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EDITORIAL

Beyond superiority: preserved cardiovascular efficacy and emerging signals in SURPASS-CVOT

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Cardiovascular outcome trials (CVOTs) in type 2 diabetes have moved beyond placebo-controlled safety assessments, relying on comparisons with therapies that confer cardiovascular benefit. In this context, the SURPASS-CVOT trial comparing tirzepatide with dulaglutide in patients with established atherosclerotic cardiovascular disease should not be interpreted simply as a study that failed to demonstrate superiority, but as a trial that illustrates how preserved efficacy, statistical governance, and drug mechanism jointly shape contemporary cardiovascular inference [1].

Two design features are central to understanding its results. First, dulaglutide is an active comparator with proven cardiovascular benefit, as demonstrated in the REWIND trial [2]. Second, the non inferiority margin adopted in SURPASS-CVOT (upper bound of the hazard ratio, 1.05) is unusually stringent, calibrated to preserve a substantial fraction of the comparator's established effect and aligned with regulatory expectations for cardiovascular protection [1, 3]. Within this framework, demonstration of noninferiority should be interpreted not as mere exclusion of harm, but as preservation of cardiovascular efficacy relative to a therapy with known benefit.

Notably, point estimates for the primary MACE-3 endpoint consistently favored tirzepatide, indicating a directionally greater effect that could not be formally adjudicated within the prespecified inferential framework [1]. Thus, SURPASS-CVOT establishes cardiovascular efficacy at least comparable to dulaglutide while excluding excess risk under exceptionally conservative assumptions.

The trial's statistical architecture clarifies why superiority could not be claimed. SURPASS-CVOT employed a group-sequential design with prespecified control of the family-wise error rate through a graphical multiple-testing strategy [1, 4]. All available alpha was allocated to the primary endpoint, with conditional transfer to key secondary endpoints only if superiority was achieved. Because superiority was not demonstrated, the testing hierarchy was intentionally halted, rendering all secondary outcomes descriptive by design (Fig. 1). Secondary endpoints are therefore not neutral because of insufficient power or biological implausibility, but because the trial was not statistically authorized to test them once the primary superiority gate was not crossed [1, 4].

Beyond the primary endpoint, the pattern of secondary outcomes, though descriptive, invites clinically meaningful reflection. In particular, the numerically favorable trend in all-cause mortality, observed despite the absence of superiority for the MACE-3 composite, raises questions about endpoint–mechanism alignment for metabolically dominant therapies [1]. Traditional MACE composites were designed to capture therapies acting predominantly on atherothrombotic risk, privileging first nonfatal myocardial infarction or stroke as drivers of benefit [5]. Dual GIP–GLP-1 receptor agonists, however, exert pleiotropic effects extending beyond classical atherosclerosis, including substantial improvements in body weight, insulin resistance, systemic

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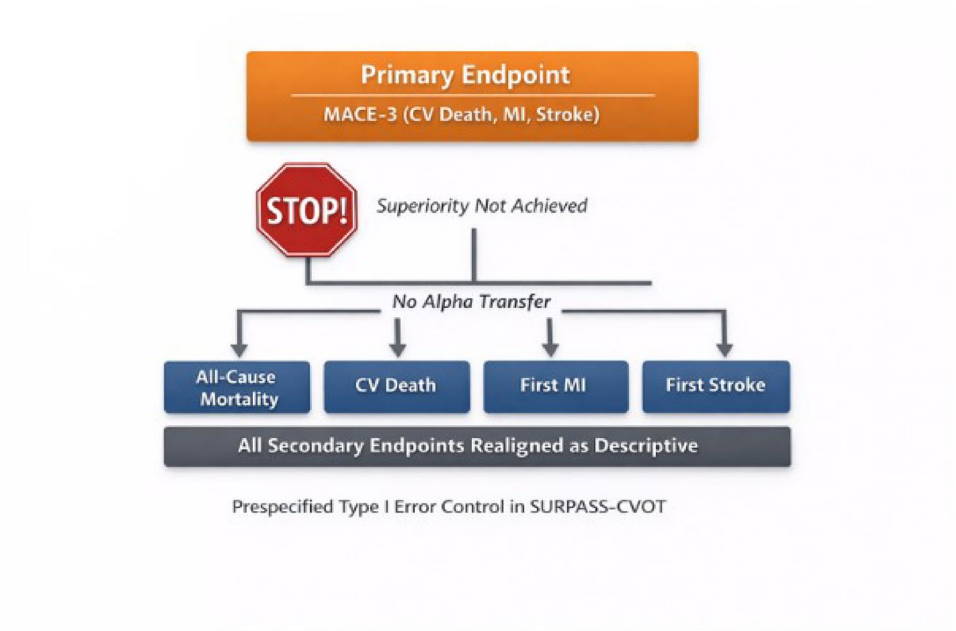

Fig. 1 Prespecified Type I Error Control Strategy in SURPASS-CVOT. All available alpha was allocated to the primary MACE-3 end point. Because superiority was not achieved, alpha was not transferred to key secondary hypotheses, which are therefore descriptive by design

inflammation, hepatic steatosis, and cardiorenal physiology [6].

From a biological standpoint, it is therefore plausible that the most integrated signal of benefit for dual agonism may emerge not in time-to-first atherothrombotic composites, but in all-cause mortality, an endpoint that aggregates effects across cardiovascular, renal, metabolic, and noncardiovascular domains [7, 8]. Time-to-first-event analyses may underestimate therapies that reduce recurrent events, competing risks, or systemic vulnerability without substantially altering the incidence of a single dominant atherothrombotic outcome [9].

Methodology reinforces this interpretation. The primary analysis in SURPASS-CVOT followed an intention-to-treat estimand, preserving randomisation and addressing a policy-relevant question: what is the cardiovascular effect of assigning tirzepatide rather than dulaglutide in routine clinical practice? [1].

Yet tirzepatide is a dose-escalated therapy with dynamic patterns of interruption and reinitiation. When treatment exposure is heterogeneous and discontinuation is clinically informative, intention-to-treat analyses may attenuate estimates of maximal biological effect. While on-treatment or per-protocol contrasts can be informative, they require explicit causal methods to address informative censoring and time-varying confounding [7, 8].

Looking forward, SURPASS-CVOT highlights a broader inflection point in CVOT design. As background therapy improves, comparators become more effective, and statistical guardrails more stringent, superiority on MACE composites will become difficult to demonstrate even for biologically potent agents [3, 4]. The future of cardiovascular outcomes research therefore lies not in larger trials alone, but in better alignment between drug mechanism and endpoint architecture.

For metabolically dominant therapies such as dual incretin agonists, this may involve complementing traditional MACE endpoints with outcomes that better reflect systemic vulnerability, including all-cause mortality, recurrent-event frameworks, and multistate models integrating heart failure, renal decline, and death [7–9]. Precision-oriented designs enriching for populations in whom metabolic stress and cardiorenal disease drive risk may further clarify where preserved efficacy translates into incremental clinical benefit over time [6].

Accordingly, SURPASS-CVOT closes one chapter decisively establishing cardiovascular efficacy at least comparable to a GLP-1 receptor agonist with proven benefit—while opening another. The central scientific question is no longer whether tirzepatide is cardiovascularly safe, but how, where, and through which endpoints its broader metabolic effects translate into meaningful clinical advantage.

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Declarations

Conflict of interest The authors declare that they have no financial interests and no conflicts of interest.

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