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EDITOR'S PAGE

When Causal Is Not Enough

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I was a cardiology fellow when the encainide and flecainide arms of CAST (Cardiac Arrhythmia Suppression Trial) were stopped. Ventricular ectopy after myocardial infarction predicted death, and encainide and flecainide made the ectopy disappear. We had watched the monitor quiet and felt reassured. In the main CAST trial, patients were randomized after ectopy suppression had been demonstrated, yet encainide and flecainide increased arrhythmic death and cardiac arrest.[1] The drugs did what we asked, and patients did worse. What CAST taught me was that changing what we can measure is not the same as improving what happens to patients.

I thought of CAST again this summer. ZEUS (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Cardiovascular Disease, Chronic Kidney Disease and Inflammation) randomized 6,376 people with atherosclerotic cardiovascular disease, chronic kidney disease, and inflammation to monthly ziltivekimab or placebo. According to the company's topline announcement, ziltivekimab reduced markers of interleukin-6 activity but did not demonstrate a reduction in major cardiovascular events (HR: 0.99; 95% CI: 0.88-1.11).[2,3] Five weeks later, Novartis announced that pelacarsen lowered lipoprotein(a) (Lp[a]) in Lp(a)-HORIZON (Assessing the Effect of Lipoprotein[a] Lowering With Pelacarsen on Major Cardiovascular Events in Patients With CVD and Elevated Lp[a]) but did not meet the primary endpoint in the overall population; at the time of writing, the estimate, components, safety findings, and the result in the prespecified higher-Lp(a) group had not been released.[4,5] Days later, HERMES (Effects of Ziltivekimab Versus Placebo on Morbidity and Mortality in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction and Systemic Inflammation) and ATHENA (Effects of Ziltivekimab Versus Placebo on Heart Failure Symptoms and Physical Function in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction and Systemic Inflammation), ziltivekimab trials in heart failure, were stopped after a data monitoring committee judged them unlikely to succeed.[6,7] These were futility decisions, not 2 additional completed negative trials.[7]

These were not speculative programs. For Lp(a), much of the variation in circulating levels is explained by the LPA gene locus, and genetically predicted levels show graded associations with coronary disease across ancestry groups.[8-10] For interleukin (IL)-6, investigators built a genetic instrument intended to mimic ziltivekimab and found concordant biomarker effects and predicted reductions in atherosclerotic events.[11] The results do not show that causal inference failed. The genetic studies estimated the consequences of genetically influenced differences in exposure over the life course. The trials estimated the effect of a particular treatment that was begun after disease was established, continued for several years, and added to contemporary care. Both are causal questions, but not the same one. ZEUS and HORIZON may have different explanations; what they share is the distance between evidence about a pathway and evidence about a treatment strategy.

The familiar lesson is that surrogates can mislead. The harder lesson is that causal is not enough. Epidemiology can establish that a marker predicts risk. Genetics can strengthen the case that a lifelong exposure contributes to disease. Phase 2 trials can show that a molecule changes the intended biology. A yes to all 3 does not answer whether changing the pathway late in life, with this drug, in these patients, in addition to contemporary care, improves outcomes. Evidence of very different kinds can converge while leaving that inference untested.

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The complete trial reports may reveal a smaller benefit, differences among components or populations, delayed effects, an offsetting harm, or no persuasive clinical signal. Those findings will determine what happened in these trials. They will not change what the earlier evidence could and could not establish. The 3 gaps that follow are therefore not explanations offered after the result. They are the parts of the clinical inference that remained untested before the trials began.

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The first is timing and reversibility. Mendelian randomization estimates the consequences of generally small differences present from conception; a trial tests a larger change introduced for several years after disease is established.[12] The models that set expectations for Lp(a) lowering estimated that reducing Lp(a) by roughly 65 to 100 mg/dL might produce a benefit comparable with lowering low-density lipoprotein (LDL) cholesterol by 1 mmol/L.[8,13] The investigators were explicit that this translation held only if Lp(a) and LDL cholesterol have similar cumulative relationships with coronary disease over time, and they supported that assumption as far as observational and genetic evidence allowed.[8] The randomized trial remained the first direct test of it. Some injury accumulates over decades and may not be reversible once disease is established. Lp(a) is largely set early in life, and even a first infarction at 55 follows 5 decades of exposure. Testing the same drug at a different stage of disease is a different causal question.

The second is that the target and the drug are not the same. In ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events), torcetrapib raised high-density lipoprotein cholesterol by 72% and lowered LDL cholesterol by 25%, yet cardiovascular events and deaths increased. The drug also raised blood pressure and aldosterone. The trial established harm but could not determine whether it arose from the intended mechanism, off-target effects, or both.[14]

The third is that the clinical value of targeting a pathway depends on the whole treatment strategy. An outcome trial integrates the intended effect with everything else the drug does, with background care, disease stage, adherence, competing events, and the choice of endpoint. HORIZON tested pelacarsen as an addition to contemporary care in people whose other risk factors the investigators described as generally well managed.[4] Genetically, the association of Lp(a) is much stronger for myocardial infarction and large-artery stroke than for total ischemic stroke, and no association was detected with small-vessel stroke.[9] Whether that mattered in HORIZON remains unknown until the components are reported. The broader point is that only the outcome trial captures the effect of the complete strategy across all the events it was designed to count.

