Estimating the Population Impact of Lp(a) Lowering on the Incidence of Myocardial Infarction and Aortic Stenosis—Brief Report

Mehdi Afshar, Pia R. Kamstrup, Ken Williams, Allan D. Sniderman, Børge G. Nordestgaard, George Thanassoulis

Objective—High lipoprotein(a) (Lp[a]) is the most common genetic dyslipidemia and is a causal factor for myocardial infarction (MI) and aortic stenosis (AS). We sought to estimate the population impact of Lp(a) lowering that could be achieved in primary prevention using the therapies in development.

Approach and Results—We used published data from 2 prospective cohorts. High Lp(a) was defined as ≥50 mg/dL (=20th percentile). Relative risk, attributable risk, the attributable risk percentage, population attributable risk, and the population attributable risk percentage were calculated as measures of the population impact. For MI, the event rate was 4.0% versus 2.8% for high versus low Lp(a) (relative risk, 1.46; 95% confidence interval [CI], 1.45–1.46). The attributable risk was 1.26% (95% CI, 1.24–1.27), corresponding to 31.3% (95% CI, 31.0–31.7) of the excess MI risk in those with high Lp(a). The population attributable risk was 0.21%, representing a population attributable risk percentage of 7.13%. For AS, the event rate was 1.51% versus 0.78% for high versus low Lp(a) (relative risk, 1.95; 95% CI, 1.94–1.97). The attributable risk was 0.74% (95% CI, 0.73–0.75), corresponding to 48.8% (95% CI, 48.3–49.3) of the excess AS risk in those with high Lp(a).

Conclusions—Lp(a) lowering among the top 20% of the population distribution for Lp(a) could prevent 1 in 14 cases of MI and 1 in 7 cases of AS, suggesting a major impact on reducing the burden of cardiovascular disease. Targeting the top 10% could prevent 1 in 20 MI cases and 1 in 12 AS cases. (Arterioscler Thromb Vasc Biol. 2016;36:2421-2423. DOI: 10.1161/ATVBAHA.116.308271.)

Key Words: aortic valve stenosis • atherosclerosis • coronary disease • epidemiology • genetics • lipoproteins • prevention and control

Elevations in lipoprotein(a) (Lp[a]) represent the most common genetic dyslipidemia worldwide affecting at least 1 in 5 individuals.1 Lp(a) has been confirmed as a risk factor for myocardial infarction (MI) and aortic stenosis (AS) and 1 in 3 individuals with levels >30 mg/dL are at high cardiovascular risk.2–4 Genetic studies, using the Mendelian randomization approach, have also provided strong evidence for causation. Taken together, the evidence suggests that Lp(a) may be a novel therapeutic target for preventing cardiovascular disease.3 However, the lack of targeted effective treatments for Lp(a) lowering has limited its clinical relevance. Recently, several novel lipid-lowering therapies, including PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and antisense oligonucleotides, have been developed that can markedly lower Lp(a).5–8

With potent Lp(a)-lowering therapies on the horizon, we sought to estimate the potential population impact of Lp(a) lowering that may be achieved by these therapies in primary prevention. Accordingly, we estimated the attributable risk proportion and population attributable risk proportion for MI and aortic valve stenosis if all individuals with high Lp(a) ≥50 mg/dL, a level above which Lp(a) has been shown to be most pathogenic,9 were treated to normalize their Lp(a) levels to <50 mg/dL.

Materials and Methods
Materials and Methods are available in the online-only Data Supplement.
Results
Reducing High Lp(a) Could Potentially Prevent up to 1 in 14 Cases of MI
For MI, the event rate for Lp(a) ≥50 mg/dL was 4.0%, whereas for <50 mg/dL it was 2.8% (relative risk, 1.46; 95% confidence interval, 1.45–1.46). The population attributable risk was 0.21%, which represents a population attributable risk percentage (PARP) of 7.1% of the total risk for MI in the population (Table).

Reducing High Lp(a) Could Potentially Prevent up to 1 in 7 Cases of Aortic Valve Stenosis
For AS, the event rate for Lp(a) ≥50 mg/dL was 1.5%, whereas for <50 mg/dL it was 0.8% (relative risk, 1.95; 95% confidence interval, 1.94–1.97). The population attributable risk was 0.13%, which represents a PARP of 13.9% of the total risk for AS in the population (Table).

