

# Auxiliendo, Primum Non Nocere: A Preliminary View of the DEVOTE Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Type 2 Diabetes

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## ABSTRACT

A demonstration of cardiovascular safety is mandatory for all newly developed glucose-lowering agents, including insulin analogues. The vascular benefit of insulin is evident from the Diabetes Control and Complication Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), and the cardiovascular safety of insulin glargine has been demonstrated in individuals with newly diagnosed diabetes or prediabetes in the ORIGIN trial (Outcome Reduction with an Initial Glargine Intervention). The top-line results of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) have proven the cardiovascular safety of insulin degludec in persons with type 2 diabetes. In this commentary I discuss the interrelationship of insulin and cardiovascular health, while comparing the results of DEVOTE and ORIGIN.

**Keywords:** Cardiovascular outcome trials; Hypoglycaemia; Insulin; Insulin analogues; Nocturnal hypoglycaemia; Type 2 diabetes

Insulin is a well-established treatment for both type 1 and type 2 diabetes and has been in use now for nearly a century. During this time, the source, structure, purity and delivery of insulin has changed significantly. What has not changed, however, is the ability of insulin to control blood glucose, improve quality of life, avoid complications and save lives. The ability of insulin to prevent micro- and micro-vascular complications has been demonstrated in two landmark trials, namely the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) [1, 2].

While the above-mentioned benefits of insulin are not disputed, the occurrence of side effects, such as weight gain and hypoglycaemia, did lead to concerns about the cardiovascular safety of this drug [3–5]. One large study reported that intensive and rapid glycaemic control measures using insulin as one of many interventional components increased the risk of cardiovascular events and all-cause mortality [3]. The authors, however, did comment that the study was not designed to identify the particular component causing increased events. A meta-analysis also showed that fasting hyperinsulinemia is significantly associated with

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cardiovascular mortality in non-diabetic adults [6]. However, this hyperinsulinemia may be due to insulin resistance, which itself is linked to cardiovascular dysfunction.

Certain insulin analogues were also thought to be linked to increased cancer risk because of their growth-promoting properties [7–12]. Unfounded concerns about the “pushing “of insulin by manufacturers added fuel to fire [13]. These uncertainties led to a debate on whether insulin use to achieve euglycemia in type 2 diabetes follows the dictum ‘*primum succurrere*’ (first hasten to help) without respecting the philosophy of ‘*primum non nocere*’ (first do not harm). However, these issues, raised by non-specialists in the field, have effectively been put to rest with the ORIGIN and DEVOTE trials.

The ORIGIN trial (Outcome Reduction with an Initial Glargine Intervention) showed insulin glargine to have cardiovascular safety when administered to participants with newly diagnosed type 2 diabetes or prediabetes [14]. The authors of the ORIGIN trial highlighted the large difference in insulin use between the insulin glargine and control group, as well as the glycaemic equipoise achieved between them. Hence, the cardiovascular safety demonstrated in the intervention (glargine) group related more to glargine or insulin per se than to good glycaemic control.

The DEVOTE trial (Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) studied 7637 participants with type 2 diabetes and a high cardiovascular risk profile who were being treated with one or more oral or injectable anti-diabetic agent, with a glycated haemoglobin A1c (HbA1c) of >7.0%. Participants with a HbA1c of <7.0% were included in the trial if their current basal insulin requirement was >20 U/day. All participants were randomized in a double-blinded manner, in a 1:1 ratio, to either an insulin degludec + standard of care arm or an insulin glargine + standard of care arm. They were seen weekly for 2 weeks, monthly for 6 months and quarterly for the rest of the trial [15]. This trial design differed from ORIGIN with respect to inclusion criteria, trial

structure and choice of comparator arm and frequency of follow-up (Table 1). It must be noted that ORIGIN had a placebo arm, while DEVOTE used an active comparator arm.

The DEVOTE trial included participants with a longer duration of diabetes and a higher cardiovascular risk profile. The inclusion criteria were reflective of a real world diabetes outdoor clinic which included participants of a similar background who could be initiated on (or switched to) a basal insulin analogue. The primary endpoint of the study, i.e. the MACE composite outcome of first occurrence of cardiovascular death, non-fatal stroke and myocardial infarction, showed a hazard ratio of 0.91 in favour of degludec relative to insulin glargine U100, but this difference was not statistically significant [16]. Thus, degludec demonstrated cardiovascular safety, relative to glargine, allaying concerns about its use in type 2 diabetes patients at risk of cardiovascular disease.

