were minor allele homozygotes and heterozygotes combined: 0.02% and 2.48%, respectively, for rs3798220; and 0.64% and 13.61%, respectively, for rs10455872.

**STATISTICAL ANALYSES.** We used Stata SE (version 13.1, StataCorp, College Station, Texas). A 2-sided \( p < 0.05 \) was considered significant. One-way analysis of variance was used to estimate the contribution of the LPA genotypes to the variation in plasma lipoprotein(a) levels. The Cuzick nonparametric test for trend was used to test for differences in lipoprotein(a) levels across LPA genotypes.

For further analyses, participants were divided into groups based on tertiles of the lipoprotein(a) concentration distribution, and with another top tertile stratification to better examine the effect of extreme levels (90th to 99th percentiles, >99th percentile) (5,11,20). For genetic analyses, participants were divided into groups based on SNP carrier status or based on KIV-2 repeat percentile groups corresponding to plasma lipoprotein(a) percentile groups. Importantly, to avoid potential bias due to using different lipoprotein(a) assays (although comparable) and KIV-2 genotyping platforms, percentile groups were defined separately for each assay and/or platform and then combined. Lipoprotein(a) cut-points in milligrams per deciliter, corresponding to percentile cut-points, were based on fresh sample Denka Seiken (a widely available commercial assay) measurements \( n = 20,618 \). LPA KIV-2 cutpoints given as number of repeats were based on genotype results from the ABI (Applied Biosystems) platform.

We used nonparametric cumulative incidence estimation (21), which accounted for the competing risk of death, to plot the cumulative incidence of HF as a function of lipoprotein(a) levels. Cox regression analysis, including only prospectively ascertained events, was used to estimate hazard ratios of HF (or MI or AVS) with 95% confidence intervals (CIs) as a function of lipoprotein(a) levels. Logistic regression (including all first-time events, i.e., also those before examination dates) was used to estimate odds ratios of HF with 95% CIs as a function of genotypes. Analyses were age- and sex-adjusted, or also multivariable-adjusted for cardiovascular risk factors, which included total cholesterol [adjusted for the lipoprotein(a) contribution (6)], HDL cholesterol, triglycerides, body mass index, alcohol intake, leisure time physical activity, hypertension, smoking, diabetes mellitus, lipid-lowering therapy, and also for menopausal status and hormone replacement therapy in women. Hazard ratios for increased lipoprotein(a) levels were corrected for regression dilution bias (22). Proportionality of hazards over time was assessed by plotting the cumulative hazard (on a log scale) versus analysis time. Suspect of nonparallel lines was further tested using Schoenfeld residuals. No major violations of the proportional hazards assumption were detected. Interaction of lipoprotein(a) levels (on a continuous scale) with other covariates was evaluated by comparing models with and without 2-factor interaction tests using maximum likelihood ratio tests. No interactions were observed, including no interactions with sex.

We also calculated the population-attributable risk of HF for elevated lipoprotein(a) levels as: \( \frac{f(RR - 1)}{1 + f(RR - 1)} \times 100\% \), where \( f \) is the prevalence of the exposure [in this case 0.33 corresponding to the top tertile of lipoprotein(a) levels], and \( RR \) is the associated multifactorially adjusted hazard ratio (17).

We conducted instrumental variable analysis, which is a formal test for causality, integrating the association of genotype with plasma lipoprotein(a)
levels and the association of genotype with risk of HF. Analyses based on each of the 3 separate LPA genotypes was used to estimate causal relative risk estimates of HF for a 10-fold increase in lipoprotein(a) levels (6). In addition, we estimated the causal relative risk based on all 3 genotypes combined using an individual participant data approach, thus including only participants with complete information on genotypes and lipoprotein(a) measurements (13). For comparison with genetic estimates, we also estimated the observational multivariable adjusted odds ratio of HF for a 10-fold increase in plasma lipoprotein(a) levels.

Age- and sex-adjusted mediation analyses (16) were conducted to estimate the proportion of increased risk of HF due to elevated lipoprotein(a) plasma levels or LPA risk genotypes that was mediated through MI and/or AVS.

RESULTS

Table 1 shows baseline characteristics of the 98,097 CCHS and CGPS participants [all and by lipoprotein(a) percentiles], of whom 4,122 had a diagnosis of HF. Online Table 1 lists the baseline characteristics stratified on LPA KIV-2 percentile groups. Online Figure 1 shows the number of participants included in main analyses; a total of 98,097 participants were included in at least 1, and the large majority (>79,000) in at least 2, main analyses.