Reducing High Lp(a) in Those at Highest Risk Could Have a Significant Impact on the Burden of CVD
In sensitivity analyses targeting individuals at the top 10% of the Lp(a) distribution (≥77 mg/dL), the PARP estimates were 5.2% for MI and 7.8% for AS, indicating that ≈1 in 20 MI cases and 1 in 12 AS cases could be preventable by treating only those at highest risk.

Discussion
Our analysis using data from a large prospective European cohort provides estimates for the population impact of lowering high Lp(a) ≥50 mg/dL for MI and aortic valve stenosis. Treating all individuals with an Lp(a) ≥50 mg/dL to <50 mg/dL could potentially reduce the incidence of MI and AS by as much as 13 and 7 per 1000 individuals, respectively. Accordingly, Lp(a) seems to be responsible for 31% and 49% of the excess risk of MI and AS in individuals with Lp(a) ≥50 mg/dL. In the general population, Lp(a) lowering to <50 mg/dL would, therefore, be expected to reduce the overall incidence of MI and AS by 7.1% and 13.9%, respectively. Put differently, our results suggest that potent Lp(a) lowering of all individuals with Lp(a) ≥50 mg/dL, which represents ≈20% of the population, could be expected to prevent up to 1 in 14 MI cases and 1 in 7 AS cases.

Estimates of the population impact of high Lp(a) on cardiovascular disease have been limited in the literature. A small case–control study of MI in Hawaiian men suggested a PARP of 14%, whereas a study investigating the PARP for high Lp(a) in stroke reported a PARP of 6.8% across several prospective cohorts. Our estimates of 7.1% and 13.9% for MI and AS, respectively, from a large prospective cohort strongly support the notion that potent Lp(a) lowering could make significant contributions to reducing cardiovascular disease in the near future. Our estimate of 13.9% for AS is higher than that for both MI and stroke and demonstrates that Lp(a) is a larger contributor to the excess risk for AS than other cardiovascular diseases and could reduce a greater proportion of the burden of AS in the population. To our knowledge, this represents the first published estimate of the population impact of lowering Lp(a) for AS.

The use of PARP as a relevant metric of population impact has been criticized because of the limited ability to infer causality of many exposures or to markedly change exposure rates in the population. Furthermore, the use of PARP has been discouraged in genetics, as there is currently no effective way to directly modify a genotype, limiting the public health relevance of calculating the impact of such modification. Nonetheless, these limitations should not apply to PARP estimates of Lp(a). First, although Lp(a) is a genetic exposure, its adverse effects are mediated by circulating plasma Lp(a), which can substantially be reduced by emerging therapies. Second, unlike many other cardiovascular biomarkers, the evidence for causality for Lp(a) is particularly strong based on Mendelian randomization studies. In fact, causal estimates of Lp(a) in cardiovascular disease seem stronger than observational estimates, suggesting that our measures of population impact may be underestimated.

Our study has several limitations. First, we have assumed that a potent Lp(a)-lowering agent will become available in the near future that will be highly tolerable, will have no important side effects, will be affordable, and will achieve 100% compliance. Although emerging therapies demonstrate excellent efficacy in lowering Lp(a) and tolerability with limited side effects, no outcome studies in high Lp(a) patients have been performed, and therefore, the efficacy and cost-effectiveness of these novel therapies remain unknown. We also acknowledge that the use of injectable therapy or plasmapheresis may be limited by patients’ willingness to

Table. Estimated Population Impact of Lowering Lp(a) to <50 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Lp(a), mg/dL</th>
<th>Event Rate</th>
<th>RR (95% CI)</th>
<th>AR (95% CI)</th>
<th>ARP (95% CI)</th>
<th>PARP Preventable Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>≥50</td>
<td>4.0%</td>
<td>1.46 (1.45–1.46)</td>
<td>1.26% (1.24–1.27)</td>
<td>31.3% (31.0–31.6)</td>
<td>7.13% 1 in 14</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>2.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>≥50</td>
<td>1.5%</td>
<td>1.95 (1.94–1.97)</td>
<td>0.74% (0.73–0.75)</td>
<td>48.8% (48.3–49.2)</td>
<td>13.9% 1 in 7</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>0.8%</td>
<td></td>
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</tr>
</tbody>
</table>

