# How to read a cardiovascular outcome trial (CVOT)

## Why are CVOTs required?

People with diabetes are significantly more at risk of cardiovascular disease (CVD) than the general population. It is, therefore, important that the drugs used to treat diabetes do not further increase these risks. A 2007 meta-analysis appeared to demonstrate increased CV risk in those treated with rosiglitazone. Following this, the US Food and Drug Administration (FDA), in 2008, and the European Medicines Agency (EMA), in 2010, mandated that all new drugs for glucose lowering in type 2 diabetes must demonstrate CV safety. All DPP-4 inhibitor drugs (apart from vildagliptin), all SGLT2 inhibitor drugs (ertugliflozin study awaited) and all GLP-1 receptor agonist drugs have been studied in CV outcome trials (CVOTs).

## What is the usual study design?

As with all randomised controlled trials, the investigators ensure that the treated and placebo (or comparator) groups are as similar as possible at baseline. Both groups receive standard care, including multifactorial interventions designed to reduce the risk of CV events. In addition, the study population receives the specific glucose-lowering drug being studied while the control group receives either placebo (most CVOTs) or an active comparator. Most CVOTs to date have compared the active drug to placebo but, in the CAROLINA trial, linagliptin, which had previously been found to be non-inferior to placebo in the CARMELINA study, was used as an active comparator against glimepiride (a sulfonylurea).

Since the trial seeks to check whether the drug (and only the drug) has had any impact on increasing or decreasing CV outcomes, the investigators aim to achieve **glycaemic equipoise** throughout the study. That is, they try to keep the glycaemic control as similar as possible in the active and placebo groups by adding extra drug treatment in the placebo group. This can be difficult to achieve and most of the recent CVOTs included differences in $HbA_{1c}$ between active and placebo groups, ranging from 3 mmol/mol to 11 mmol/mol (0.3% to 1%). There were also small differences in systolic BP and weight between active and placebo groups. These may have contributed a small amount to the CV benefits.

It is important to understand that CVOTs do not seek to demonstrate the glucose-lowering potential of the drugs. Small differences in glycaemic control can be misconstrued as demonstrating poor glycaemic benefits of the drug versus placebo, instead of this being recognised as unintentional differences in glycaemic control between the groups studied.

The studies are event-driven, meaning there is an agreed number of events required to demonstrate the hypothesised non-inferiority or superiority between the groups. When this number has been achieved, the study is usually terminated and the results evaluated. Studies need to be at least 18 months long, but often longer durations and large numbers of participants are involved to ensure the outcome is demonstrated.

## Here is a simple structure to apply when reading and reviewing CVOT papers

### Which drug?

Take note of the drug being studied in the trial and to which class it belongs. Note that different drugs within a class may have different impacts on CV risk and so results cannot be generalised across drugs in a class.

### What are the baseline characteristics of the study population?

Look at the baseline characteristics – age, duration of type 2 diabetes, percentage with existing CVD – and get a feel for the overall CVD risk of people recruited into the study. These influence the risk and number of CV events and duration of the study. Review other factors likely to impact on CV risk (e.g. eGFR and urinary albumin creatinine ratio [UACR]), as those with type 2 diabetes and chronic kidney disease are at high risk of CV events, even if they have not yet had an event. How does the study population compare with your patients? **Results of CVOTs cannot be generalised to other populations.**

If an adverse event has been identified with drugs of the same class, explore the specific inclusions and exclusions in the trial populations. For example, there was a significant increase in worsening retinopathy in those with existing retinopathy and insulin treatment at baseline who were treated with semaglutide in SUSTAIN 6. This was postulated to be due to rapid reductions in $HbA_{1c}$. Since there was also a non-significant increased risk of retinopathy worsening in those treated with liraglutide in LEADER, it is important to know that people with retinopathy were included in REWIND (dulaglutide), with no significant increase in retinopathy but that the upper limit of $HbA_{1c}$ for inclusion was ≤81 mmol/mol (9.5%), whereas in SUSTAIN 6 there was no upper limit (and median $HbA_{1c}$ was 72 mmol/mol [8.7%]). Caution should continue in those with retinopathy with all GLP-1 RAs until further guidance is available.

### What is the primary outcome?

Look at the primary outcomes for the study. For most of the CVOTs, this is a 3-point major adverse cardiovascular event (MACE) composite endpoint, including CV death, non-fatal myocardial infarction (MI) and non-fatal ischaemic stroke. Some studies, such as TECOS with sitagliptin, used 4-point MACE as the primary endpoint,

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which also included hospitalisation for unstable angina. In DECLARE-TIMI 58 with dapagliflozin, there were two co-primary endpoints, 3-point MACE and a composite of hospitalisation for heart failure (HHF) and CV death. The 3-point MACE demonstrated CV safety, but was not superior to placebo. However, the CV death and HHF co-primary endpoint was superior, driven by a significant reduction in HHF. This study recruited a population at much lower CV risk than the other SGLT2i CVOTs, with only 41% of participants having established CVD at baseline and the rest multiple risk factors only – more similar to our primary care population.

