The impact of cardiovascular outcome trials on the choice of insulins in the management of type 2 diabetes mellitus: An expert review

ABSTRACT

Introduction. This expert review aims to address the epidemiology and pathophysiology of cardiovascular disease (CVD) in persons with type 2 diabetes mellitus (T2DM), help understand the various statistical considerations and interpretational nuances of cardiovascular outcome trials (CVOTs) in general, and discuss in particular, the CVOTs with insulins, and their impact on the choice of insulins in day-to-day clinical practice.

Material and methods. The expert panel critically analysed published data from observational studies, randomized clinical trials, meta-analyses and CVOTs regarding cardiovascular (CV) safety of insulin preparations, and agreed on a series of consensus statements supported by available scientific evidence and the collective clinical judgement of the experts.

Results. A proportion of persons with T2DM have a high risk of CVD and CV mortality, which is partly contributed by insulin resistance-related, and hyperglycaemia-related, risk factors. Over the past decade, CVOTs have become an integral part of the drug approval process of anti-diabetic therapies by the United States Food and Drug Administration (FDA). Most insulin preparations in use today, barring a few modern insulins, were introduced much before this regulatory requirement was put in place, and hence, have not undergone rigorous CVOTs. There is a large body of observational data concerning the CV safety of insulin preparations, which are often confusing and, at times, contradictory. In this background, it is reassuring to note that CVOTs of two basal insulin analogues, namely insulin glargine, studied in the Basal Insulin and Cardiovascular and Other Outcomes in Dysglycaemia Trial (ORIGIN), and insulin degludec, studied in the Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes Trial (DEVOTE), established their long-term CV safety. The DEVOTE trial provided additional safety data reporting fewer severe hypoglycaemic events with insulin degludec in comparison to insulin glargine.

Conclusions. This review critically analyses the two CVOTs of basal insulin analogues, in tandem with a general review of the methodological and interpretational aspects of CVOTs in general. The long-term CV safety of analogue basal insulins is discussed. The lack of CVOTs with prandial and pre-mixed insulins, either human or analogue, was identified as the main research gap in this area. (Clin Diabetol 2018; 7, 5: 234–246)

Key words: type 2 diabetes, insulin treatment, basal insulin, analogue insulin, cardiovascular safety, cardiovascular outcome trials, ORIGIN, DEVOTE

Introduction

Diabetes mellitus is a growing public health problem worldwide. According to the eighth edition of the International Diabetes Federation (IDF) Diabetes Atlas 2017, the number of people living with diabetes...
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Globally was 425 million in 2017, and is estimated to reach 629 million by 2045 [1, 2]. India has the second highest number of people with the disease in the world.

People with type 2 diabetes mellitus (T2DM) have at least a two-fold higher risk of cardiovascular (CV) mortality than those without T2DM [4–6]. The risk of having a myocardial infarction (MI) in a person with T2DM of > 8 years duration who has had no previous MI is as high as the risk in a non-diabetic person who has had a previous MI [7–9]. The CVD burden is higher among Asian Indian individuals, who not only have a higher predisposition to T2DM that develops at a younger age but also have a higher risk of coronary heart disease (CHD) as compared to their western counterparts [10].

Typical manifestations of cardiovascular disease (CVD) in a person with T2DM include CHD, ischaemic stroke, peripheral artery disease, and heart failure [3].

Exogenous insulin is an established blood-glucose-lowering agent, which has seen a steady growth in its use in people with T2DM over the recent years.; this rise in use is partly due to various guidelines recommending early use of insulin, and partly because of the availability of modern analogue insulins offering ease of administration, less weight gain, and lesser risk of hypoglycaemia [11–13]. However, in view of the growing concern on the CV safety profile of once-common therapies [14–16], there is a need for a more close evaluation of the CV safety profile of exogenous insulin in T2DM [12, 17].

The guidance issued by FDA in 2008 recommended that any new anti-diabetic agent should not increase CV risk to an unacceptable extent [18]. Since then, cardiovascular outcome trials (CVOTs) have become an integral part of drug approval process of anti-diabetic therapies.

