Composite Primary End Points in Cardiovascular Outcomes Trials Involving Type 2 Diabetes Patients: Should Unstable Angina Be Included in the Primary End Point?

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Reductions in cardiovascular (CV) outcomes in recently reported trials, along with the recent approval by the U.S. Food and Drug Administration of an additional indication for empagliflozin to reduce the risk of CV death in type 2 diabetes patients with evidence of CV disease, have renewed interest in CV outcome trials (CVOTs) of glucose-lowering drugs. Composite end points are a pragmatic necessity in CVOTs to ensure that sample size and duration of follow-up remain reasonable. Combining clinical outcomes into a composite end point increases the numbers of events ascertained and thus statistical power and precision. Historically, composite CV end points in diabetes trials have included a larger number of components, while more recent CVOTs almost exclusively use a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke—the so-called three-point major adverse CV event (3P-MACE) composite—or add hospitalization for unstable angina (HUA) to these three outcomes (4P-MACE). The inclusion of HUA increases the number of events for analysis, but noteworthy disadvantages include clinical subjectivity in ascertainment of HUA and its lower prognostic relevance compared with CV death, MI, or stroke. Furthermore, results from recent CVOTs indicate that glucose-lowering agents seem to have minimal impact on HUA. Its inclusion therefore potentially favors a shift of the hazard ratio (HR) toward the null, which is especially problematic in trials designed to demonstrate noninferiority. The primary outcome of 3P-MACE may offer a better balance than 4P-MACE between statistical efficiency, operational complexity, the likelihood of diagnostic precision (and therefore clinical relevance) for each of the component outcomes, clinical importance, and the aim to adequately capture any potential treatment effect of the intervention. Nevertheless, as individual medications may mechanistically differ in their impact on CV outcomes, no particular individual or composite end point can be seen as a "gold standard" for CVOTs of all glucose-lowering drugs.

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Cardiovascular (CV) disease is a common comorbidity in type 2 diabetes, and CV-related death remains a leading cause of premature mortality in people with type 2 diabetes (1). Over the past 15 years, more than 25 CV outcome trials (CVOTs) involving over 200,000 patients with type 2 diabetes have been initiated (2). These studies were designed either to test an intensive versus traditional antihyperglycemic treatment strategy by attempting to achieve a meaningful HbA_{1c} reduction to evaluate

its impact on CV events or to investigate specific glucose-lowering compounds. In the latter, the glucose-lowering agent is usually compared with placebo in addition to current standard of care with the primary intention of demonstrating CV safety (i.e., statistical noninferiority), as required by international regulatory agencies to support approval of diabetes medications. To date, CVOTs testing intensive antihyperglycemic strategies have not convincingly demonstrated improved CV outcomes in patients with type 2 diabetes. In contrast, the recent BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)—a placebo-controlled trial of empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor—was the first CVOT evaluating a glucose-lowering medication to demonstrate a significant reduction in CV events (3). Based on this trial, the U.S. Food and Drug Administration (FDA) recently approved a new indication for empagliflozin to reduce the risk of CV death in adults with type 2 diabetes and CV disease (4,5). The Committee for Medicinal Products for Human Use of the European Medicines Agency has also recommended revising the empagliflozin label to reflect its beneficial effects on both glycemic control and CV events (6).

In addition, CVOTs of two glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have now reported beneficial CV outcomes. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial with the daily GLP-1 RA liraglutide reported significant reductions in CV events versus placebo (7). The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), with the investigational weekly GLP-1 RA semaglutide, also reported a reduction in major adverse CV events (MACE), although this trial was not designed to test a superiority hypothesis (8). These three CVOTs used the same composite MACE outcome for the primary end point: the time to the first event of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, i.e., 3P-MACE. However, other recently concluded CVOTs of a GLP-1 RA and a dipeptidyl peptidase 4 (DPP-4) inhibitor—Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS), respectively—used a 4P-MACE composite primary end point that included hospitalization for unstable angina (HUA).

Herein, we discuss the necessity of composite end points in CVOTs for type 2 diabetes, illustrate their historical evolution, describe the two most commonly used composite end points for assessment of atherosclerotic CV disease outcomes (3P-MACE and 4P-MACE), and highlight their key strengths and weaknesses. We also discuss the emerging interest in hospitalization for heart failure (HHF) and the issues with its inclusion as a primary or secondary end point.