Lipoprotein(a) Levels and Risk of Heart Failure. We observed stepwise increases in the risk of incident HF as a function of elevated lipoprotein(a) levels in prospective analyses, including 48,896 participants who were free of HF at baseline and followed for up to 21 years (mean 7), during which time 2,078 were diagnosed with HF (Figure 1; cumulative incidences, Figure 2; hazard ratios). Elevated lipoprotein(a) levels were associated with multivariable adjusted hazard ratios for HF of 1.10 (95% CI: 0.97 to 1.25) for the 34th to 66th percentiles (95% CI: 8 to 19 mg/dl), 1.24 (95% CI: 1.08 to 1.42) for the 67th to 90th percentiles (95% CI: 20 to 67 mg/dl), 1.57 (95% CI:1.32 to 1.87) for the 91st to 99th percentiles (95% CI: 68 to 153 mg/dl), and 1.79 (95% CI: 1.18 to 2.73) for levels >99th percentile (>153 mg/dl) versus levels <34th percentile (<8 mg/dl) (trend, p < 0.001). Results were

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 98,097)</th>
<th>1-33 (n = 16,578)</th>
<th>34-66 (n = 16,480)</th>
<th>67-90 (n = 11,561)</th>
<th>91-99 (n = 4,433)</th>
<th>&gt;99 (n = 494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>55</td>
<td>52</td>
<td>55</td>
<td>55</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>58 (48-67)</td>
<td>58 (47-67)</td>
<td>58 (48-68)</td>
<td>59 (48-68)</td>
<td>60 (50-69)</td>
<td>61 (53-70)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.6 (4.9-6.4)</td>
<td>5.5 (4.8-6.2)</td>
<td>5.7 (4.9-6.4)</td>
<td>5.7 (5.0-6.5)</td>
<td>5.9 (5.2-6.7)</td>
<td>6.2 (5.5-7.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.6 (1.2-1.9)</td>
<td>1.6 (1.2-1.9)</td>
<td>1.6 (1.2-1.9)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.6 (1.3-2.0)</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.4 (1.0-2.1)</td>
<td>1.4 (1.0-2.1)</td>
<td>1.4 (1.0-2.1)</td>
<td>1.4 (1.0-2.1)</td>
<td>1.5 (1.0-2.2)</td>
<td>1.6 (1.1-2.2)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 (23-28)</td>
<td>26 (23-28)</td>
<td>26 (23-28)</td>
<td>26 (24-28)</td>
<td>26 (23-29)</td>
<td>26 (23-29)</td>
</tr>
<tr>
<td>Alcohol intake, g/day</td>
<td>14 (5-25)</td>
<td>14 (5-25)</td>
<td>12 (5-24)</td>
<td>12 (5-24)</td>
<td>13 (5-24)</td>
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<td>Leisure time physical activity</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td>&lt;2 h/week, %</td>
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<td>8</td>
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<td>2-4 h/week, %</td>
<td>45</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>47</td>
<td>47</td>
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<tr>
<td>&gt;4 h/week, %</td>
<td>42</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Age &gt;4 h strenuous activity/week,%</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Hypertension, %</td>
<td>56</td>
<td>53</td>
<td>53</td>
<td>53</td>
<td>57</td>
<td>62</td>
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<td>Smoking, %</td>
<td>22</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td>27</td>
<td>29</td>
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<td>Diabetes, %</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td>67</td>
<td>65</td>
<td>68</td>
<td>61</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>Hormone replacement therapy, %</td>
<td>17</td>
<td>20</td>
<td>16</td>
<td>18</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Lipid-lowering therapy, %</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dl</td>
<td>12 (6-31)</td>
<td>4 (3-6)</td>
<td>12 (9-15)</td>
<td>38 (26-52)</td>
<td>86 (73-112)</td>
<td>173 (162-193)</td>
</tr>
<tr>
<td>LPA rs3798220, % carriers</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>LPA rs10455872, % carriers</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>34</td>
<td>54</td>
</tr>
<tr>
<td>LPA KIV-2, No. repeats</td>
<td>36 (30-41)</td>
<td>37 (33-42)</td>
<td>36 (32-40)</td>
<td>31 (27-36)</td>
<td>27 (23-31)</td>
<td>22 (20-28)</td>
</tr>
</tbody>
</table>

Values (continuous covariates) are reported as median (interquartile range) or %. *Women only. †Among postmenopausal women.
HDL = high-density lipoprotein; KIV-2 = kringle IV type 2.
similar in age- and sex-adjusted and in multivariable-adjusted analyses (Figure 2A). The population-attributable risk of HF was 9% for elevated lipoprotein(a) levels.