However, despite their simplicity in design, many primary care physicians, and the occasional expert, misinterpret glycaemic efficacy trials as CVOTs [17, 19].

Therefore, this expert panel set out to address the epidemiology and pathophysiology of CVD in T2DM, assess the statistical considerations and interpretation of CVOTs in terms of regulatory guidance, review the available CVOTs with insulin, and their impact on the choice of insulin in people with T2DM in clinical practice.

**Methods**

A panel of endocrinologists and physicians specialising in the management of diabetes met to develop a consensus statement regarding the CV safety of the various insulin preparations and its impact on the choice of insulin in people with T2DM in the Indian setting. The panel critically analysed published data from observational studies, randomized clinical trials, meta-analyses, and CVOTs with insulin, and agreed on a series of consensus statements supported by scientific evidence and experts’ clinical judgement. The expert panel approached the task by reviewing and addressing four areas; a) diabetes and CVD (basic pathophysiology and CVD risk of antidiabetic agents), b) understanding and interpreting CVOTs (regulatory guidance and statistical considerations), c) insulin trials and CV outcomes (landmark glycaemic control trials, dedicated CVOTs), d) clinical implications of the evidence (Fig. 1).

**Diabetes as potential CHD risk equivalent**

People with T2DM have a 2–4 fold higher risk of coronary artery disease (CAD) and ischaemic stroke, 2–8 fold higher risk of heart failure, and at least

<table>
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<th>Insulins and cardiovascular outcomes</th>
<th>Diabetes and cardiovascular disease</th>
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<th>Clinical implications of the evidence</th>
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<td>Basic pathophysiology</td>
<td>Antidiabetic agents and CV risk</td>
<td>Regulatory guidance and statistical considerations</td>
<td>Interpretation of CVOTs</td>
<td>Landmark glycaemic control trials</td>
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</table>

**Figure 1. Framework for expert panel approach**
a two-fold higher risk of CV mortality than those without diabetes [4–6].

The Cardiovascular disease research using Linked Bespoke studies and Electronic health Records (CALIBER) program, a population-based study of nearly 2 million individuals, of whom 1.2% had T2DM, with a median follow-up of 5.5 years, revealed a strong association between T2DM and 12 specific CVD disease outcomes [21].

The East-West study from Finland with 1,373 non-diabetic and 1,059 people with T2DM revealed that a person with T2DM without a previous MI has as high a risk of suffering from a MI as a non-diabetic individual with a previous MI over 7 [7] and 18-year [8] follow-up. This led to the designation of T2DM as a “CHD risk equivalent”, and this was also recommended by the National Cholesterol Education Program (NECP) Adult Treatment Panel (ATP) III guidelines in 2001 [22]. However, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) risk assessment guidelines recommended consideration of diabetes as a predictor of, rather than an automatic CHD risk equivalent, and suggested the use of global risk assessment to help discriminate those with a higher CVD risk from those with a lower risk [23].

Pathophysiology of CVD in diabetes: The role of hyperglycaemia and insulin resistance

Hyperglycaemia, insulin resistance and/or hyperinsulinemia, dyslipidaemia, inflammation, reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification are among the many factors that contribute to atherosclerotic CVD in diabetes [3]. In addition, people with T2DM have greater atherosclerotic plaque burden, higher atheroma volume, and smaller coronary artery lumen diameter than persons without diabetes [3, 24].

Insulin resistance is evident prior to the onset of pre-diabetes or diabetes whereas dysglycaemia develops only when pre-diabetes sets in and worsens with development of diabetes [3]. There is a direct association between hyperglycaemia and microvascular disease, whereas CV risk is related to insulin resistance, much before the development of T2DM [4, 25].

Paradoxical increase in cardiovascular risk with certain anti-hyperglycaemic agents

CV risk associated with sulphonylureas became a concern when an interim analysis of University Group Diabetes Program (UGDP) in 1969 showed a statistically significant increase in CV deaths associated with tolbutamide [33].

