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Opinion

Constructive Insight into: Thirty-Year Risk of Cardiovascular Disease Among Healthy Women According to Clinical Thresholds of Lipoprotein(a)

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Abstract

This prospective analysis from the Women's Health Study evaluates the long-term cardiovascular risk associated with elevated lipoprotein(a) [Lp(a)] in a primary prevention population. Nearly 28,000 initially healthy women were followed for up to 30 years to assess the impact of genetically determined Lp(a) levels on cardiovascular outcomes. Very high Lp(a) concentrations (>99th percentile, ≥131 mg/dL) were associated with a substantially increased relative risk of major cardiovascular events, translating into a clinically meaningful absolute risk increase over three decades. In contrast, mild to moderate elevations showed only modest and inconsistent associations with outcomes. Risk patterns demonstrated a threshold effect rather than a linear relationship, a finding supported by genetic analyses. Adding Lp(a) to established risk prediction models did not significantly improve overall risk discrimination. These findings suggest that while extremely elevated Lp(a) is an important lifelong cardiovascular risk factor, routine population-wide screening may have limited value. A targeted screening strategy focused on identifying individuals with very high Lp(a) levels is likely to be the most clinically effective approach, particularly in light of emerging Lp(a)-lowering therapies.

Discussion

This large prospective analysis from the Women's Health Study offers one of the most thorough looks to date at the long-term cardiovascular risk associated with elevated lipoprotein(a) [Lp(a)] in a primary prevention setting. Following nearly 28 000 initially healthy women for up to 30 years, the investigators were able to examine how a genetically determined lipid factor influences cardiovascular risk across much of the adult lifespan. Overall, the findings reinforce the idea that very high Lp(a) levels matter clinically, while also making clear why Lp(a) is a challenging marker to apply broadly in population wide screening. One of the major strengths of this study is its exceptionally long follow up. Many earlier studies of Lp(a) were limited to 10 to 15 years, which may underestimate the impact of an exposure that is present from early life. In contrast, this analysis shows that cardiovascular risk associated with Lp(a) builds slowly over decades, particularly for coronary heart disease. Women with Lp(a) levels in the highest percentile (>99th percentile, ≥131 mg/dL) had roughly a 74% higher risk of major cardiovascular events compared with those with low levels. The important point is, this relative increase amounted to roughly a 10% higher absolute risk over 30 years, a difference that is clinically

meaningful and on par with other inherited lipid disorders like familial hypercholesterolemia. Also, this study helps to clarify where Lp(a) might not be as useful as being thought. As compared to LDL cholesterol or hsCRP, which generally show steady rising risk across their entire range, Lp(a) seems to matter most at the very highest levels. Mild to moderate increase, around 30 to 60 mg/dL were related to only small increases in risk, and connections to stroke or cardiovascular death were not consistent unless levels were extremely high. This kind of non-proportional effect explains why guidelines on routine Lp(a) screening aren't consistent and why its role in everyday risk assessment is still a topic of debate.

The spline analyses make this point especially clear. While risk did rise across the board when Lp(a) was treated as a continuous measure, the increase became much sharper at the highest levels. In other words, it's less of a smooth, step by step relationship and more of a threshold effect. From a clinical perspective, this means Lp(a) shouldn't just be treated like any other biomarker to plug into a standard risk calculator. Instead, it's better thought of as a risk amplifier that really matters when levels are very high. The genetic data also support this. People carrying the LPA rs3798220 minor allele had much higher Lp(a) levels and a 27% higher risk of major cardiovascular events over 30 years. The fact that the genetic and observational findings line up so closely, strengthens the idea that Lp(a) is not just a marker of risk, it actually contributes to disease. At the same time, the relatively modest risk related to this variant emphasizes an important takeaway message that for most people, even genetically higher Lp(a) only translates into moderate risk, with the biggest impact reserved for those at the extreme end of the spectrum. Another important point of this study is that adding Lp(a) to the AHA PREVENT equation did not meaningfully improve risk prediction. That is to say, though high Lp(a) is strongly related to cardiovascular events, it doesn't necessarily help to identify more people at risk for cardiovascular disease when the trait is not very common. If, we look from a public health standpoint, this suggests that screening everyone may not be beneficial and in fact might be waste of resources. Instead, it makes more sense to focus on the people most likely to benefit from it, those with very high Lp(a) levels who would likely gain the most benefit from early intervention. As any other study, this study also has its limitations. This study comprises women population, and most of them were of European origin, which means the findings may not apply equally to everyone. Though by limiting the analysis to European origin it helped reduce the biological variability, it highlighted an important point that Lp(a) levels and their associated risks differ across the populations, particularly in individuals of African descent. It also suggested that risk linked to high Lp(a) may be concentrated earlier in follow up, especially for coronary events which raises the possibility that its effects may change over time which is a challenging issue that deserves further investigation in future.

Despite having those limitations this study gives a clear clinical message. Since several Lp(a) lowering drugs are in pipeline for clinical use soon, it's more than ever important to identify those people who will most likely benefit from them. This study argues against testing everyone and instead supports a more selective screening strategy which is focused on detecting very high Lp(a) levels. By using this approach, clinicians would be able to intensify risk reduction efforts now and will be able to use Lp(a) specific treatments to those who would most likely gain the benefit.

Conclusion

In conclusion this study shows that very high Lp(a) levels can be a meaningful, lifelong cardiovascular risk factor even in otherwise healthy women. At the same time, it suggests that Lp(a) shouldn't be overemphasized in routine risk assessment for everyone. Instead, a targeted screening strategy that focuses on identifying people with extremely elevated Lp(a) levels appears to be the most practical and clinically useful approach.

Conflict of Interest

Nill

Endnotes

Nill