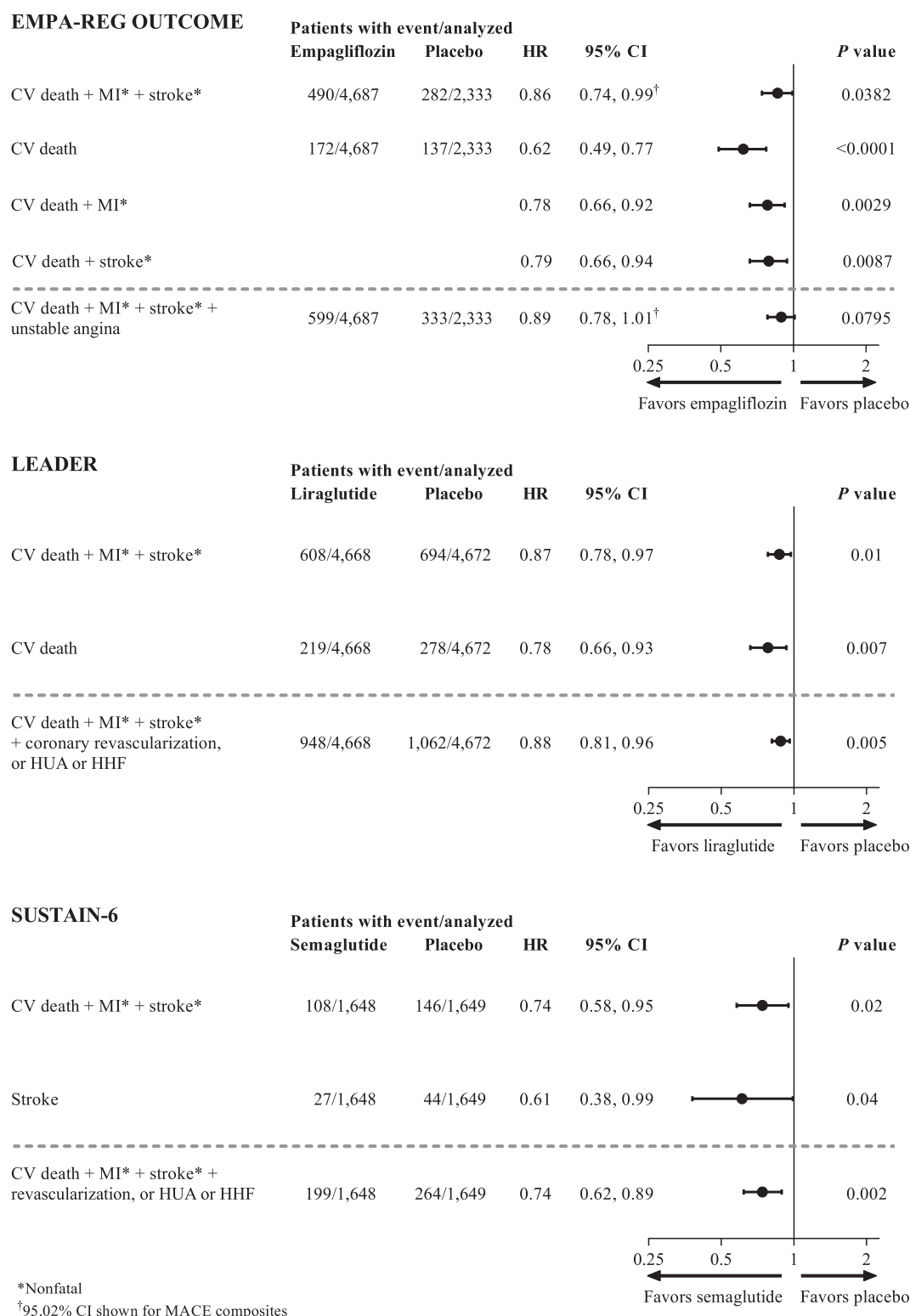## RATIONALE FOR THE USE OF COMPOSITE END POINTS

Ideally, clinical trials should have a singular (noncomposite) primary end point that fully captures the potential effect of investigational therapies, albeit there may be scenarios in which a composite end point is more clinically relevant than a single component of the composite if the intervention can have a similar beneficial effect on equally important outcomes. However, the use of singular end points would require substantially larger trial sample sizes and/or longer follow-up to provide reliable statistical power (9,10). Given that extending life is the ultimate goal of most treatments and that mortality can be determined without outcome ascertainment bias, overall (all-cause) mortality is conceptually an ideal primary end point. Concordant reduction in all-cause mortality (or no increase) would provide reassurance that reductions in CV mortality are not offset by non-CV deaths. However, mortality rates in the general population are declining (11), even in high-risk populations such as individuals with type 2 diabetes (11–17), possibly as a consequence of modern multifactorial approaches to modify CV risk factors. Consequently, to achieve statistical power for comparisons, trials that focus purely on mortality would need prohibitively large numbers of patients and lengthy follow-up, a concern when one of the objectives of modern CVOTs is to rule out potential adverse effects of novel medications in a timely manner.

Composite end points are therefore a pragmatic necessity: combining clinical outcomes that seem to share common pathophysiological mechanisms into a composite end point increases the numbers of events ascertained and thus statistical power and precision. Indeed, MACE outcomes allow a CVOT to be conducted in a more reasonable time frame while still analyzing important clinical outcomes. Furthermore, composite end points are now a regulatory standard in the realm of CV disease—as reflected in the 2008 guidance from the FDA for evaluating the CV risk of novel glucose-lowering therapies (18). Nevertheless, composite end points are not ideal from a methodological perspective, as heterogeneity of effects on the component outcomes may be observed, potentially diluting the estimate of effect on a composite. Indeed, adding components