CV hazard for the first dual-PPAR (peroxisome proliferator-activated receptor) agonist, muraglitazar was seen during extension trials indicating an excess incidence of the composite end point of death, major adverse CV events (MACE) and CHF (congestive heart failure) in muraglitazar treated persons when compared to placebo or pioglitazone [36]. Hence, further development of the drug was halted [37].

CV safety of rosiglitazone was evaluated in a meta-analysis of 42 trials that demonstrated a significant increase in the risk of MI, and a non-significant increase in CV mortality [39]. A follow-up meta-analysis of four randomized controlled trials (RCTs) involving 14,291 patients examined the long-term effects of rosiglitazone on MI, HF, and CV mortality [40]. The results confirmed the association of rosiglitazone with a significantly elevated risk of MI and heart failure, but not with an increase in CV mortality [40]. This association of rosiglitazone with increased CV risk [39, 40] emphasized the need for a closer evaluation of anti-diabetic therapies from CV safety perspective (Table 1).

In 2008, FDA issued guidance to pharmaceutical industry on the conduct of clinical studies to prove that anti-diabetic drugs confer to acceptable levels of CV safety [18]. The “FDA guidance” recommended that anti-diabetic drugs should not increase CV risk to an unacceptable extent [18]. CVOTs since then have become an integral part of the drug approval process.

Simplifying the understanding of CVOTs

Despite evaluating the same drug of interest, diabetes efficacy trials and CVOTs exhibit differences in both the design and the measured outcomes. The primary purpose of conducting a diabetes efficacy trial is to evaluate the glucose-lowering capability of the study drug when compared to either placebo or an active comparator, and CV adverse events are documented during the course of the trial. In traditional efficacy trials, CV events of interest are neither pre-specified nor independently adjudicated [26].

On the other hand, CVOTs serve to compare the rates of CV events of a study drug with that of a control, usually a placebo, in order to assess the study drug’s impact on a patient’s CV risk; both active treatment and placebo arms are assessed for their impact on MACE (Major Adverse Cardiovascular Events). The interpretation of CVOT starts with understanding the aim of the study (whether powered for non-inferiority or superiority), the study design, the background prevalence of the event(s) in question, the pre-specified primary and secondary end-points, the need for pre-adjudication of these end points, and the ability to replicate the data [27].
Table 1. Risk of all-cause mortality and CV death with oral anti-diabetic agents