In accordance with previous results (6,11), we similarly observed stepwise increases in risk of incident MI and AVS with increasing lipoprotein(a) levels (Online Figure 5). Accordingly, risk estimates for HF were attenuated when excluding participants diagnosed with MI or AVS at any time before (or at the time of) a diagnosis of HF (Figure 2B), which resulted in multivariable adjusted hazard ratios for HF of 1.09 (95% CI: 0.94 to 1.27) for 8 to 19 mg/dl, 1.14 (95% CI: 1.01 to 1.29) for number of repeats between the 11th and 33rd percentiles, and 1.32 (95% CI: 1.17 to 1.49) for number of repeats ≥70th percentile versus the number of repeats ≥67th percentile (trend, p < 0.001). Minor allele carriers of rs3798220 had multivariable adjusted odds ratios for HF of 1.50 (95% CI: 1.23 to 1.82) and of 1.12 (95% CI: 1.01 to 1.23) for rs10455872 compared with non-carriers. Overall, results were similar in age- and sex-adjusted and in multivariable-adjusted analyses (Figure 3).

**INSTRUMENTAL VARIABLE ANALYSES.** A 10-fold increase in genetically determined lipoprotein(a) levels was associated with an odds ratio for HF of 1.44 (95% CI: 1.23 to 1.69) based on KIV-2 genotype, of 2.06 (95% CI: 1.46 to 2.96) based on the rs3798220 genotype, of 1.16 (95% CI: 1.02 to 1.32) based on the rs10455872 genotype, and of 1.18 (95% CI: 1.04 to 1.34) based on all 3 genotypes combined in individual participant data analysis, which were comparable to the observational odds ratio of 1.22 (95% CI: 1.11 to 1.35) for a 10-fold increase in plasma lipoprotein(a) levels (Figure 4). When we excluded individuals with previous MI or AVS, genetic odds ratios were generally attenuated, but remained significant for KIV-2 and rs3798220 genotypes, as was the observational estimate (Figure 4).

**MEDIATION ANALYSES.** Forty-seven percent (95% CI: 32% to 77%) of increased HF risk due to elevated lipoprotein(a) levels was mediated through MI, and likewise 21% (14% to 34%) through AVS (Table 2).

**DISCUSSION**

In the present general population study, we demonstrated a stepwise increase in risk of HF with increasing levels of lipoprotein(a), and risk was increased 1.6- to 1.8-fold for levels >90th percentile. Furthermore, we demonstrated a clear association of 3 LPA risk genotypes [determining elevated allele carrier status for rs3798220 or rs10455872] associated with elevated lipoprotein(a) levels. A low number of KIV-2 repeats was associated with increased risk of HF (Figure 3) with multivariable adjusted odds ratios of 1.06 (95% CI: 0.97 to 1.16) for the number of repeats between the 34th and 66th percentiles, 1.12 (95% CI: 1.01 to 1.23) for number of repeats between the 11th and 33rd percentiles, and 1.32 (95% CI: 1.17 to 1.49) for number of repeats ≥10th percentile versus the number of repeats ≥67th percentile (trend, p < 0.001). Minor allele carriers of rs3798220 had multivariable adjusted odds ratios for HF of 1.50 (95% CI: 1.23 to 1.82) and of 1.12 (95% CI: 1.01 to 1.23) for rs10455872 compared with non-carriers. Overall, results were similar in age- and sex-adjusted and in multivariable-adjusted analyses (Figure 3).
lipoprotein(a) levels] with increased risk of HF, and accordingly, results from instrumental variable analyses were consistent with a causal association of lipoprotein(a) with HF. However, when we excluded participants diagnosed with MI or AVS, 2 conditions that have been previously causally associated with elevated lipoprotein(a) levels (4–12), with both conditions representing common underlying causes of HF (1,3), HF risk estimates were attenuated. Accordingly, mediation analyses suggested that 63% of the increase in HF risk due to elevated lipoprotein(a) levels was mediated through MI and AVS. Our findings are novel and identify elevated lipoprotein(a) levels as a likely causal risk factor for HF in the general population and as contributing to HF incidence at least partly by promoting MI and AVS, which are common underlying causes of HF.

We found a population-attributable risk of HF of 9% for elevated lipoprotein(a) levels, indicating that HF incidence in our population might theoretically be reduced by up to 9% in case of effective lowering of lipoprotein(a) levels.