**Is the primary outcome non-inferior (no increased CV risk) or superior (significant CV benefit)?**

The primary outcome will be explored for non-inferiority and then, if appropriately powered, for superiority. Look at the value for superiority (usually expressed as a hazard ratio) and the 95% confidence interval (CI) and *P*-values. The 95% CI should not cross 1.0 (unity) and, for a single primary endpoint, a significant *P*-value will be <0.05.

Authors of CVOT publications may also include a number needed to treat (NNT) for the primary outcome. This is calculated by finding the absolute risk reduction (ARR) achieved (**not** the relative risk reduction [RRR]) and dividing this number into 1, expressed over the time period of the study.

**Look at the secondary outcome(s) and hierarchy**

Review other reported outcomes. There will be a variety of secondary outcomes pre-planned at the start of the study. Those undertaking the study must define the order in which these are to be considered and, during statistical testing, once there is an outcome that is non-significant, results below this in the testing hierarchy will be described as "exploratory" or "hypothesis generating", which both mean that further study will be required to confirm any apparently significant findings. For example, several CVOTs have renal secondary endpoints and some of these sit below non-significant results in the testing hierarchy, so will need to be confirmed by additional studies.

**Look at the sub-analyses**

Sub-analyses look only at part of the dataset. These can be *pre-planned* at the start or during the study prior to data unmasking, or *post hoc* once data are seen. For example, CVOTs including a significant proportion of people without established CVD at baseline may include a pre-planned sub-analysis looking at the primary endpoint(s) in those with and without baseline CV events or other baseline characteristics.

**Look at the discussion – what are the strengths and limitations of this study?**

With all clinical papers, including CVOTs, the discussion section summarises the findings, and compares and contrasts with other studies. It also highlights the strengths and weaknesses of the study. These may not be easily identified in other parts of the paper.

**Are there guidance notes in the paper?**

The format of some journals includes a summary box highlighting what was known before this study and what this study adds. This can help to put the results into context. However, it is important to remember that the **study populations in each CVOT are very different and that direct comparisons cannot be made.**

**Look at any accompanying editorials**

Again, these may help compare and contrast this (and other similar) studies.

## CVOT summary

CVOTs for the DPP-4 inhibitor drug class demonstrated CV safety in the MACE primary endpoints. Saxagliptin demonstrated an increased risk of HHF, so this should be avoided in those with HF.

When applying CVOT data, note the established CVD (secondary prevention) to multiple risk factors (primary prevention) split (*Table 1*).

Look out for a practical guide, *How to apply CVOT studies in primary care*, in 2020.

**Table 1. Baseline CV risk in CVOTs demonstrating CV benefit.**

| | EMPA-REG OUTCOME[1] (empagliflozin) | CANVAS[2] (canagliflozin) | DECLARE-TIMI 58[3] (dapagliflozin) | LEADER[4] (liraglutide) | SUSTAIN 6[5] (semaglutide) | REWIND[6] (dulaglutide) |
|---|---|---|---|---|---|---|
| **Numbers** | 7020 | 10 142 | 17 160 | 9340 | 3297 | 9901 |
| **CV disease at baseline** | >99% | 66% | 41% | 81% | 83% | 31% |
| **Primary prevention group (no CVD): CV risk factors for inclusion** | n/a | Aged ≥50 years with ≥2 risk factors: diabetes duration ≥10 years; SBP >140 mmHg on treatment; daily smoker; micro- or macroalbuminuria; HDL-C <1 mmol/L | Men aged ≥55 years or women ≥60 years with ≥1 risk factors: hypertension; dyslipidaemia; smoker | Aged ≥60 years with ≥1 risk factors: microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction by imaging; or ankle–brachial index <0.9 (CKD stage 3+ or chronic HF [NYHA II or III] included in the CVD group) | Aged ≥60 years with ≥1 risk factors: persistent micro-albuminuria or proteinuria; hypertension and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction by imaging; ankle–brachial index <0.9 | Aged ≥60 years with ≥2 risk factors: smoker; lipid drug or LDL-C ≥3.4 mmol/L, HDL-C <1.0 mmol/L for men or <1.3 mmol/L for women or TG ≥2.3; ≥1 BP drug or SBP ≥140 or DBP ≥95 mmHg; waist–hip ratio >1.0 for men and >0.8 for women |

Note that direct comparisons between studies cannot be made as the populations were very different.
CKD=chronic kidney disease; HF=heart failure; NYHA=New York Heart Association; TG=triglyceride.


**References**

[1]Zinman B et al (2015) *N Engl J Med* **373**: 2117–28

[2]Neal B et al (2017) *N Engl J Med* **377**: 644–57

[3]Wiviott SD et al (2018) *N Engl J Med* **380**: 347–57

[4]Marso SP et al (2016) *N Engl J Med* **375**: 311–22

[5]Marso SP et al (2016) *N Engl J Med* **375**: 1834–44

[6]Gerstein HC et al (2019) *Lancet* **394**: 121–30