to a composite end point that are to a lesser degree (or not at all) affected by the intervention, or which may be difficult to adjudicate, increases the likelihood of shifting the HR toward the null (19); this problem is exacerbated when the primary analysis is planned for noninferiority, raising the probability of type II error. This is particularly true for less well defined and clinically heterogeneous events such as HUA or end points impacted by clinical or interventional decision-making such as coronary or peripheral revascularization (20). In these cases, when the results for the composite end point are not driven comparably by each of its components, the addition of more end points to a single component such as mortality moves the HR of the composite closer to unity (Fig. 1).

COMPOSITE END POINTS IN CVOTS IN PATIENTS WITH TYPE 2 DIABETES

Historically, CVOTs in type 2 diabetes have included a variable number of clinical outcomes within their composite primary end points. For example, the composite in the UK Prospective Diabetes Study (UKPDS) ("any diabetes-related outcome") comprised over 10 different end points, including vascular and nonvascular intermediate biomarkers admixed with clinical outcomes (21). Similarly, the primary end point in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) comprised seven different outcomes: overall mortality, MI, stroke, acute coronary syndrome, coronary or peripheral revascularization, and amputation above the ankle. This heterogeneity clearly shifted the results of the composite toward null, as the between-group difference

EMPA-REG OUTCOME

	Patients with event/analyzed					
	Empagliflozin	Placebo	HR	95% CI		P value
CV death + MI* + stroke*	490/4,687	282/2,333	0.86	0.74, 0.99[†]		0.0382
CV death	172/4,687	137/2,333	0.62	0.49, 0.77		<0.0001
CV death + MI*			0.78	0.66, 0.92		0.0029
CV death + stroke*			0.79	0.66, 0.94		0.0087
CV death + MI* + stroke* + unstable angina	599/4,687	333/2,333	0.89	0.78, 1.01[†]		0.0795

0.25   0.5   1   2
Favors empagliflozin   Favors placebo

LEADER

	Patients with event/analyzed					
	Liraglutide	Placebo	HR	95% CI		P value
CV death + MI* + stroke*	608/4,668	694/4,672	0.87	0.78, 0.97		0.01
CV death	219/4,668	278/4,672	0.78	0.66, 0.93		0.007
CV death + MI* + stroke* + coronary revascularization, or HUA or HHF	948/4,668	1,062/4,672	0.88	0.81, 0.96		0.005