<table>
<thead>
<tr>
<th>Trials/registries</th>
<th>Study design/study duration/follow-up/time interval</th>
<th>Study participants</th>
<th>Proportion of patients with event</th>
<th>CV outcome results</th>
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<tr>
<td>Nissen et al. [37] (2005) n = 3725</td>
<td>Prospective, randomized, double-blind 24–104 weeks</td>
<td>Type 2 diabetes patients with HbA1c between 7% and 10% Randomized to differing doses of muraglitazar, pioglitazone, or placebo as monotherapy or in combination with metformin or glyburide</td>
<td>Death, MI, or stroke occurred in 35 of 2374 (1.47%) in muraglitazar arm vs. 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone arm</td>
<td>Relative risk (RR) of death, MI, or stroke — 2.23; 95% CI 1.07–4.66; p = 0.03 in muraglitazar arm vs. placebo + pioglitazone arm</td>
</tr>
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<td>Nissen et al. [39] (2007)</td>
<td>Meta-analysis of 42 RCTs</td>
<td>T2DM patients Mean age — 56 years Baseline HbA1c — 8.2% Any patients receiving rosiglitazone assigned to rosiglitazone arm, control arm included any patients receiving OADs other than rosiglitazone</td>
<td>86 myocardial infarctions in the rosiglitazone group and 72 in the control group; 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in control arm</td>
<td>Odds ratio (OR) for myocardial infarction was 1.43 (95% CI 1.03–1.98; p = 0.03) and 1.64 (95% CI 0.98–2.74; p = 0.06) for death from cardiovascular causes with rosiglitazone vs. control arm</td>
</tr>
<tr>
<td>University Group Diabetes Program (UGDP) [33] (1970) n = 1027</td>
<td>Tolbutamide compared with placebo 1961–1978</td>
<td>Recruitment from 12 diabetes clinic from 1961–1966 within one year from diagnosis of diabetes. Absence of history of ketoacidosis, minimum life expectancy of 5 years; sum of fasting and 1, 2, 3 hrs post challenge glucose exceeding 500 mg/dL Phenformin treatment added in one existing and five new clinics between 1962–1963</td>
<td>26 CV death out of 204 at-risk patients in tolbutamide arm; 10 CV death out of 205 at-risk patients in placebo arm</td>
<td>CV mortality higher in tolbutamide (12.7%) vs. 4.9% in placebo arm, p = 0.003 All-cause mortality higher in tolbutamide (14.7%) vs. 10.2% in placebo arm, p = 0.030</td>
</tr>
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<td></td>
<td>Phenformin compared with combined placebo/insulin groups 1961–1978</td>
<td></td>
<td>30 total death out of 204 at-risk patients in tolbutamide arm; 21 total death out of 205 at-risk patients in placebo arm</td>
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<td></td>
<td>26 CV death out of 204 at-risk patients in Tolbutamide arm; 11 CV death out of 205 at-risk patients in placebo + insulin arm</td>
<td>CV mortality higher in tolbutamide (12.7%) vs. 5.6% in placebo + insulin arm, p = 0.005 All-cause mortality higher in tolbutamide (15.2%) vs. 8.1% in placebo + insulin arm, p = 0.006</td>
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<td>31 total death out of 204 at-risk patients in tolbutamide arm; 16 total death out of 205 at-risk patients in placebo arm</td>
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<tr>
<td>Evans et al. [72] (2006) Diabetes Audit and Research in Tayside Scotland (DARTS) diabetes information system and the Medicines Monitoring Unit (MEMO), Tayside Scotland n = 5730</td>
<td>Tolbutamide compared with placebo 1994–2001</td>
<td>Patients newly prescribed with OADs were classified into five study cohorts according to treatment received: metformin only, sulfonylureas only, sulfonylureas added to metformin, metformin added to sulfonylureas, and both drugs simultaneously</td>
<td>Unadjusted RR of mortality — 3.12 (95% CI 2.54–3.84) and unadjusted RR of CV mortality — 3.71 (95% CI 2.64–5.22) adjusted RR of mortality — 1.43 (95% CI 1.15–1.77) and adjusted RR of CV mortality — 1.70 (95% CI 1.18–2.45)</td>
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<td>Rao et al. [73] (2008) n = 101,733</td>
<td>Medline search for published studies between 1966–2007</td>
<td>Mean age 58.9 to 71.3 years; mean follow-up time 2.1 to 7.7 years</td>
<td>Combination therapy of metformin and sulfonylurea, n = 25,091 Reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy)</td>
<td>Pooled RRs (95% CI) of prescribed combination therapy of sulfonylureas and metformin were 1.19 (0.88–1.62) for all-cause mortality, 1.29 (0.73–2.27) for CVD mortality, and 1.43 (1.10–1.85) for a composite end point of CVD hospitalizations or mortality (fatal or nonfatal events)</td>
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</table>
A pre-defined number of MACEs have to occur during the clinical program to provide adequate statistical power for the outcome of interest. Assuming that a study drug is neutral with respect to its CV safety, there must be approximately 122 MACE events to provide sufficient statistical power to rule out CV harm with an upper confidence limit of 1.8. Approximately 611 MACE events need to accrue to provide sufficient statistical power to rule out harm with an upper confidence limit of 1.3.

As per FDA guidance, CVOTs should include a sufficient number of persons with T2DM who are at higher risk for CV events. This shall allow for an adequate number of events to provide a sound estimate of risk. High-risk category includes those with advanced age, longer duration of diabetes, history of CV disease, presence of proteinuria, and/or chronic kidney disease [28, 29].

One potential disadvantage of the regulatory requirement for any new anti-diabetic drug to demonstrate at least no CV harm in a dedicated CVOT is the potential delay in the introduction of the newer antidiabetic medications for glycaemic control. The new anti-diabetic medication can be made available earlier by following any one of the three strategies (Fig. 2) [27].

