THE CHALLENGES AND PITFALLS OF INCORPORATING EVIDENCE FROM CARDIOVASCULAR OUTCOMES TRIALS IN HEALTH ECONOMIC MODELING OF TYPE 2 DIABETES

Authors: Marc Evans[1], Sasha Berry[2], Avideh Nazeri[2], Samuel JP Malkin[3], Donna Ashley[2], Barnaby Hunt[3], Stephen C Bain[4]

Affiliations:

[1] University Hospital Llandough, Cardiff, UK

[2] Novo Nordisk Ltd., Gatwick, UK

[3] Ossian Health Economics and Communications, Basel, Switzerland

[4] Swansea University Medical School, Swansea, UK

Corresponding author: Marc Evans

University Hospital Llandough

Penlan Road, Llandough, Penarth, CF64 2XX

UK

Telephone: +44 292 071 1711

E-mail: marclyndon1@hotmail.com

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ABSTRACT

The clinical evidence base for evaluating modern type 2 diabetes interventions has expanded greatly in recent years, with numerous efficacious treatment options available (including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors). The cardiovascular safety of these interventions has been assessed individually versus placebo in numerous cardiovascular outcomes trials (CVOTs), statistically powered to detect differences in a composite endpoint of major adverse cardiovascular events (MACE). There have been growing calls to incorporate these data in the long-term modeling of type 2 diabetes interventions, as current diabetes models were developed prior to the conduct of the CVOTs, and therefore rely on risk equations developed in the absence of these data. However, there are numerous challenges and pitfalls to avoid when utilizing data from CVOTs. The primary concerns are around the heterogeneity of the trials, with different study durations, inclusion criteria, rescue medication protocols and endpoint definitions – this results in significant uncertainty when comparing two or more interventions evaluated in separate CVOTs, as robust adjustment for these differences is difficult. Analyses using CVOT data inappropriately can dilute clear evidence from head-to-head clinical trials, and blur healthcare decision making. Calibration of existing models may represent an approach to incorporating CVOT data into diabetes modeling, but this can only offer a valid comparison of one intervention versus placebo based on a single CVOT. Ideally, model development should utilize patient-level data from CVOTs to prepare novel risk equations that can better model modern therapies for type 2 diabetes.

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INTRODUCTION

Modern interventions for type 2 diabetes are associated with an almost overwhelming amount of clinical data, and deciphering the ever-growing evidence base is a challenge. Medication classes including glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which are associated with reductions in glycated hemoglobin (HbA1c) and body weight, while also having a low risk of hypoglycemia, have been evaluated versus an array of comparators in the diabetes treatment algorithm in head-to-head clinical trials, indirect treatment comparisons (ITCs), and network meta-analyses (NMAs).[1] Alongside head-to-head clinical trials, studies evaluating the cardiovascular outcomes of all newly marketed treatments for type 2 diabetes were requested by the Food and Drug Administration (FDA) in the United States in 2008, in response to concerns around the cardiovascular safety of the thiazolidinedione, rosiglitazone.[2] These cardiovascular outcomes trials (CVOTs) were designed to evaluate the safety of modern therapies for type 2 diabetes versus placebo, with a longer follow-up period than standard phase 2 or 3 trials, and through the collection of data on the incidence of diabetes-related complications directly, rather than changes in surrogate outcomes. The primary outcome of CVOTs is a combined endpoint of three or four major adverse cardiovascular events (MACE), most commonly cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (an example of three-point MACE). CVOTs have been performed for the SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin and ertugliflozin (CANVAS, DECLARE-TIMI, EMPA-REG OUTCOME and VERTIS-CV), and for the GLP-1 receptor agonists efpeglenatide, lixisenatide, exenatide, liraglutide, oral semaglutide, injectable semaglutide and dulaglutide (AMPLITUDE-O, ELIXA, EXSCEL, LEADER, PIONEER 6, SUSTAIN 6 and REWIND), as well as for dipeptidyl peptidase-4 (DPP-4) inhibitors linagliptin, alogliptin, saxagliptin and sitagliptin (CARMELINA and CAROLINA, EXAMINE, SAVOR-TIMI and TECOS).[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19]