0.25   0.5   1   2
Favors liraglutide   Favors placebo

SUSTAIN-6

	Patients with event/analyzed					
	Semaglutide	Placebo	HR	95% CI		P value
CV death + MI* + stroke*	108/1,648	146/1,649	0.74	0.58, 0.95		0.02
Stroke	27/1,648	44/1,649	0.61	0.38, 0.99		0.04
CV death + MI* + stroke* + revascularization, or HUA or HHF	199/1,648	264/1,649	0.74	0.62, 0.89		0.002

0.25   0.5   1   2
Favors semaglutide   Favors placebo

*Nonfatal
[†]95.02% CI shown for MACE composites

Figure 1—Selected end points in the EMPA-REG OUTCOME study of empagliflozin (ref. 3 and Boehringer Ingelheim, data on file), the LEADER study of liraglutide (7), and the SUSTAIN-6 study of semaglutide (8), each compared with placebo.

versus placebo failed to achieve nominal statistical significance even though the "prioritized secondary" outcome of 3P-MACE was significantly superior for pioglitazone versus placebo (22).

More recent CVOTs in type 2 diabetes almost exclusively use a much more focused composite outcome as the primary end point, particularly after the 2008 FDA guidance. Although most of these trials use 3P-MACE, some have also added HUA to form 4P-MACE. Figure 2 illustrates the change over time in primary end points of CVOTs in type 2 diabetes.
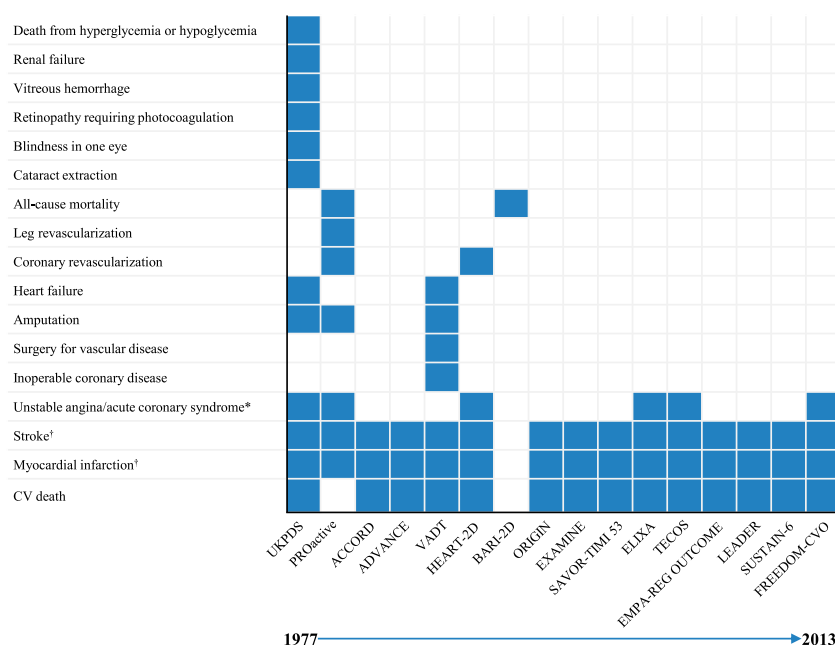
Figure 2—Evolution of prospectively planned primary end points in completed CVOTs of antihyperglycemic treatments for type 2 diabetes, listed in order of year of initiation (3,7,8,21,22,37–47). ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; BARI-2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome; FREEDOM-CVO, Study to Evaluate Cardiovascular Outcomes with ITCA 650 in Patients Treated with Standard of Care for Type 2 Diabetes; HEART-2D, Hyperglycemia and Its Effect after Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; VADT, Veterans Affairs Diabetes Trial. *Includes events requiring hospitalization. †Includes fatal and nonfatal events.

HUA AS AN END POINT

The inclusion of HUA is a matter of significant and ongoing debate. There are cogent arguments for its inclusion in composite primary end points when assessing atherosclerotic vascular disease outcomes. The addition of unstable angina to 3P-MACE may enhance the statistical efficiency of a study by incrementing accrual of events contributing to the primary end point. Furthermore, from a clinical perspective, unstable angina and MI both belong to the spectrum of pathophysiological processes collectively described as acute coronary syndromes. The FDA's 2008 guideline recommends that hospitalization for acute coronary syndrome, urgent revascularization, and possibly other end points could be added to the 3P-MACE primary end point (18). However, important challenges that come with adding unstable angina to a composite end point have to be considered.

