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Lipoprotein(a) and progression of aortic valve calcification: a case of collider bias? Reply

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This commentary refers to 'Lipoprotein(a) is associated with the onset but not the progression of aortic valve calcification', by Y. Kaiser *et al.*, https://doi.org/10.1093/eurheartj/ehac377 and the discussion piece 'Lipoprotein(a) and progression of aortic valve calcification: a case of collider bias?', by M. G. Levin and S. M. Damrauer, https://doi.org/10.1093/eurheartj/ehac638.

We thank Levin and Damrauer for their letter about our manuscript on the link between lipoprotein(a) (Lp(a)) and aortic valve calcification (AVC).[1] They raise the concern that index event bias potentially obscured an association of Lp(a) with the progression of AVC.[2] They suggest that by making this selection based on having AVC at baseline, we implicitly select individuals with high Lp(a) levels. Hence, individuals without high Lp(a), but with AVC may have other risk factors causing progression which are unaccounted for in our analysis. As potential suggestions to tackle this bias, they suggest the use of propensity scores and novel correction factors in genetic epidemiological studies to mitigate the effect of this bias.

Index event bias typically occurs when participants are selected based on a first event and investigators attempt to assess risk factors for the recurrence of an identical event. Although the progression of AVC differs slightly from disease recurrence, there is indeed a certain selection bias that occurs when individuals are included based on AVC presence. We experienced this in our previous work, in which we matched high and low Lp(a) individuals who had advanced AVC. This resulted in an increased incidence of competing risk factors in individuals with low Lp(a): their average blood pressure and low-density-lipoprotein cholesterol were significantly higher.[3] Nevertheless, cholesterol- and blood pressure-lowering strategies have failed to impact AVC progression.[4] This is in line with substantial pathophysiological evidence that AVC disease initiation and propagation are two distinct processes, rather than a recurrence of the same disease.[5] Initiation is driven by endothelial damage, lipid influx, and inflammation, which triggers the osteogenic transformation of valvular interstitial cells. The propagation phase seems more self-perpetuating: calcium deposits lead to increased mechanical stress and injury, aggravating further calcification and possibly overruling the effect of the previously mentioned risk factors that initiated the disease.

In the current observational study, it would, unfortunately, be impossible to assess disease progression without prior selection of those with AVC at baseline. One way to address index event bias is to adjust for the risk factors for the index event. We adjusted for all known major risk factors for AVC, but cannot fully preclude the possibility that there is residual confounding from unknown risk factors. If their progression would be driven by these unknown risk factors, the use of propensity scores, a summary metric of known variables, would not solve this issue, as propensity scores only adjust for measured variables. Of course, we fully agree with the authors that it is challenging to infer causality from observational analyses and that definitive answers to whether Lp(a) lowering can prevent AVC progression should be drawn from randomized trials. Yet, if we were to design an Lp(a)-lowering trial in AVC, we believe shifting the attention toward the initiation rather than the propagation phase is crucial, as that is likely where the largest benefit is to be found.

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