Healthcare systems worldwide are coming under increased pressure, and economic evaluation of new technologies is helping to inform how limited monetary resources are allocated, with the aim of maximizing health across the population within a constrained healthcare budget. This is particularly important in the treatment of diabetes, as the prevalence of the disease continues to rise, from 151 million globally in 2000 to 536.6 million in 2021, and a predicted increase to 783.7 million by 2045.[20] Accurate assessment of the cost-effectiveness of interventions for the treatment of type 2 diabetes

requires a long-term time horizon, aiming to fully capture the impact of each treatment on the risk of diabetes-related complications over patient lifetimes. As such, the time horizon of economic evaluations is well beyond the typical follow-up period of trials, and computer simulation models are widely used.

Conventional health economic models of type 2 diabetes take changes in risk factors such as HbA1c, blood pressure, lipid profiles and body mass index from short-term clinical trials and project the cumulative incidence of diabetes-related complications and life expectancy using risk equations developed based on long-term studies, such as the United Kingdom Prospective Diabetes Study (UKPDS).[21,22,23,24,25,26,27,28] However, analyses using short-term data to project long-term outcomes typically use data from only one clinical trial, ITC or NMA at a time, as the evidence informing short-term changes in surrogate outcomes must correspond to the research question, specifically the patient population and the stage in the diabetes treatment algorithm. The predictive accuracy of the risk equations built into the model should also be considered, as existing health economic models of type 2 diabetes were developed before CVOTs were conducted, and therefore rely on risk equations developed in the absence of these data. There is concern that these models cannot fully capture the cardiovascular benefits associated with new treatments observed in the CVOTs, which may be beyond the effects of changes in HbA1c and body weight, and there has been a growing call for inclusion of these data in long-term diabetes modeling.[29,30,31] This has also aligned with a shift in general health technology assessment to use not only the best available evidence, but to capture all available evidence relating to the evaluated intervention. However, there are numerous challenges and pitfalls to avoid when utilizing data from CVOTs. Analyses using CVOT data inappropriately can dilute clear evidence from head-to-head clinical trials and blur healthcare decision making.

The aims of the present review are to explore the common pitfalls that can occur when attempting to incorporate data from CVOTs into modeling studies of type 2 diabetes; to review modeling studies from the past 5 years incorporating data from CVOTs in comparisons of active agents, examining the methods used and evaluating their appropriateness; and to suggest alternative approaches that could be used in future modeling analyses.

THE CHALLENGES OF USING DATA FROM CVOTS IN ECONOMIC EVALUATIONS OF INTERVENTIONS FOR TYPE 2 DIABETES

The challenges when incorporating data from CVOTs into health economic analyses aiming to compare two or more active interventions assessed in separate CVOTs can be considered in two categories:

1. Difficulties due to heterogeneity across the CVOTs such that the inputs used to inform each trial arm are not comparable. CVOTs have differences in population inclusion criteria, background medications administered in the active treatment and standard of care arms, endpoint definitions, and study durations. The lack of comparability between CVOTs is exemplified by the differences in the MACE rates in the placebo arms of each trial, which range from 2.42 events per 100 patient years in DECLARE-TIMI to 5.63 events per 100 patient years in CARMELINA (Table 1).[5,15] This shows that conclusions on relative efficacy between treatments cannot be drawn without substantial adjustment to control for all the differences between the CVOTs (including population characteristics at baseline, differences in treatment effects associated with the interventions, study durations, and endpoint definitions, as discussed below). Possible methods for adjustment include propensity score matching with patient-level data, or matching-adjusted indirect comparisons, methods that have been previously described.[32,33] The differences around heterogeneity affect not only health economic studies, but, perhaps more importantly, guidelines focused only on clinical efficacy, as it is not clear to what extent differences in the study designs and populations have impacted the observed hazard ratios for MACE in the various CVOTs.
2. Difficulties in incorporating data from CVOTs into a suitable modeling approach with a robust underlying model structure. Even if suitable measures of the relative impact of each intervention on the risk of diabetes-related complications can be generated, it is crucial that they are built into an appropriate model structure in order for reliable conclusions to be drawn.