First, in contrast to death, nonfatal MI, or nonfatal stroke, the diagnosis of unstable angina involves significant subjectivity on the part of the treating clinician, the investigator, and adjudication committees (23). To address these challenges, incrementally more specific adjudication criteria have been applied to CVOTs in recent years. These are reflected in a consensus document on the adjudication of HUA for CVOT end points, which requires symptoms at rest consistent with angina lasting at least 10 min that necessitate an unscheduled visit to a health care facility and at least an overnight observation, as well as evidence of ischemia by electrocardiography or imaging but with no cardiac enzyme elevations (23). Given the heterogeneous clinical presentation of chest pain syndromes, and despite the widespread clinical adoption of highly sensitive assays for biomarkers of myocardial injury such as high-sensitivity troponin (hsTn) assays, central adjudication of unstable angina remains extremely challenging. Even at the bedside, the distinction between unstable angina and myriad other causes of chest pain is a clear clinical conundrum, challenging the specificity of the diagnosis clinically and the outcome in research projects—whether as coded by the clinician or investigator or as adjudicated in a clinical trial. Consequently, concordance between the assessment of local clinicians and study investigators and that of central trial adjudication committees is often quite low (24–26), and both processes have important degrees of imprecision and inaccuracy.

Second, with the ever-broadening clinical adoption of hsTn assays for the diagnostic assessment of MI, chest pain or anginal-equivalent presentations with normal hsTn assessments remain categorized as possible unstable angina, but with a wide variety of alternative diagnoses that are most often not CV related.

Third, unstable angina is of much lower prognostic relevance than nonfatal stroke or nonfatal MI and, of course, CV death in the composite. For example, unstable angina is distinguished from non–ST-elevation MI by substantially lower risk of mortality (27) and commensurately less absolute benefit from intensive antiplatelet therapy and early invasive treatment (27).

Fourth, all CVOTs in type 2 diabetes conducted after the FDA's 2008 guidance have demonstrated that HUA is a challenging outcome to influence with glucose-lowering agents, thus weighting results of composite analyses toward the null and confounding analyses of noninferiority. In these studies, the HRs for HUA range from 0.82 to 1.19 (Table 1). Therefore, inclusion of HUA within the composite primary end point is likely to dilute the treatment effect. Consequently, while the addition of HUA may make it more likely that noninferiority of a medication is demonstrated, it may also mask potential CV benefit or harm by shifting the HR toward the null. In summary, while HUA could be a valuable end point in the assessment of some therapies, such as antiplatelet agents, this does not seem to be the case with glucose-lowering medications.

HEART FAILURE AS AN END POINT

Heart failure is a common complication of type 2 diabetes, and its prognostic implications—including high mortality—are often underappreciated (28,29). A case could therefore be made for including heart failure outcomes within the primary composite end point in diabetes CVOTs, as recently suggested (28,29). However, different glucose-lowering medications may have markedly different

Table 1—Hazard ratio for HUA in recently completed CVOTs in type 2 diabetes, listed in approximate order of completion from earliest to most recent

CVOT (reference)	Glucose-lowering drug	Class	Hazard ratio	95% CI
SAVOR-TIMI 53 (44)	Saxagliptin	DPP-4 inhibitor	1.19	0.89, 1.60
EXAMINE (48)	Alogliptin	DPP-4 inhibitor	0.90*	0.60, 1.37
ELIXA (45)	Lixisenatide	GLP-1 RA	1.11	0.47, 2.62
TECOS (46)	Sitagliptin	DPP-4 inhibitor	0.90	0.70, 1.16
EMPA-REG OUTCOME (3)	Empagliflozin	SGLT2 inhibitor	0.99	0.74, 1.34
LEADER (7)	Liraglutide	GLP-1 RA	0.98	0.76, 1.26
SUSTAIN-6 (8)	Semaglutide	GLP-1 RA	0.82	0.47, 1.44
FREEDOM-CVO (47)	ITCA 650 (exenatide minipump)	GLP-1 RA	Not yet available	Not yet available

EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome; FREEDOM-CVO, Study to Evaluate Cardiovascular Outcomes with ITCA 650 in Patients Treated with Standard of Care for Type 2 Diabetes; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53. *Urgent revascularization due to unstable angina.

impacts on heart failure; combining such outcomes with other end points that have substantially disparate pathophysiology is hard to defend, and the results may be difficult to interpret. Nevertheless, HHF should always be prospectively captured, adjudicated, and analyzed in CVOTs as a secondary outcome at least. Alternatively, HHF can be designated as a primary outcome combined with CV mortality in studies of agents whose mechanism of action may impact heart failure, such as in the planned studies of the SGLT2 inhibitors dapagliflozin (30) and empagliflozin (31).