### Evidence from observational studies

Initial concerns regarding CV safety of insulin in T2DM emerged from epidemiological data. A population-based study in Canada found a dose-response relationship between insulin use and all-cause mortality [45]. In another epidemiological study in UK, insulin treatment was reported to be associated with increased mortality compared to a combination of metformin and sulfonylurea [46]. A number of other observational studies have also reported an increased risk of cardiac events [47, 48] and CVD [49] in insulin-treated persons with T2DM.

Epidemiological data from the 2000–2010 UK General Practice Research Database revealed that insulin monotherapy resulted in a poorer outcome when compared to either metformin or sulfonylurea monotherapy for the primary end point of CV events and stroke, and all-cause mortality [12]. However, there were significant differences between the cohorts in terms of baseline characteristics, such as higher rate of prior vascular morbidity, and higher HbA1c in the insulin-treated group, which could be responsible for the observed poor outcomes [12]. US NHANES I study revealed that the use of insulin was associated with a non-significant increase in all-cause mortality, but here was no significant increase in CVD [50].

However, these observational studies were not specifically designed to address the CV safety of insulin. In the absence of randomisation, a number of confounding variables including differences in age, duration of diabetes, presence of comorbidities, prevailing CV risk and severity of insulin resistance make it difficult to compare the treatment groups [12, 45, 51–55]. A dedicated CVOT with insulin, with pre-specified and adjudicated end points, is necessary to address the CV safety of insulin (Table 2).

### Insulins and cardiovascular outcome trials

ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial [68] assessed the effect of basal insulin glargine, compared to standard of care, on three point MACE (CV death, non-fatal MI, non-fatal stroke) in persons with newly diagnosed T2DM or with pre-diabetes. There were two co-primary composite cardiovascular outcomes. The first was death from
Table 2. Risk of all-cause mortality and CV death with insulins