THE CHALLENGE OF HETEROGENEITY

Population variations

Populations enrolled in CVOTs are heterogeneous, with differences in the proportion of enrolled individuals with prior cardiovascular disease, as well as baseline risk factors such as age, HbA1c levels and body weight, which can influence the incidence of cardiovascular complications and the relative efficacy of the trial intervention versus placebo (Table 2).[34,35,36,37] The percentage of the population with prior cardiovascular disease ranges from 31% in REWIND to 100% in ELIXA, while age at baseline ranges from 60.3 years to 66.2 years (in ELIXA and REWIND, respectively).[6,12] Moreover, duration of diabetes at baseline in the placebo arm of EXAMINE is less than half that of the population in PIONEER 6 (7.1 years versus 14.9 years, respectively).[10,17] Baseline HbA1c in TECOS was 7.2%, compared with 8.7% in LEADER and SUSTAIN 6, whilst baseline BMI in EXAMINE was 28.7 kg/m^2 compared with 32.8 kg/m^2 in SUSTAIN 6.[9,13,17,19] Therefore, evidence from CVOTs cannot be directly compared between trials, due to differences in population inclusion criteria.

An example of how much population variations can influence outcomes was demonstrated in a published matching-adjusted indirect comparison (MAIC) of SUSTAIN 6 and REWIND, which aimed to assess how the efficacy of once-weekly injectable semaglutide would change if the CVOT had enrolled the REWIND population.[38] This analysis found that the hazard ratio for MACE for semaglutide versus placebo was lowered from 0.75 (95% confidence interval 0.58 to 0.95) to 0.65 (95% confidence interval 0.48 to 0.87). This 10-percentage-point change in risk, driven entirely by the population assessed, would have a notable impact on any health economic analysis. This shows how important controlling for differences in the study populations is, in order to generate a robust comparison of relative efficacy.

Study duration and the hazards of hazard ratios

Study durations of CVOTs ranged from 1.3 years (PIONEER 6) to 5.4 years (REWIND), which is particularly important given that hazard ratios describe relative efficacy of one treatment versus another at a single time point, and these may not remain constant over time.[39] The assumption that a hazard ratio is constant over time is known as the proportional hazards assumption, and is most

commonly tested through visual assessment of Kaplan-Meier curves, log(−log) plots and testing of scaled Schoenfeld residuals.

Whether the hazard ratios observed in the CVOTs would change over time (and how they would change over time) is unknown. The effect of time on hazard ratios is particularly notable for diabetes trials as differences in modifiable and non-modifiable risk factors drive differences in the incidence of complications, and modifiable risk factors may change at different rates with different medications.[34,35,36,37] Therefore, if all CVOTs were conducted over the same duration of follow-up, the hazard ratios observed would almost certainly differ (greatly) from the values that have been published, and extrapolation beyond the trial period should be treated with great caution.

Endpoint definitions

A crucial aspect to consider is that endpoint definitions are not consistent across CVOTs. As an example, the definition of myocardial infarction in SUSTAIN 6, PIONEER 6 and LEADER included silent events (detected by changes in routinely collected electrocardiogram traces), but these were excluded from the myocardial infarction and MACE endpoints in EMPA-REG OUTCOME.[7,9,10,13] This is highly significant, as when the FDA requested a re-analysis of the primary three-point MACE endpoint from EMPA-REG OUTCOME with silent myocardial infarction included, the hazard ratio for MACE changed from 0.86 to 0.92, with the difference for empagliflozin versus placebo no longer statistically significant.[40] This shows how the endpoint definitions are crucial, and that variation across the CVOTs drives differences in efficacy that are not reflective of the medications themselves.

THE CHALLENGES OF INCORPORATING DATA APPROPRIATELY WITHIN A ROBUST MODEL STRUCTURE

Difficulties when choosing which endpoints to include in a modeling study

In the CVOTs, the power calculations to select the number of participants and the study durations were based on expected frequency of MACE in the study populations. Therefore, the trials were not powered to detect differences in the individual components of MACE, or the other diabetes-related complication endpoints that may be of interest, such as microvascular complications. Existing health

economic models of diabetes calculate the risk of each complication individually, and cannot use information based on composite endpoints (such as MACE) and, therefore, there is a risk of using CVOT data in a way that was not intended in the original trial design. Data were also collected on the incidence of microvascular complications as secondary endpoints, with different outcomes reported across the CVOTs. As secondary endpoints, studies were not specifically designed or powered to detect differences in these outcomes. Modelers therefore face a difficult decision, as to whether to model differences in rates of diabetes-related complications that CVOTs were not powered to detect, or to not include these aspects and model a potentially incomplete picture of the impact of interventions. While data from other trials (such as renal outcomes studies) could be used to predict microvascular outcomes, combination of these data with CVOT outcomes would be challenging, due to trial heterogeneity. Decisions around this issue therefore need to be justified, and care should be taken to avoid 'cherry picking' endpoints to suit a particular agenda.