SHOULD THE FOCUS PURELY BE ON THE PRIMARY END POINT?

A single component of a composite end point often disproportionately affects the treatment outcome compared with the other components. However, even if all components contribute relatively equally for a clinically significant composite but not enough for each individually to be clinically significant, it is usually not valid to conclude efficacy for a single component based on the findings for the composite (32). Furthermore, Pocock and Stone (33) recently made the following pertinent observation: "There is a natural tendency to simplify the findings of a clinical trial into a binary conclusion: 'Was there a positive outcome—or not?' In order to address this question with some objectivity, attention is typically focused on whether the prespecified measure of success for the primary outcome has been met—that is, whether a P value of less than 0.05 has been achieved for the difference in treatments. In reality, a more nuanced interpretation requires a

thorough examination of the totality of the evidence, including secondary end points, safety issues, and the size and quality of the trial." One recent example is the EMPA-REG OUTCOME trial (3), where the primary end point (3P-MACE) was driven by a substantially reduced rate of CV death ($n = 309$ events; HR 0.62; 95% CI 0.49, 0.77; $P < 0.001$) and was strengthened by similar findings for all-cause mortality ($n = 463$ events; HR 0.68; 95% CI 0.57, 0.82; $P < 0.001$) and HHF ($n = 221$ events; HR 0.65; 95% CI 0.50, 0.85; $P = 0.002$) (3). However, there was no significant effect on nonfatal MI or nonfatal stroke. This example also illustrates the importance of separating out HHF from 3P-MACE as a stand-alone end point, because of both the heterogeneity of efficacy that a therapy may have on HHF compared with MACE outcomes and the disparate underlying pathobiology of heart failure compared with atherosclerotic vascular disease.

3P-MACE: A SUITABLE COMMON STANDARD FOR CVOTS IN DIABETES?

In light of the above considerations, 3P-MACE appears to be the most suitable end point for evaluating CV outcomes in large CVOTs with glucose-lowering medications. The 3P-MACE composite end point best captures clinically relevant CV outcomes, has individual components that are reasonably straightforward to adjudicate (thus ensuring precision of the diagnosis), is relatively easy to implement, and is well accepted by regulatory authorities. For these reasons, the large majority of ongoing CVOTs in type 2 diabetes required by regulatory authorities use

3P-MACE as their primary end point (Table 2). Indeed, a recent FDA recommendation is to prefer the use of 3P-MACE to more reliably exclude a CV risk upper margin of 1.3 (34). In the absence of regulatory or academic consensus on end points, this alignment of primary end points across CVOTs should make between-study comparisons—including meta-analyses—more robust and enhance the clinical relevance of these megatrials, which demand substantial time, effort, and resources from clinical investigators, patients, and study sponsors. Nevertheless, even 3P-MACE itself suffers from potential problems with heterogeneity of effects on the component outcomes, as the mechanism of action of a glucose-lowering medication may differentially impact the three components of this end point. This phenomenon occurred in the EMPA-REG OUTCOME study, as discussed above, in which empagliflozin significantly reduced the incidence of CV death (HR 0.62; 95% CI 0.49, 0.77) but not that of nonfatal MI (HR 0.87; 95% CI 0.70, 1.09) or nonfatal stroke (HR 1.24; 95% CI 0.92, 1.67), which thus diluted the estimate of the overall treatment effect as measured by the 3P-MACE primary end point (HR 0.86; 95% CI 0.74, 0.99) (3). Similarly, the incidence of CV death (HR 0.78; 95% CI 0.66, 0.93) was significantly reduced with liraglutide in the LEADER study, but not that of nonfatal MI (HR 0.88; 95% CI 0.75, 1.03) or nonfatal stroke (HR 0.89; 95% CI 0.72, 1.11) (7). In the selection of composite end points, therefore, sufficient consideration needs to be given to the question of whether individual components are likely to be differentially impacted.