<table>
<thead>
<tr>
<th>Trials/registries</th>
<th>Study design/duration/follow-up /time interval</th>
<th>Participants</th>
<th>Proportion of patients on insulin</th>
<th>HbA1c at study end (insulin arm vs. comparator arm)</th>
<th>CV outcome results (insulin arm vs. comparator arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORIGINALE [74] n = 9489</td>
<td>Prospective, 2.7 years post-trial follow-up of ORIGIN study participants</td>
<td>IFG, IGT, T2DM Mean age = 63.5 years, 40% prior CVD</td>
<td>84% in intensive arm vs. 11% in standard arm</td>
<td>6.6% vs. 6.7%</td>
<td>Neutral for MACE</td>
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<td>DIGAMI-2 [76] n = 1253</td>
<td>Prospective 2.1 years</td>
<td>T2DM with suspected MI; mean age = 68 years; three groups: insulin based arm (n = 474), insulin during hospitalization + conventional glucose control arm (n = 473), conventional treatment (n = 306)</td>
<td>81% of insulin-based treatment arm</td>
<td>7.6% vs. 7.7% vs. 7.8%</td>
<td>↑ Non-fatal CV events (OR 1.89) ↑ Trend in mortality in insulin-based treatment arm</td>
</tr>
<tr>
<td>Colayco et al. [47] n = 55,758</td>
<td>Nested case-control using data from Kaiser Permanente Southern California health plan</td>
<td>44,628 T2DM without CV outcome (as control subjects) matched to 11,157 T2DM with CV outcome (as case subjects)</td>
<td>42%</td>
<td>Average A1C ≤ 6% vs. average A1C of &gt; 6–8%</td>
<td>OR for CV outcome with 95% CI: No antidiabetic drugs: 1.00 (reference group) Insulin only: 2.65 (2.31–3.05) Insulin + oral: 2.56 (2.19–3.00)</td>
</tr>
<tr>
<td>Lenzen et al. [75] Euro Heart Survey n = 4961</td>
<td>Prospective 374 days</td>
<td>Patients with CAD; normal glucose (n = 947) IGR (n = 1116), DM new (n = 452), DM known (n = 1425), not classified (n = 736), mean age = 67 years</td>
<td>37%</td>
<td>Not available</td>
<td>↑ CV events (HR 1.3) and mortality (HR 2.2) vs. non-insulin glucose-lowering</td>
</tr>
<tr>
<td>Bruno et al. [50] n = 1967</td>
<td>Population based cohort study 1988–1995</td>
<td>Type 2 (non-insulin-dependent) diabetes mellitus, comprising mainly elderly patients</td>
<td>Not available</td>
<td>Insulin-treated diabetes was found to be an independent predictor of mortality (HR 4.30, 95% CI 1.69–10.94)</td>
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<td>Smooke et al. [49] n = 544</td>
<td>Single-centred cohort study 2005</td>
<td>Advanced systolic HF (EF 24.6 ± 7.4); mean age = 52 years; patients were stratified into 3 groups based on presence or absence of diabetes and insulin use</td>
<td>Not available</td>
<td>Insulin-treated diabetes was found to be an independent predictor of mortality (HR 4.30, 95% CI 1.69–10.94)</td>
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<tr>
<td>Trials/registries</td>
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<td>HbA₁c at study end (insulin arm vs. comparator arm)</td>
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<tr>
<td>Currie et al., UK General Practice Research Database [46] n = 47,970</td>
<td>Retrospective cohort study 1986–2008</td>
<td>T2DM patients ≥ 50 years of age; n = 27,965 intensified from oral monotherapy to combination oral therapy, n = 20,005 changed from oral to insulin based regimens</td>
<td>100% in insulin arm</td>
<td>Not available</td>
<td>HR for all-cause mortality in insulin-based regimens cohort (2834 deaths) vs. those given combination oral agents (2035) — 1.49 (95% CI 1.39–1.59) HR for CV disease (only in patients without CV disease at baseline)*: 1.31 (1.22–1.42)</td>
</tr>
<tr>
<td>UK-based Clinical Practice Research Datalink Registry (CPRD)** n = 6072</td>
<td>Median follow-up time — 3.1 years 2000–2012</td>
<td>Insulin add-on to metformin therapy</td>
<td>100%</td>
<td>Not available</td>
<td>† Mortality and MACE for insulin monotherapy vs. insulin + metformin, aHRs for people prescribed insulin plus metformin vs. insulin monotherapy were 0.60 (95% CI 0.52–0.68) and for all-cause mortality 0.75 (0.62–0.91) for MACE</td>
</tr>
<tr>
<td>Gamble et al. [45], Administrative databases of Saskatchewan Health n = 12272</td>
<td>Retrospective cohort study of T2DM patients, 5.1 years 1991–1996</td>
<td>Mean age — 65 years; users grouped as per cumulative insulin exposure based on total insulin dispensations per year: no exposure (reference group); low exposure (0 to &lt; 3); moderate exposure (3 to &lt; 12) and high exposure (≥ 12)</td>
<td>100%</td>
<td>Not available</td>
<td>Graded risk of mortality associated with increasing exposure to insulin: low exposure [adjusted HR (aHR): 1.75; 95% CI: 1.24–2.47], moderate exposure (aHR: 2.18; 1.82–2.60) and high exposure (aHR: 2.79; 2.36–3.30); p = 0.005 for trend</td>
</tr>
<tr>
<td>Margolis et al. [48], The Health Information Network (THIN) data system n = 63,579</td>
<td>Retrospective cohort study 2002–2006</td>
<td>T2DM patients ≥ 40 years of age; 13,576 newly diagnosed T2DM patients</td>
<td>25%</td>
<td>Not available</td>
<td>aHRs of association with CV outcome were 2.0 (1.7, 2.5) for overall cohort aHRs of association with CV outcome were 2.4 (2.0, 2.9) for newly diagnosed T2DM cohort</td>
</tr>
<tr>
<td>Roumie et al. [54], National Veterans Health Administration, Medicare, and National Death Index databases n = 178,341</td>
<td>Retrospective cohort study of T2DM 2008–2011</td>
<td>Propensity score matched participants who were added insulin or sulfonylurea to metformin</td>
<td>Metformin + insulin = 2436 Metformin + SU = 12,180</td>
<td>aHR = 1.30 for combined acute myocardial infarction (AMI), stroke, or death; 95% CI 1.07–1.58; p = 0.009; aHR for death = 1.44; 95% CI 1.15–1.79; p = 0.001 No difference in stroke and AMI</td>
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ORIGINALE — ORIGIN and Legacy Effects; IFG — impaired fasting glucose; IGT — impaired glucose tolerance; T2DM — type 2 diabetes mellitus; IGR — impaired fasting glucose or impaired glucose tolerance; aHRs — adjusted hazard ratios; *CV disease includes myocardial infarction, stroke, coronary revascularization, carotid or peripheral arterial revascularization, angina of cardiac origin; **12,020 subjects treated with insulin were identified, including 6,484 treated with monotherapy.
cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second was a composite of any of these events, a revascularization procedure (cardiac, carotid, or peripheral), or hospitalization for heart failure. Insulin glargine had a neutral effect on CV outcomes. Rates of the first co-primary CV outcome of MI, stroke, or CV death, and the second co-primary outcome of MI, stroke, CV death, revascularization and heart failure were similar in the insulin glargine and the standard care groups (2.94 vs. 2.85 per 100 person-years; and 5.52 vs. 5.28 per 100 person-years, respectively). Results showed that the progression from pre-diabetes to diabetes was delayed by 28% in the insulin glargine arm at one month following completion of the trial, and the number of persons in remission was 20% when reassessed after 100 days (Fig. 3, Table 3) [68].