Non-inferior does not equal superior

The majority of CVOTs use a non-inferiority design, where the null hypothesis is that the active intervention is inferior to placebo on a background of standard of care.[41,42] This can offer advantages when clinically evaluating interventions in CVOTs, as the incidence of clinical events that constitute MACE is typically low, meaning significant differences between treatment arms are difficult to elucidate without enrolling very large numbers of patients. A non-inferiority design therefore requires far fewer enrolled patients to sufficiently power the trial than a superiority trial, where the null hypothesis is that the novel intervention is not superior to the comparator.[2,41] However, the distinction that *not superior* does not equal *non-inferior* is important to consider when evaluating outcomes from CVOTs (the null hypothesis being proven true in a superiority trial only indicates that the intervention is not superior, meaning it could be non-inferior, equivalent, or inferior), as many of these trials were not designed to detect superiority in MACE, its components, or other endpoints for which data were collected. Applying differences in the rates of complications in health economic analyses (particularly when the confidence intervals for these hazard ratios cross 1.0) can lead to conclusions in cost-effectiveness based on highly uncertain input data. A Bayesian approach with sampling of the hazard ratios applied based on the reported confidence intervals could capture this uncertainty in modeling

analyses, but point estimates are often used with no inclusion or testing of variance around these values.

Differences between the cohorts enrolled in CVOTs and the modeled cohort

While there is some variation, the CVOTs enrolled patients at high risk of cardiovascular disease. The REWIND trial included the patient population at the lowest risk, but even in this study 31% of participants had prior cardiovascular disease.[12] It has been suggested that relative differences between treatments would remain the same in populations with different underlying risks of complications.[43] However, the evidence to support this is mixed, and may be intervention-specific. In REWIND, the hazard ratio for dulaglutide versus placebo for MACE was consistent in patients with and without prior cardiovascular disease, and post-hoc analysis of SUSTAIN 6 suggests that once-weekly semaglutide is associated with a reduced risk of MACE in all subjects irrespective of history of cardiovascular disease.[12,44] However, SGLT-2 inhibitors appear to be associated with reduced frequency of MACE only in patients with pre-existing atherosclerotic cardiovascular disease.[45] These sub-group analyses should be treated with caution, as the patient numbers are greatly reduced compared with the overall trial population, but illustrate that application of hazard ratios generated in a specific trial population in a modeled cohort with different characteristics may be inappropriate.

Differences between cohorts enrolled in CVOTs and cohorts used to develop health economic models

Care should be taken when using implementations of the UKPDS Outcomes Model to model CVOTs, as there are a number of differences in the populations enrolled in the UKPDS and in CVOTs that could limit the predictive accuracy of the model.[46] While the UKPDS Outcomes Model is likely to perform well in populations similar to the derivation cohort, validation studies against CVOTs have been mixed, which could be due to differences between the studies.[30] The UKPDS enrolled individuals with newly diagnosed diabetes, who were consequently younger with fewer complications at baseline than the typical cohort of patients enrolled in a CVOT.[47] Background medication use also differs between the UKPDS and recent CVOTs, with a low proportion of patients receiving statins in the UKPDS compared with 76.5% of patients receiving lipid-lowering medications in SUSTAIN 6.[13]

Moreover, modern interventions for type 2 diabetes (particularly GLP-1 receptor agonist and SGLT-2 inhibitors) are typically associated with weight loss, compared with the interventions received during the UKPDS that are generally associated with weight neutrality or weight gain. Changes in BMI therefore have a limited impact in the UKPDS Outcomes Model, but may be influencing outcomes in CVOTs.[21,22]

