been the same as NOBLE, the EXCEL trial would have been failed to show noninferiority. EXCEL also included mortality, stroke, myocardial infarction (MI), or RR as a secondary powered outcome. In this case, the noninferiority margin was set to 8.4%, which is more than double the margin set in NOBLE for the same composite outcome (with the exception of including only spontaneous MI). Noninferiority trials are a great tool but may easily be manipulated to arrive to the intended outcomes.

Considering that no trial has demonstrated noninferiority of PCI and that pooled analysis from meta-analysis have shown greater risk for MI and RR, logic follows that equipoise is not met and therefore guidelines should reflect on it.

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Commentary: The fate of patients with left main coronary artery disease may be dictated by distorted science

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Gaudino and Brophy¹ impart a didactic approach examining the evidence on whether left main coronary artery disease may be considered a separate entity within the spectrum of coronary artery disease, and adds to the growing stir over the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial and the assertions

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CENTRAL MESSAGE

The alleged flaws with the EXCEL trial led to growing stir over misconduct. Some deviations from the original protocol may have caused the conclusion to be contradictory with clinical findings.

of misconduct, analyzing every contradictory aspect related to the EXCEL trial.

The earlier claim from the EXCEL trial authors that they were unable to determine the per-protocol prespecified secondary end point of myocardial infarction (MI) rate according to the universal definition of MI (UDMI) because

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troponin samples had not been properly collected was refuted by letting them know that the UDMI alternatively considers creatine kinase-MB analysis rather than troponin.²⁻⁴ Consequently, the authors compulsorily reported the UDMI protocol-specified analysis based on creatine kinase-MB data, revealing a stark difference from the original article, with a higher rate of periprocedural MI related to the percutaneous coronary intervention arm, hence invalidating the conclusion published in the *New England Journal of Medicine*.^{5,6}

Another concern was the disclosure of the formal hypothesis testing, prespecified as a demonstration of noninferiority at 3 years, and without explanation was switched to a superiority test in the 5-year analysis.⁶ If, as prespecified, the same noninferiority analysis had been conducted at 5 years it would not have met the criteria for statistical significance, and the published conclusion would not have been possible.^{7,8} The statistically significant 38% higher mortality in the percutaneous coronary intervention arm raises clinical concern because this difference is actively accelerating over time in a cohort of patients relatively young (mean age, 66 years) and therefore a potential life expectancy of 15 to 20 years. In a clinical trial, a finding of a statistically significant higher mortality in 1 arm than the other should be strongly emphasized and included in the conclusion of the abstract and of the main article, which did not happen.⁹ The heightened rate of noncardiovascular death associated to second-generation drug-eluting stent as seen in EXCEL trial, the Randomized Comparison of CABG and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial,¹⁰ and others,³ mainly related to cancer and infection, brings apprehension because these data have reappeared again in the International Study of Comparative Health Effectiveness With Medical and Invasive Approach (ISCHEMIA) and ISCHEMIA-Chronic Kidney Disease (ISCHEMIA-CKD) trials, where noncardiovascular deaths trended higher in invasive strategy versus the conservative.^{11,12} Until these issues are addressed, the EXCEL trial has the potential to become an

example of distrust as a distorted form of science, leaving both the public and medical community to question how this happened. All reputable medical societies worldwide, abiding by their core mission of protecting patient safety, cannot stay silent. All must come forward in unison to find ways to avert it recurring.

The data generated by the EXCEL trial, the largest ever on this subject, are crucial to understand the influence of therapies in this deadly condition and, accordingly, must be made open for unbiased and truthful independent scrutiny. In the meantime, a provisional retraction of the article⁶ should be issued for judicious reassessment to prevent patients from encountering serious potential harm.

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