The secondary endpoint, i.e. hypoglycaemia, occurred in fewer participants on degludec than in those on glargine. While 27% fewer participants in the degludec arm experienced an episode of severe hypoglycaemia, there was a 40% reduction in the number of total episodes of adjudicated severe hypoglycaemia and a 54% relative reduction in the rate of nocturnal severe hypoglycaemia, with all these difference achieving statistical significance. These results are concordant with those reported in the BEGIN and BOOST clinical trial programmes of insulin degludec and degludec aspart [17, 18].

Hypoglycaemia per se is a risk factor for cardiovascular mortality and is known to impair quality of life [19, 20]. Hence, avoidance of hypoglycaemia is one of the aims of safe and effective diabetes care and is included in the glycaemic pentad [21].

While detailed data of the DEVOTE trial will be reported at a later time, the top-line results are encouraging. The trial provides evidence that one can use insulin degludec to achieve better glycaemic control without fear of hypoglycaemia and without fear of cardiovascular adverse effects. This will encourage the timely use of insulin in persons with type 2 diabetes, including those with cardiovascular risk factors. In the debate between two contrasting

**Table 1** Parameters of the ORIGIN and DEVOTE trials

Parameter	DEVOTE trial	ORIGIN trial
Inclusion criteria	Patients with T2D treated with $\geq 1$ OAD or insulin with high CV risk profile	Patients with T2D at high risk of CV events with IFG, IGT and newly detected or established diabetes (on 0 or 1 oral agent)
Trial design	Multicentre, international, randomised, double-blind, active comparator-controlled, event-driven trial	Multicentre, international, randomised, open label, $2 \times 2$ factorial design
Objective	Investigated the CV safety profile of insulin degludec compared with insulin glargine U100, each added to standard of care	Evaluated the effects of insulin glargine U100 vs. standard of care, a treatment regimen selected by investigators according to local guidelines
Primary endpoint	Time from randomisation to first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke)	Composite of the first occurrence of CV death, non-fatal myocardial infarction or non-fatal stroke
Patient population	7637 people with T2D with existing or at high risk of CV disease	12,537 people with CV risk factors plus IFG/IGT or type 2 diabetes
Mean patient duration of diabetes	16 years	5 years
Randomization	1:1	$2 \times 2$ factorial design
Comparator arm	Insulin glargine OD (blinded vial) + standard of care	Placebo + standard of care
Frequency of follow up	Weekly for 2 weeks, monthly for 6 months and quarterly for the remaining part of the trial	At 0.5, 1, 2, and 4 months after randomization and every 4 months thereafter
Follow-up	Information collected on use of concomitant medications, incidence of serious AEs and severe AEs and investigational product compliance at every visit. HbA1c measured at 7 and 30 days and at every visit thereafter	Clinical outcomes, adherence and adverse events ascertained 0.5, 1, 2, and 4 months after randomisation and every 4 months thereafter HbA1c recorded at every visit starting at 2 months in people with diabetes and at 2, 4, 8 months, and annually for others
Results: efficacy	Achieved its primary endpoint by demonstrating non-inferiority of MACE (HR, 0.91) in favour of insulin degludec relative to insulin glargine U100 (NS)	At an average of 6.2 years of follow-up, there was no difference in the frequency of the primary endpoint between people treated with insulin glargine U100 or those in the standard of care group (HR, 1.02; 95% CI 0.94–1.11)

Table 1 continued

Parameter	DEVOTE trial	ORIGIN trial
Results: safety	Demonstrated superiority on the secondary confirmatory end point: 27% fewer patients in the insulin degludec-treated group experienced an episode of severe hypoglycaemia, resulting in a 40% overall reduction of total episodes of adjudicated severe hypoglycaemia. A significant 54% reduction in the rate of nocturnal severe hypoglycaemia was noted	Early use of basal insulin was associated with an increased risk of both hypoglycaemia (1.00 vs. 0.31 per 100 person-years) and weight gain (median weight + 1.6 kg in the insulin-glargine group versus -0.5 kg in the standard care group)
		There was no significant difference in cancers (HR 1.00; 95% CI 0.88–1.13; $P = 0.97$ )
<i>AEs</i> : adverse events, <i>CI</i> confidence interval, <i>CV</i> cardiovascular, <i>DEVOTE</i> Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events <i>HbA1c</i> glycated haemoglobin <i>A1c HR</i> hazard ratio, <i>IFG</i> impaired fasting glucose, <i>IGT</i> impaired fasting tolerance, <i>MACE</i> major adverse cardiovascular event, <i>NS</i> not significant, <i>OAD</i> oral anti diabetic drug, <i>OD</i> once daily, <i>ORIGIN</i> Outcome Reduction with an Initial Glargine Intervention <i>T2D</i> Type 2 diabetes		

philosophies of action, ‘Primum succurrere’, and ‘Primum non nocere’, degludec proves its DEVOTion to diabetes care: Auxiliendo, Primum non nocere.

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