The risk of double counting

While CVOTs were designed to achieve "glycemic equipoise" between the treatment arms, aiming to reduce the confounding impact of differences in glycemic control, this was not achieved in any trial (for example, CANVAS, ELIXA and EMPA-REG OUTCOME had statistically significant reductions in HbA1c in the intervention arm, while EXSCEL, LEADER and SUSTAIN 6 had numerically greater reductions in HbA1c with the intervention, all versus placebo).[3,6,7,8,9,13,48] The mechanisms of action of the observed outcomes in CVOTs is, as yet, unknown, but it is possible that reductions in cardiovascular outcomes are at least in part due to reductions in known surrogate parameters included in conventional risk equations. For example, a correlation between HbA1c difference and reduction in the risk of MACE has been observed in a review of CVOTs (though any causative relationship has not been assessed).[49] However, other mechanisms of action have also been suggested, specific to SGLT-2 inhibitors and GLP-1 receptor agonists.[50] Applying both reductions in surrogate parameters and direct reductions in the incidence of events in modeling analyses, therefore, risks double counting of benefits if hazard ratios are not adjusted for the differences in modified risk factors.

CONTROLLING FOR HETEROGENEITY USING INDIRECT COMPARISONS

Several NMAs of CVOTs have been conducted, with the aim of combining data from several trials to provide a comparative hierarchy of modern type 2 diabetes interventions relating to cardiovascular outcomes. However, as acknowledged in many of these publications, comparison of treatments from different CVOTs remains challenging due to the differences in trial designs, patient characteristics, background therapy and endpoint definitions (as discussed above).[51,52,53,54,55] Moreover, the disparity

in the conclusions of these NMAs shows the uncertainty when drawing conclusions around relative efficacy. For example, Fei et al. concluded that SGLT-2 inhibitors showed “clear superiority” in reducing cardiovascular mortality and hospitalization for heart failure, despite both SGLT-2 inhibitors and GLP-1 receptor agonists being associated with significantly reduced MACE and hospitalization for heart failure versus placebo. In contrast, in the analysis conducted by Alfayez et al., the only conclusion drawn was that novel antidiabetic medications do not impose any additional CV risk (in line with the original aims of the CVOTs), with indirect comparison between medication classes yielding no significant differences in cardiovascular outcomes.[51,52] Further NMAs conducted by the Institute for Clinical and Economic Review in the US and the National Institute for Health and Care Excellence (NICE) in the UK did not publish their full methodology, and little adjustment to control for differences between the CVOTs was seemingly performed, as hazard ratios for all outcomes were closely matched to their counterparts for all interventions versus placebo in the individual CVOTs.[56,57] Indirect comparisons conducted to date have been based on population-level data, and the lack of access to patient-level data for all CVOTs severely limits the methodology that can be applied and adjustments that can be made. Access to patient-level would allow more complex methodologies to be used, and this may provide a more robust assessment of relative efficacy.

HEALTH ECONOMICS STUDIES INCORPORATING CVOT DATA

Several long-term diabetes modeling studies have included data from CVOTs in cost-effectiveness analyses aiming to compare active interventions from multiple CVOTs. These studies provide examples of the different methodologies possible for incorporating data from CVOTs into current modeling approaches for type 2 diabetes, and include long-term cost-effectiveness analyses of:

- Liraglutide versus empagliflozin and oral semaglutide versus empagliflozin in the UK (both published by Ramos et al. in 2020).[58,59]
- Liraglutide versus empagliflozin in Denmark (published by Ehlers et al. in 2021).[60]
- Sitagliptin versus empagliflozin in the US (published by Reifsnider et al. in 2021).[61]
- Liraglutide versus empagliflozin in the US (published by Reifsnider et al. in 2022).[62]

- Oral semaglutide versus empagliflozin and sitagliptin in Sweden (published by Eliasson et al. in 2022) and the US (published by the Institute for Clinical and Economic Review in 2019).[56,63]
- A 2022 update of the type 2 diabetes guidelines by NICE in the UK.[57]