AR indicates attributable risk; ARP, attributable risk percentage; PARP, population attributable risk percentage; and RR, relative risk.
accept such treatments and their associated costs; however, our objective was to provide the maximal theoretical benefit for lowering high Lp(a) in the population; the actual benefits produced from such interventions may be lower. Second, the estimated population impact assumes that approximately one-fifth of the population will be treated. It may be more reasonable to target Lp(a) lowering to the top 10%, where risk is known to be highest. As we have shown in our sensitivity analysis, this would still be expected to significantly reduce the incidence of MI and AS cases. Third, our estimates assume that Lp(a) will be reduced to <50 mg/dL in all individuals. Given the highly skewed distribution of Lp(a), it may not be possible to normalize Lp(a) in all individuals, which would reduce the population impact of Lp(a) lowering. Nonetheless, given that antisense agents can lower Lp(a) by up to 90%7,8 and PCSK9 inhibitors by an average of 25%,5,6 individuals with Lp(a) as high as 500 mg/dL may be able to achieve an Lp(a) <50 mg/dL, depending on the agent used. However, PCSK9 inhibitors will lower LDL-C more than Lp(a) even when LDL-C itself may not require intervention, and this could limit their utility for Lp(a) lowering. Finally, because Lp(a) is a lifelong genetic exposure starting at birth, it is unclear whether pharmacological Lp(a) lowering in later life will have the same expected impact.

If potent Lp(a) lowering could be achieved using novel agents in development, targeting the top 20% of the population distribution for Lp(a) would be expected to prevent 1 in 14 cases of MI and 1 in 7 cases of AS. Lowering Lp(a) is expected to have a major impact on reducing the burden of cardiovascular disease and should be pursued as a therapeutic target.

**Sources of Funding**

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**Disclosures**

Dr Thanassoulis has received speaker fees from Servier Canada; has participated in Advisory Boards for Servier Canada, Amgen, and Ionis Pharmaceuticals; and is a consultant to Ionis Pharmaceuticals. He is a Clinical Research Scholar of the Fonds de Recherche Quebec–Sante (FRQS) and has received research grants from FRQS, Heart and Stroke Foundation of Canada, and the Canadian Institute of Health Research. The other authors report no conflicts.

**Highlights**

- Lipoprotein(a) levels are genetically predetermined.
- Novel lipoprotein(a)-lowering agents are currently in development.
- If potent lipoprotein(a) lowering could be achieved using such agents, 1 in 14 cases of myocardial infarction and 1 in 7 cases of aortic valve stenosis could be prevented.
- Lowering Lp(a) is expected to have a major impact on reducing the burden of cardiovascular disease.

**References**

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Estimating the population impact of Lp(a) lowering on the incidence of myocardial infarction and aortic stenosis – Brief Report

Running Head: Population impact of lowering Lp(a)

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METHODS

We used estimates of event rates by Lp(a) levels for both MI and AS from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) [1, 2]. Details of the participants and risks associated with different Lp(a) levels have been previously published in the original reports [1, 2].

For our primary analysis, we considered individuals with Lp(a) ≥50 mg/dL to be at risk for Lp(a)-mediated disease based on prior reports showing that risk for CV disease increases markedly above this level [1-3]. Individuals with Lp(a) <50 mg/dL were considered at baseline risk as they shown to have no to negligible increased risk below this threshold [1-3]. Lp(a) ≥50 mg/dL represents the top ~20% of the Lp(a) distribution [1-3]. We used unadjusted estimates for all analyses as multivariable adjustment for age, sex, total cholesterol, triglycerides, body mass index, hypertension, diabetes mellitus, smoking, and use of lipid lowering therapy, and in women also for menopause and hormone therapy, did not materially change the reported associations with the outcomes of interest. Lp(a) is largely genetically mediated and therefore there are few, if any, major confounders of its plasma levels or its association with cardiovascular events. We calculated the relative risk (RR), attributable risk (AR), the attributable risk percent (ARP) and the population attributable risk percent (PARP) as measures of the population impact of Lp(a) ≥50 mg/dL (corresponding to ≥84th percentile for the Lp(a) distribution or, approximately, the top fifth) [1] using standard well-accepted formulae.

We also performed a sensitivity analysis examining treatment of individuals with Lp(a) ≥77 mg/dL (corresponding to upper ≥90th percentile of the Lp(a) distribution) [1] where attributable risk would be highest and therefore treatment should be most effective.
REFERENCES

1) Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009; 301: 2331-2339.


Population Impact of Lowering Lipoprotein(a) to < 50 mg/dL

↓ Lp(a) to < 50 mg/dL

1 in 7 Aortic Stenosis Prevented

1 in 14 Myocardial Infarctions Prevented