**MECHANISM OF ACTION.** The pathophysiological mechanism of action behind our findings may relate to the ability of lipoprotein(a) to promote atherosclerotic stenosis, possibly thrombosis at extreme levels, and ultimately coronary heart disease, as evidenced by data from in vitro, animal, and large genetic epidemiological studies (5,6,8,23). Thus, lipoprotein(a) can cross the endothelial barrier, may be preferentially retained in the arterial intima at sites of injury, and may contribute to foam cell formation and smooth muscle cell proliferation, as well as plaque inflammation and instability, which are all key processes in atherosclerosis (5,24–26). Notably, lipoprotein(a) has been identified as the main carrier of oxidized phospholipids that are considered to be proinflammatory and proatherogenic (27). In addition, in vitro and animal studies have indicated that lipoprotein(a) may inhibit fibrinolysis, thus
promoting thrombosis, through competitive inhibition of plasmin activation and function (4,5,24,25). However, large genetic epidemiological studies have not found a notable prothrombotic effect of lipoprotein(a), except for perhaps at very extreme levels (23). Elevated lipoprotein(a) levels have also recently been identified as a likely causal risk factor for AVS, although the mechanism of action is unclear, but it may be related to a proposed wound healing effect of lipoprotein(a) (10–12).

Results from the present study are consistent with elevated lipoprotein(a) levels promoting HF at least partly via an increased risk of coronary heart disease and aortic valve disease, where lipoprotein(a) levels >90th percentile predict a 2- to 3-fold increased risk of these diseases (6,11). Risk estimates for HF were attenuated, but were generally still statistically significant after excluding participants diagnosed with MI or AVS before HF. Of note, upon such exclusion, the genetic instrumental variable risk estimate based on all 3 combined LPA genotypes lost statistical significance. However, we had limited statistical power in this analysis when we included only the subset of participants with complete information on all 3 LPA genotypes and plasma lipoprotein(a) levels. For elevated lipoprotein(a) levels, risk estimates were even more attenuated when we excluded participants ever diagnosed with MI or AVS, which was done to ensure exclusion of participants who did not have obvious ischemic cardiovascular disease or AVS at the time of diagnosis of HF. However, some of the remaining association with HF might still be due to not clinically diagnosed ischemic heart disease or AVS in our general population sample. Nonetheless, we cannot exclude an additional contribution from lipoprotein(a) also acting via other presently unknown mechanisms that affected cardiac function independently of coronary heart disease and AVS. The mechanism behind the atherosclerotic stenotic effect of high lipoprotein(a) levels (23) may possibly also lead to increased arterial stiffness, including vascular noncompliance in the aorta, which will increase afterload, and which has been strongly associated with increased risk of HF (28).

**Comparison with previous studies.** Although numerous previous studies have demonstrated the
association of elevated lipoprotein(a) levels with increased risk of coronary heart disease (5, 6, 20, 29, 30), reports on HF are scarce; 1 small case-control study (n = 142) noted elevated lipoprotein(a) levels among HF patients and cardiac transplantation patients compared with healthy control subjects (31). In addition, although several previous studies demonstrated the strong association of LPA genotypes with plasma lipoprotein(a) levels (4–6, 8, 11), to the best of our knowledge, no studies have examined the association of LPA genotypes with the risk of HF.

**STUDY LIMITATIONS.** Limitations of our study include ascertainment of HF diagnoses from ICD-based patient registries; thus, we did not assess echocardiography or other imaging data of ventricular function. Our registry-derived diagnoses likely included both HF with reduced (representing more than one-half of HF diagnoses in Western high-income societies) and preserved ventricular ejection fraction (1). Furthermore, we included only participants of Danish descent living in Denmark, which might limit the generalizability of our results because lipoprotein(a) concentrations vary with ethnicity (4) and because common causes of HF vary among countries (3). Importantly, the uniformity of study participants excluded population admixture, which might lead
to false positive findings and incorrect causality conclusions in Mendelian randomization studies (13,14).

Limitations of Mendelian randomization studies have been extensively discussed; however, only few apply to studies with positive findings. In addition to population admixture, genetic linkage disequilibrium may, if present, lead to spurious findings (13,14). However, because we genotyped for the LPA KIV-2 polymorphism, which is considered directly responsible for a large part of the variation in plasma lipoprotein(a) levels, and because of the stepwise association of LPA KIV-2 repeats with risk of HF, it is highly unlikely that our results stem from linkage disequilibrium and genetic confounding. Furthermore, the rs3798220 nonsynonymous SNP in the LPA gene has been described as being associated with very elevated lipoprotein(a) levels in several publications (5,8,11); however, the mechanism behind the association is unknown and likely cannot be simply explained by the partial tracking of the KIV-2 polymorphism. One possible explanation is that the SNP is in linkage disequilibrium with other variations in the LPA gene promoter region that directly affects apolipoprotein(a) transcription rates, and thus, lipoprotein(a) plasma levels. Importantly, the lack of a known explanation for the association with plasma lipoprotein(a) levels does not invalidate the use of this SNP as an instrumental variable in instrumental variable analyses.