The two studies published by Reifsnider et al., evaluating liraglutide and sitagliptin versus empagliflozin in the US, estimated outcomes using different methods for simulated patients without and with existing cardiovascular disease, with a cardiovascular event during the patient-level simulation resulting in a change in the method used to calculate risk. The studies used UKPDS Outcomes Model 2 risk equations to predict the incidence of diabetes-related complications in patients without cardiovascular disease (with outcomes extrapolated from short-term changes in surrogate outcomes), and published event-free survival curves developed from EMPA-REG OUTCOME data to directly estimate the incidence of complications in patients with cardiovascular disease (without any short-term changes in surrogate outcomes applied).[61,62] These studies were based on an original analysis by Kansal et al., developed to directly model empagliflozin versus placebo based on EMPA-REG OUTCOME, but caution must be used when calibrating and comparing interventions from multiple CVOTs in one analysis.[64] In this case, a published but non-peer-reviewed ITC was used to inform the relative risks of events with liraglutide and sitagliptin versus empagliflozin. The validity of the cost-effectiveness outcomes in patients with cardiovascular disease at baseline or experiencing cardiovascular disease during the analysis was therefore entirely dependent on the strength of the ITC, the methodology of which was not fully described (as it was published only in abstract form).[65] The overall soundness of these analyses is therefore difficult to judge, as it is unclear whether appropriate adjustments in hazard ratios (for differences in population characteristics at baseline, differences in treatment effects associated with the interventions, study durations, and endpoint definitions) were performed in the ITC.

The study performed by Ramos et al. evaluating oral semaglutide versus empagliflozin in the UK was a typical type 2 diabetes modeling analysis using the IQVIA CORE Diabetes Model, with changes in physiological parameters (including HbA1c, blood pressure and body weight) applied from a head-to-head clinical trial of oral semaglutide versus empagliflozin.[59,66] However, alongside these reductions, a further risk reduction in hospitalization for heart failure was incorporated in the empagliflozin arm. This falls into several of the pitfalls previously described, including the potentially inappropriate application of a hazard ratio from a population with high cardiovascular risk in a more general

population with type 2 diabetes, and the risk of double counting when changes in surrogate outcomes and additional risk reductions are applied. Moreover, this relative risk of 0.63 was stated to be based on data from EMPRISE, but the referenced publication was an evaluation of SGLT-2 inhibitors versus DPP-4 inhibitors (rather than GLP-1 receptor agonists) and the value of 0.63 could not be found in the published material. Application of this risk reduction was shown to be a key driver of the projected clinical benefits with empagliflozin, as removal of the risk reduction in a sensitivity analysis switches the conclusions of the analysis from empagliflozin being more clinically effective to oral semaglutide being more clinically effective.[59]

The studies by Ramos et al. and Ehlers et al., evaluating the long-term cost-effectiveness of liraglutide versus empagliflozin in the UK and Denmark, respectively, aimed to calibrate the IQVIA CORE Diabetes Model to match the clinical event rates observed in EMPA-REG OUTCOME in the empagliflozin arm, and such that relative risks of complications for liraglutide versus empagliflozin matched an ITC of EMPA-REG OUTCOME and LEADER (the same ITC informing relative risks in the analyses by Reifsnider et al.).[58,60] This comparison associated empagliflozin with a significantly lowered risk of all-cause mortality, numerically lowered risk of cardiovascular-related mortality and hospitalizations due to heart failure, and numerically increased risk of non-fatal stroke compared with liraglutide.[65] The methodology of this indirect comparison is hard to judge, as it has only been published in abstract form, but all of the previously described pitfalls of combining data from heterogenous CVOTs should have been considered.

The Swedish study by Eliasson et al. used the Institute for Health Economics Diabetes Cohort Model to evaluate oral semaglutide versus empagliflozin and sitagliptin.[63,67,68] While the base case analysis of this study did not incorporate CVOT data, scenario analyses were conducted that applied reductions in the risk of myocardial infarction, stroke, heart failure and cardiovascular mortality based on hazard ratios sourced from PIONEER 6, EMPA-REG OUTCOME, and TECOS.[7,10,19] In one set of analyses, hazard ratios were adjusted to apply only for patients in the baseline PIONEER 2 cohort who matched the inclusion criteria for PIONEER 6, while in the other set of analyses, hazard ratios were applied directly from PIONEER 6, EMPA-REG OUTCOME and TECOS in the full PIONEER 2 population. This approach risks double counting of benefits (as changes in surrogate physiological parameters, such as HbA1c and body weight, were also applied). However, the study can be commended for adjusting the hazard ratios to match those expected in the PIONEER 2 population,

thereby overcoming the potential inappropriateness of applying hazard ratios from high cardiovascular risk populations in more general type 2 diabetes populations. Application of these hazard ratios led to improved clinical outcomes with oral semaglutide versus empagliflozin and sitagliptin.[63]