Table 2—Primary end points in ongoing CVOTs of glucose-lowering drugs for type 2 diabetes reporting after 2016, listed in order of trial start date from earliest to most recent

CVOT	Glucose-lowering drug	Class	Primary end point	ClinicalTrials.gov identifier
TOSCA.IT	Pioglitazone	Thiazolidinedione	3P-MACE plus unplanned coronary revascularization	NCT00700856
CANVAS	Canagliflozin	SGLT2 inhibitor	3P-MACE	NCT01032629
EXSCEL	Exenatide (once weekly)	GLP-1 RA	3P-MACE	NCT01144338
CAROLINA	Linagliptin	DPP-4 inhibitor	3P-MACE	NCT01243424
REWIND	Dulaglutide	GLP-1 RA	3P-MACE	NCT01394952
DECLARE-TIMI 58	Dapagliflozin	SGLT2 inhibitor	3P-MACE	NCT01730534
CARMELINA	Linagliptin	DPP-4 inhibitor	3P-MACE	NCT01897532
DEVOTE	Insulin degludec	Basal insulin	3P-MACE	NCT01959529
VERTIS CV	Ertugliflozin	SGLT2 inhibitor	3P-MACE	NCT01986881
HARMONY	Albiglutide	GLP-1 RA	3P-MACE	NCT02465515
PIONEER 6	Semaglutide (oral)	GLP-1 RA	3P-MACE	NCT02692716

3P-MACE: CV death, nonfatal MI, nonfatal stroke. CANVAS, CANagliflozin cardioVascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events; DEVOTE, A Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events; EXSCEL, EXenatide Study of Cardiovascular Event Lowering trial; HARMONY, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes; REWIND, Researching cardiovascular Events with a Weekly INcretin in Diabetes; TOSCA.IT, Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents.Intervention Trial; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease.

In conclusion, as individual drugs may mechanistically differ in their impact on CV outcomes, no particular end point can be seen as a "gold standard" for all CVOTs of glucose-lowering drugs. However, 3P-MACE is generally likely (albeit not guaranteed) to offer the best balance between statistical efficiency and operational complexity, to ensure diagnostic precision (and therefore clinical relevance) for each of its components, and to adequately capture any potential treatment effect of the intervention. In this regard, 3P-MACE appears to be superior to its variants that include HUA (4P-MACE), HHF, revascularization, or other CV outcomes.

Consequently, the steering committees of two ongoing CVOTs of the DPP-4 inhibitor linagliptin—Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) and Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) (clinical trial reg. nos. NCT01243424 and NCT01897532, respectively, clinicaltrials.gov)—which include the authors, have unanimously decided to adopt 3P-MACE as the primary end point of these studies, replacing the originally planned primary end point of 4P-MACE long before these studies are finalized. The 4P-MACE end point will remain a pre-defined end point of both trials following analyses of 3P-MACE.

There is clear precedent for such actions from other large CVOTs, where concerns emerged during the studies that the inclusion of components less affected by the treatment may dilute the treatment effect or may mask the true treatment effect. A notable example is the Study of Heart and Renal Protection (SHARP), in which the primary composite CV end point was similarly revised from a broader one to a more focused one during trial conduct (35). An absolute prerequisite for such a modification in study analysis during trial conduct is that the decision is made without access to unblinded data. Indeed, the respective steering committees and sponsor of CAROLINA and CARMELINA had absolutely no access to any interim results from these two ongoing CVOTs and, at the time of protocol modifications of the primary composite end points, the studies remained fully blinded to the steering committees, sponsor, trial teams, investigators, and participants. The adoption of 3P-MACE as the primary end point will align these two trials with other ongoing and completed CVOTs in type 2 diabetes (Table 2).

Finally, the position taken here is directly supported in a recent opinion paper on the assessment of CV safety profiles of novel pharmacotherapies, in which the Cardiovascular Working Party of the European Medicines Agency's Committee for Medicinal Products for Human Use expressed a preference for 3P-MACE as the primary safety end point in meta-analyses and dedicated CVOTs (36).

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