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COMMENTARY

Cardiovascular safety of long-acting insulin analogs in type 2 diabetes patients: Is there a better basal insulin?

In 2008, the US Food and Drug Administration requested that all new type 2 antidiabetic drugs, including long-acting insulin analogs, be rigorously examined to preclude undesirable cardiovascular risks. The Outcome Reduction with an Initial Glargine Intervention trial is the first trial to provide conclusive evidence of the cardiovascular safety of insulin glargine[1]. A total of 12,537 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance or type 2 diabetes were randomized to receive insulin glargine or standard care. During a median follow up of 6.2 years, insulin glargine neither increased nor decreased cardiovascular outcomes, including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and these events plus revascularization or hospitalization for heart failure. Five years later, the results of the Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events study were published for the cardiovascular safety of a new ultra-long insulin analog, degludec[2]. The large double-blind head-to-head Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events trial aimed to enroll more vulnerable patients, including those with chronic heart failure New York Heart Association functional class III, chronic kidney disease corresponding to an estimated glomerular filtration rate of 30–59 mL/min/1.73 m^2 and those that received coronary artery bypass graft surgery (Table 1) for cardiovascular safety evaluation. The results showed that insulin degludec was non-inferior to glargine (which has already been proved to have a neutral effect) as to the incidence of major cardiovascular events (hazard ratio 0.91, 95% confidence interval 0.78–1.06; $P < 0.001$ for non-inferiority), with comparable mean glycated hemoglobin levels in both groups. The established cardiovascular safety of degludec relative to glargine was reflected in the individual components of the primary composite outcome, and was consistent across multiple prespecified subgroups. These data reassure us that insulin degludec has a cardiovascular safety profile at least not worse than insulin glargine for type 2 diabetes patients at high risk of a cardiovascular event.

The Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events study also found that insulin degludec was superior to insulin glargine relating to hypoglycemia risk, with a reduced rate of both severe and nocturnal severe hypoglycemia by 40 and 53%, respectively. Of note, the active comparison drug used in that trial was insulin glargine 100 units/mL (G100), which in many countries has been replaced by insulin glargine 300 units/mL (G300), a novel formulation that contains a higher concentration of insulin, and a better pharmacokinetic and pharmacodynamic property than G100. The comparative efficacy and safety between G300 and G100 has been extensively evaluated across a broad spectrum of type 2 diabetes populations, including Japanese people with lower body mass index, requiring lower insulin doses, and hence might have lower insulin resistance and higher hypoglycemia risks (Table 1). Results from the Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus EDITION 1, 2, 3[3–6] and EDITION JP2 trials[7] consistently showed that G300 has a lower risk of confirmed (≤70 mg/dL) or severe hypoglycemia occurring during the night (00.00–05.59 hours) or at any time of day as compared with G100. The annualized rate of nocturnal confirmed or severe hypoglycemia was 31% lower with G300 than with G100 in the Caucasian population, and 55% lower in the Japanese population, whereas the annualized rate of such an event at any time of day was 14% lower with G300 vs G100 in the Caucasian population and 36% lower in the Japanese population, respectively. For type 2 diabetes patients, severe hypoglycemia is well-known to be an important risk factor for cardiovascular events and mortality. Currently, there is no head-to-head randomized trial comparing G300 with insulin degludec in terms of cardiovascular and hypoglycemia risks. A network meta-analysis of small, randomized efficacy trials reported no significant difference in the documented symptomatic hypoglycemia rate of G300 vs insulin degludec[8]. However, differences in participants' inclusion and exclusion criteria, targeted glycemic goal, and the definition of hypoglycemia across these trials make interpretation of the results from indirect comparison very difficult. Further well-designed studies, such as pragmatic randomized trials or randomized cross-over trials, are required to provide more data regarding hypoglycemic risk between insulin degludec and G300.

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Table 1 | Summary of characteristics of study participants enrolled in randomized controlled trials of long-acting insulin analogs

	DEVOTE[2]	ORIGIN[1]	EDITION[3–5] 1, 2, 3	EDITION[7] JP 2
Inclusion criteria	• Type 2 diabetes with predefined cardiovascular or renal disease (age ≥50 years) or predefined cardiovascular risk factors (age ≥60 years) • A1c ≥7.0% or A1c <7.0 on basal insulin ≥20 U/day	• Age ≥50 years with prior cardiovascular event/risk factors and also had with IFG, IGT, T2D	Type 2 diabetes age ≥18 years • Current basal insulin ≥42 U/day for ≥1 year (EDITION 1) • ≥6 months on basal insulin and ≥42 U/day within last 4 weeks (EDITION 2) • Insulin naïve on oral agents for ≥6 months (EDITION 3)	Adult type 2 diabetes • Diagnosed ≥1 year treated with basal insulin and oral agents ≥6 months • A1c ≥7% and ≤10%
Important exclusion criteria	• Acute coronary event or stroke within 60 days • Planned revascularization • Heart failure NYHA class IV • On dialysis or eGFR <30 mL/min/1.73 m^2 • End-stage liver disease • Cancer	• A1c ≥9% • CABG within the 4 years prior to screening • Serum creatinine >2.0 • Active liver disease • Heart failure NYHA class III or IV • Cancer affecting survival	• A1c <7% • A1c >10% (EDITION 1,2) and >11% (EDITION 3)	• BMI ≥35 kg/m^2 • Severe hypoglycemia resulting in coma/seizure
SMBG fasting glucose before breakfast target	71–90 mg/dL (90–126 mg/dL for vulnerable)	≤95 mg/dL	80–100 mg/dL	80–100 mg/dL
Total number enrolled	7,637	12,537	2,496	241
Comparison groups	Insulin degludec vs insulin glargine G100	Insulin glargine G100 vs standard care	Insulin glargine G300 vs insulin glargine G100	Insulin glargine G300 vs Insulin glargine G100
Blinding	Double-blind	Open-label	Open-label	Open-label
Follow-up duration (year)	1.99	6.2	0.5	0.5
Mean age (year)	65	63.5	58.6	60.8
Male (%)	63	65	52.4	61
Mean BMI, kg/m^2	33.6	29.9	34.8	25.3
Duration of diabetes, years	16.4	5.4	12.7	14
Mean or median A1c (%)	8.4	6.4	8.3	8.0
Primary cardiovascular outcome	Cardiovascular death, non-fatal MI, non-fatal stroke	Cardiovascular death, non-fatal MI, non-fatal stroke	–	–
Hypoglycemia endpoint	Severe hypoglycemia	Severe hypoglycemia	Confirmed (≤70 mg/dL) or severe hypoglycemia	Confirmed (≤70 mg/dL) or severe hypoglycemia

A1c, glycated hemoglobin; CABG, coronary artery bypass graft surgery; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EDITION, the Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus; eGFR, estimated glomerular filtration rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MI, myocardial infarction; NYHA, New York Heart Association; ORIGIN, The Outcome Reduction with an Initial Glargine Intervention; T2D, type 2 diabetes.

There are more and more concerns about the prices of new insulin analogs, as they have escalated during recent years. Further cost-effectiveness research of these new long-acting insulin analogs are required to have a full understanding of whether their higher drug costs will convert into fewer hypoglycemia events, improved health-related quality of life or even a better outcome resulting in total net cost-savings for the entire healthcare system.

DISCLOSURE

The authors declare no conflict of interest.

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