Lessons learnt
Data from DEVOTE and ORIGIN established the CV safety of the basal insulin analogues glargine and degludec. ORIGIN revealed that glargine had a neutral effect on CV outcome despite an increased incidence of hypoglycaemia and modest increase in body weight [68]. DEVOTE is the first dedicated regulatory CVOT trial with an insulin, where insulin degludec was compared to insulin glargine. Insulin degludec was non-inferior to insulin glargine in demonstrating CV safety. There was less hypoglycemia in the degludec arm when compared to glargine [69].

Research gap
There is very limited information concerning the cardiovascular safety of various insulin preparations. Observational data, with all its limitations and biases, have tended to attribute an increased CV risk to insulin. However, in contrast, data from the two large CVOTs with basal insulin analogues is very reassuring. However, to date, there is no CVOT data concerning the CV safety of short/rapid acting human or analogues insulins, premixed human or analogue insulins, co-formulation insulin, or the intermediate acting insulin NPH.

Conclusion
Insulin therapy has remained an important therapeutic agent in the treatment of diabetes mellitus, and it is thus crucial to assess its CV safety as mandated by FDA. CV safety of insulins was earlier assessed through data from observational studies, which yielded conflicting results, till the availability of CV outcome data
Figure 3. ORIGIN Study — Study design and Outcome. Adapted from [68]

ORIGIN was designed to assess the effects of insulin glargine on CV outcomes

3-P MACE

Glargine had a neutral effect on cardiovascular outcomes and cancers with increased hypoglycemia and modestly increased weight

Better efficacy was seen with insulin glargine with increased risk of hypoglycemia as compared to standard of care

REMISSION

Findings from ORIGIN suggest a degree of glycemic remission introduced by early insulin use which persisted for at least 3 month after treatment was stopped
from randomised controlled trails with basal insulin analogues. The ORIGIN and DEVOTE trials have demonstrated the cardiovascular safety of insulin degludec and insulin glargine. There was lesser hypoglycaemia, and lesser day-to-day fasting glycaemic variability with insulin degludec when compared to insulin glargine, but this did not translate into CV benefits. More evidence is required concerning the CV safety of other insulin preparations, including human and analogue prandial and pre-mixed insulins to allow appropriate insulin choices.

**Author statement**

The authors declare that: The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.
REFERENCES


Conflict of interest
None declared.