None of this makes the trials disappear. ZEUS materially reduces confidence that chronic IL-6 ligand inhibition with ziltivekimab improves cardiovascular outcomes in patients with established atherosclerosis, chronic kidney disease, and inflammation. HERMES and ATHENA provide no publicly reported treatment-effect estimates, but they show that a program spanning atherosclerosis and heart failure shared one premise: that sustained IL-6 inhibition with this molecule would improve clinical outcomes. HORIZON did not establish the broad clinical benefit many expected from pelacarsen in the enrolled population. The trial was designed to detect a 20% reduction in events[4]; missing its primary criterion lowers confidence in a benefit of that magnitude, whereas the full estimate and CI will determine what smaller or narrower effects remain compatible with the data. The results do not prove that inflammation is irrelevant or that Lp(a) is not causal; a treatment strategy can fail even when the pathway contributes to disease. Elevated Lp(a) still identifies risk and supports intensive use of therapies already proven to improve outcomes. Other molecules, populations, or stages may give different answers, but each is a new hypothesis, not a reason to discount the answer.

There are practical implications for how we publish and how we plan. When journals publish genetic, mechanistic, or biomarker evidence, we should say which claim the evidence supports and which clinical inference it leaves untested. Causal should not be read as therapeutically reversible, and target engagement should not be read as patient benefit. Investigators should state, before outcome results arrive, what findings would change their confidence, so that later interpretations can be compared with commitments made in advance; and agreement among lines of evidence should raise confidence only

to the extent that those lines are independent with respect to the question being asked.

Thirty-seven years after CAST, I can still see the monitor with the ectopy gone and remember how good it felt to be helping. CAST taught me not to confuse changing a marker with helping a patient. ZEUS and HORIZON add a harder lesson. Epidemiology, genetics, mechanism, and target engagement may all point in the same direction and still answer a different causal question from the one a clinician needs answered. The complete trial reports will sharpen the clinical interpretation. They cannot retroactively make earlier evidence answer the treatment question. Our responsibility is to state precisely what each line of evidence establishes, to identify the assumptions required to move from one to the next, and to change our confidence when the treatment strategy is finally tested.

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REFERENCES

1. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.

2. Ridker PM, Baeres FMM, Hvelplund A, et al. Rationale, design, and baseline clinical characteristics of the Ziltivekimab Cardiovascular Outcomes Trial: interleukin-6 inhibition and atherosclerotic event rate reduction. *JAMA Cardiol*. 2026;11:89–97. https://doi.org/10.1001/jamacardio.2025.4491

3. *Novo Nordisk provides update on the ZEUS phase 3 trial in people with ASCVD, CKD and inflammation. News release*. Novo Nordisk; July 31, 2026. Accessed October 6, 2026. https://ml-eu.globenewswire.com/Resource/Download/fe1dce1d-1300-4380-9ef2-c13623cba4e9

4. Cho L, Nicholls SJ, Nordestgaard BG, et al. Design and rationale of Lp(a)HORIZON trial: assessing the effect of lipoprotein(a) lowering with pelacarsen on major cardiovascular events in patients with cardiovascular disease and elevated lipoprotein(a). *Am Heart J*. 2025;287:1–9. https://doi.org/10.1016/j.ahj.2025.03.019

5. Novartis announces Lp(a)HORIZON Phase III topline results for pelacarsen in patients with elevated Lp(a) and established cardiovascular disease. *News release. Novartis*. September 4, 2026. Accessed October 6, 2026. https://www.novartis.com/news/media-releases/novartis-announces-lpahorizon-phase-iii-topline-results-pelacarsen-patients-elevated-lpa-and-established-cardiovascular-disease-cvd

6. Mendieta G, Ridker PM, Borlaug BA, et al. Ziltivekimab in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the ATHENA and HERMES trials. *Eur J Heart Fail*. Published online May 10, 2026. https://doi.org/10.1093/ejhf/xuag153

7. Joseph A. Novo Nordisk stops two cardiovascular trials of drug aimed at lowering inflammation. *STAT*. Accessed September 24, 2026. https://www.statnews.com/2026/09/07/novo-nordisk-heart-studies-inflammation-ziltivekimab/

8. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol*. 2018;3:619–627.

9. Clarke R, Wright N, Lin K, et al. Causal relevance of Lp(a) for coronary heart disease and stroke types in East Asian and European ancestry populations: a Mendelian randomization study. *Circulation*. 2025;151:1699–1711.

10. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42:e48–e60.

11. Zhang L, Omarov M, Xu L, deGoma E, Natarajan P, Georgakis MK. IL6 genetic perturbation mimicking IL-6 inhibition is associated with lower cardiometabolic risk. *Nat Cardiovasc Res*. 2025;4:1172–1186. https://doi.org/10.1038/s44161-025-00700-7

12. Larsson SC, Butterworth AS, Burgess S. Mendelian randomization for cardiovascular diseases: principles and applications. *Eur Heart J*. 2023;44:4913–4924.

13. Lamina C, Kronenberg F, Lp(a)-GWAS-Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol*. 2019;4:575–579.

14. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.