The US analysis published by the Institute for Clinical and Economic Review aimed to capture the cardiovascular data of oral semaglutide, empagliflozin and sitagliptin through an NMA of CVOT data, specifically the endpoints of MACE and hospitalization for heart failure.[56] However, the chosen approach of applying hazard ratios alongside reductions in physiological parameters (including HbA1c) risked double counting of benefits. Moreover, the analysis inappropriately applied hazard ratios derived from populations with high cardiovascular risk in a more general type 2 diabetes population.

The recent UK analysis performed by NICE aimed to provide an update of their guidance on the treatment of type 2 diabetes in adults (NG28), capturing the impact of interventions of cardiovascular risk. NICE prepared an analysis based on a standard of care arm generated with an implementation of the UKPDS Outcome Model 2, with hazard ratios for each intervention for each complication applied in a separate multi-state model to generate overall cost-effectiveness outcomes. However, the chosen modeling approach succumbed to several pitfalls associated with incorporating CVOT data into type 2 diabetes modeling. These included the application of hazard ratios from high cardiovascular risk populations in a baseline population from The Health Improvement Network (THIN) including less than 3% with prior cardiovascular disease; use of hazard ratios that appeared unadjusted from their individual CVOTs despite an NMA being conducted; and application of hazard ratios for all individual endpoints, even though no CVOT has been sufficiently powered to detect differences in anything other than the composite MACE outcome, thereby creating undue uncertainty in the analysis. While some of these limitations were acknowledged by NICE, this provides little certainty to their analysis. Moreover, recommendations arising from the NICE analysis are at odds with consensus guidelines jointly published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1,57] The analysis performed by NICE also only captured heart failure, stroke, ischemic heart disease and MI, and did not consider other diabetes-related complications that can have substantial impacts on cost-effectiveness outcomes.

AN ALTERNATIVE APPROACH TO MODELING CVOT DATA

High-quality economic evaluations should capture data from the wide range of sources currently available, including randomized controlled trials, indirect comparisons and NMAs evaluating changes in surrogate outcomes, as well as CVOTs. Real-world studies evaluating the impacts of initiating medications on direct outcomes (such as the OFFSET study, which demonstrated that the added pharmacy cost of GLP-1 receptor agonist treatment was offset by lower healthcare costs relating to cardiovascular complications when compared with standard of care) can also inform modeling analyses, but these data should be used cautiously given the their issues with confounding compared with randomized controlled trials and NMAs.[69] As discussed by Si et al. and Willis et al., there are numerous options for incorporating CVOT data as they are currently reported, including simplifying the study to a 'cost per MACE avoided' analysis, and calibration of existing type 2 diabetes models to specific trials.[30,31] However, until an NMA overcoming the heterogeneity of the CVOTs can be conducted (potentially using patient-level data) these options would only be valid for a comparison of the evaluated intervention versus placebo for the specific CVOT. Detailed data analysis could also assess whether hazard ratios were constant for each endpoint within each CVOT, potentially mitigating the effects of study duration and changing risk factors when combining data from multiple CVOTs in a single analysis.

The optimal method for conducting analyses based on data from CVOTs is likely to be preparation of new risk equations based on patient-level data. To date, this has only been conducted for single trials, and not for comparison of interventions assessed in separate CVOTs. An analysis based on DECLARE-TIMI in the UK has been prepared using Kaplan-Meier survival curves derived from the 4-year trial extrapolated over patient lifetimes, with endpoints including all-cause mortality, initial and secondary hospitalization for heart failure, initial and secondary stroke, initial and secondary myocardial infarction, hospitalization for unstable angina pectoris, and end-stage kidney disease.[70] Similarly, patient-level data from EMPA-REG OUTCOME have been used to develop parametric models to extrapolate the observed trends in the hazard of each endpoint over a lifetime horizon.[64] These two studies represent a step forward to using the CVOTs to prepare novel risk equations.