### TABLE 2 Mediation Analysis (Age- and Sex-Adjusted) for Risk of Heart Failure as a Function of Lipoprotein(a) Levels (n = 49,546) or LPA KIV-2 (n = 80,106), rs3798220 (n = 79,582), or rs10455872 (n = 79,596) Genotype

<table>
<thead>
<tr>
<th>Independent Variable/Mediator</th>
<th>Indirect Effect</th>
<th>Direct Effect</th>
<th>Proportion of Total Effect Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein(a), mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.026 (0.022 to 0.031)</td>
<td>0.030 (0.010 to 0.052)</td>
<td>47 (32 to 77)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>0.013 (0.009 to 0.017)</td>
<td>0.049 (0.029 to 0.069)</td>
<td>21 (14 to 34)</td>
</tr>
<tr>
<td>Both</td>
<td>0.038 (0.033 to 0.044)</td>
<td>0.022 (0.001 to 0.042)</td>
<td>63 (45 to 99)</td>
</tr>
<tr>
<td>LPA KIV-2, No. repeats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>-0.016 (-0.020 to -0.011)</td>
<td>-0.026 (-0.042 to -0.005)</td>
<td>38 (23 to 76)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>-0.006 (-0.011 to -0.001)</td>
<td>-0.037 (-0.055 to -0.016)</td>
<td>14 (3 to 33)</td>
</tr>
<tr>
<td>Both</td>
<td>-0.021 (-0.027 to -0.015)</td>
<td>-0.022 (-0.041 to -0.003)</td>
<td>49 (29 to 99)</td>
</tr>
<tr>
<td>LPA rs3798220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.009 (0.005 to 0.013)</td>
<td>0.027 (0.011 to 0.043)</td>
<td>25 (13 to 53)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>0.004 (0.000 to 0.007)</td>
<td>0.034 (0.015 to 0.050)</td>
<td>11 (0 to 26)</td>
</tr>
<tr>
<td>Both</td>
<td>0.013 (0.008 to 0.018)</td>
<td>0.026 (0.006 to 0.042)</td>
<td>33 (18 to 68)</td>
</tr>
<tr>
<td>LPA rs10455872</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.010 (0.007 to 0.015)</td>
<td>0.009 (-0.007 to 0.027)</td>
<td>53 (23 to 710)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>0.011 (0.007 to 0.014)</td>
<td>0.010 (-0.010 to 0.027)</td>
<td>53 (24 to 761)</td>
</tr>
<tr>
<td>Both</td>
<td>0.020 (0.015 to 0.025)</td>
<td>0.000 (-0.021 to 0.020)</td>
<td>99 (46 to 21601)</td>
</tr>
</tbody>
</table>

Values are coefficient (95% confidence intervals).
Abbreviation as in Table 1.

### CONCLUSIONS

For the first time, we demonstrated a clear stepwise association of elevated lipoprotein(a) levels with increased risk of HF in the general population. In addition, we provided genetic evidence that the association is likely causal and mediated at least partly via coronary heart disease and AVS. The implications of our findings were that lowering of lipoprotein(a) levels might potentially not only decrease risk of MI and AVS, but also, and partly by extension, decrease risk of HF. Our results emphasize the need for randomized clinical trials on the effect of lowering lipoprotein(a) levels to prevent cardiovascular disease. With the advent of novel lipid-lowering drugs, including PCSK9 inhibitors (32) and specific apolipoprotein(a) antisense oligonucleotides (33) with marked lipoprotein(a) lowering effects, such studies seem increasingly feasible in the near future.

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### REPRINT REQUESTS AND CORRESPONDENCE

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COMPETENCY IN MEDICAL KNOWLEDGE: Individuals with high lipoprotein(a) levels are at increased risk of coronary heart disease, aortic valve stenosis, and partly by extension, HF. Genetic data support that the associations are likely causal.

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5. Kamstrup PR. Lipoprotein(a) and ischemic heart disease—a causal association? A review. Atherosclerosis 2010;211:15-23.


KEY WORDS: genetics, heart failure, lipoproteins

APPENDIX: For details on participants and laboratory and statistical analyses, and supplemental figures and tables, please see the online version of this article.