For risk equations to be developed to allow comparison of multiple interventions assessed in separate CVOTs to be valid, patient-level data from multiple (ideally all) CVOTs need to be shared. This will

require collaboration from across the pharmaceutical industry and health technology assessment agencies, and an implemented code of conduct to manage how the pooled data could be used. Statistical analysis could then be conducted to work out the key risk factors that allow prediction of diabetes-related complications. This would allow the weights of risk factors currently used in health economic models to be updated, for new risk factors to be added, and for the treatment itself to be included in the risk equations, thereby capturing any additional benefit not mediated through currently measured risk factors.

CONCLUSIONS

The CVOTs represent an important source of data that should be incorporated into long-term cost-effectiveness modeling of diabetes interventions. However, it is imperative that this is done in an appropriate and robust manner, controlling for heterogeneity of the CVOTs and using a suitable model structure. Use of inappropriate methods can lead to conclusions that are uncertain or even incorrect, leading to poorer clinical outcomes and inefficient use of constrained healthcare budgets. The ideal solution of developing risk equations from pooled data across all of the CVOTs will require collaboration from across the pharmaceutical industry and health technology agencies, but calibration of existing models for individual CVOTs and evaluation of modern interventions for type 2 diabetes in comparative CVOTs could provide useful information.

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TABLES AND FIGURES

Table 1 Three-point MACE rates in the placebo arm of CVOTs

Trial	Comparator treatment	Placebo MACE rates (events per 100 patient years)
AMPLITUDE-O	Efpeglenatide	5.3
CANVAS	Canagliflozin	3.04
CARMELINA	Linagliptin	5.63
DECLARE-TIMI	Dapagliflozin	2.42
ELIXA	Lixisenatide	Event rate reported for four-point MACE
EMPA-REG OUTCOME	Empagliflozin	3.74
EXAMINE	Alogliptin	Event rate not reported
EXSCEL	Exenatide	4.0
LEADER	Liraglutide	3.9
PIONEER 6	Semaglutide (oral)	3.7
PROactive	Pioglitazone	Event rate not reported
REWIND	Dulaglutide	2.66
SAVOR-TIMI	Saxagliptin	3.7
SUSTAIN 6	Semaglutide (injection)	4.4
TECOS	Sitagliptin	3.82
VERTIS-CV	Ertugliflozin	4.59

MACE, major adverse cardiovascular event.

Table 2 CVOT baseline populations and study duration

Trial	Treatment	Prior CVD (%)	Age (years)	Duration of diabetes (years)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Median follow-up (years)
AMPLITUDE-O	Efpeglenatide	89.6	64.5	15.4	8.9	32.7	1.8
CANVAS	Canagliflozin	65.6	63.3	13.5	8.2	32.0	2.4
CARMELINA	Linagliptin	*	65.9	14.8	7.9	31.3	2.2
DECLARE-TIMI	Dapagliflozin	40.6	63.9	11.0/10.0	8.3	32.1/32.0	4.2
ELIXA	Lixisenatide	100	60.3	9.3	7.7	30.2	2.1
EMPA-REG OUTCOME	Empagliflozin	99	63.1	12.0	8.1	30.7	3.1
EXAMINE	Alogliptin	*	61.0	7.3/7.1	8.0	28.7	1.5
EXSCEL	Exenatide	73.1	62.0	12.0	8.0	31.8/31.7	3.2
LEADER	Liraglutide	81	64.3	12.8	8.7	32.5	3.8
PIONEER 6	Semaglutide (oral)	85	66.0	14.9	8.2	32.3	1.3
PROactive	Pioglitazone	*	61.9/61.6	8	7.8/7.9	30.7/31.0	2.9
REWIND	Dulaglutide	31	66.2	10.6	7.4	32.3	5.4
SAVOR-TIMI	Saxagliptin	*	65.0	10.3	8.0	31.3/31.2	2.1
SUSTAIN 6	Semaglutide (injection)	60	64.6	13.9	8.7	32.8	2.1
TECOS	Sitagliptin	74.0	65.6	11.6	7.2	30.2	3.0
VERTIS-CV	Ertugliflozin	*	64.4	12.9/13.1	8.2	31.9/32.0	3.0

*No composite value reported.