Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) – DEVOTE 1

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DEVOTE was designed to evaluate the cardiovascular safety of insulin degludec (IDeg) vs insulin glargine U100 (IGlar) in patients with T2D at high risk of cardiovascular events. DEVOTE is a phase 3b, multicenter, international, randomized, double-blind, active comparator-controlled trial, designed as an event-driven trial that would continue until 633 positively adjudicated primary events were accrued. The primary end point was the time from randomization to a composite outcome consisting of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Patients with T2D at high risk of cardiovascular complications were randomized 1:1 to receive either IDeg or IGlar, each added to background therapies. This trial was designed to demonstrate statistical noninferiority of IDeg vs IGlar for the primary end point. DEVOTE enrolled 7,637 patients between October 2013 and November 2014 at 436 sites in 20 countries. Of these, 6,506 patients had prior cardiovascular disease or chronic kidney disease, and the remainder had multiple cardiovascular risk factors. DEVOTE was designed to provide conclusive evidence regarding the cardiovascular safety of IDeg relative to IGlar in a high-risk population of patients with T2D. (Am Heart J 2016;179:175-83.)

Background

Current treatment guidelines for type 2 diabetes (T2D) highlight the importance of patient-centered engagement and support with lifestyle interventions and pharmacologic therapies to manage hyperglycemia to individualized glycemic targets.[1] Although there are now 12 classes of antihyperglycemic therapies available for the treatment of T2D, many patients do not achieve adequate glycemic control even with combination therapies. The use of basal insulin has been endorsed as an essential component of the treatment strategy for those failing to achieve glycemic targets in the absence of insulin therapy.[1] Although insulin is effective at lowering circulating glucose levels, it has a narrow therapeutic window and can be associated with hypoglycemia and weight gain. As a result, providers often underutilize, underdose, or delay insulin initiation until late in the course of diabetes. Basal insulin with improved pharmacokinetics and pharmacodynamics could potentially mitigate these risks—particularly nocturnal hypoglycemia.

Insulin degludec (IDeg) is a long-acting basal insulin analog that is administered once daily and is presently approved for the treatment of T2D. At the time of filing the US Food and Drug Administration (FDA) new drug application, the cardiovascular safety and efficacy of IDeg was evaluated in 8,959 patients, as a part of the IDeg development program. The primary cardiovascular safety end point was a meta-analysis using a prespecified, prospectively adjudicated, 4-component composite outcome of major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina requiring hospitalization). Across the individual trials, there was no consistent pattern in the incidence rates or estimated hazard ratios (HRs). Overall, the incidence rates for MACE were 1.48 and 1.44 per 100 patient-years of exposure for the

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IDeg+IDegAsp (insulin degludec/insulin aspart) and comparator groups, respectively; HR 1.097 (95% CI, 0.681-1.768).[2] A sensitivity analysis using a 3-component MACE (cardiovascular death, myocardial infarction, and stroke) was requested by the FDA. When hospitalized unstable angina was excluded, the total number of patients with a MACE fell from 80 to 54, and the HR associated with IDeg use for this reduced end point was 1.39 (95% CI, 0.76-2.57), representing a wider CI and an increased HR. Given these data, the FDA mandated a dedicated cardiovascular outcomes trial to assess the cardiovascular safety of IDeg compared with insulin glargine U100 (IGlar).

The objective of DEVOTE was to compare the cardiovascular safety of IDeg with IGlar, each added to standard of care, in an at-risk cardiovascular population.

Trial design

DEVOTE is a phase 3b, multicenter, international, randomized, double-blind, active comparator-controlled cardiovascular outcomes trial, designed as an event-driven trial that would continue until at least 633 positively adjudicated, primary cardiovascular outcome events were accrued. The primary end point was the time from randomization to the first event of a composite MACE outcome consisting of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Patients with T2D at high risk of cardiovascular events were randomized 1:1 to receive either IDeg or IGlar, each added to standard of care. An interim analysis was performed to assess the noninferiority of IDeg to IGlar for the primary end point after 150 primary events were accrued to support the resubmission of the new drug application for IDeg to the FDA. The final noninferiority analysis will be assessed at trial completion after at least 633 adjudication-confirmed primary MACE events have accrued. This trial is registered with ClinicalTrials.gov number NCT01959529. The trial was conducted in accordance with the Declaration of Helsinki[3] and Good Clinical Practice Guidelines.[4] The protocol was approved by independent ethics committees or institutional review boards before the start of the trial. Signed informed consent was obtained from each patient before any trial-related activities.

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Study population

Eligible patients included those with T2D treated with ≥1 oral or injectable antihyperglycemic therapy, a glycated hemoglobin (HbA_{1c}) ≥7.0% or HbA_{1c} <7.0%, if treated with ≥20 units/day of basal insulin. Two cohorts were eligible for recruitment into the trial:

Prior cardiovascular disease (CVD) or history of moderate chronic kidney disease (CKD) cohort: patients were eligible if they were ≥50 years old and had a history of CVD or moderate CKD. Prior CVD was defined by any 1 of the following: myocardial infarction; stroke or transient ischemic attack (TIA); coronary, carotid, or peripheral revascularization; >50% diameter stenosis found on angiography or other imaging modality of the coronary, carotid, or lower extremity arteries; history of symptomatic coronary heart disease documented by positive noninvasive stress test or unstable angina pectoris with electrocardiogram (ECG) changes; asymptomatic cardiac ischemia; New York Heart Association (NYHA) class II to III congestive heart failure; or *moderate CKD* (Stage 3) defined as estimated glomerular filtration rate (eGFR) 30 to 59 mL/min per 1.73 m^2 using the CKD-Epidemiology Collaboration (CKD-EPI) equation.[5]

No prior CVD cohort: patients were eligible if they were ≥60 years old and did not have a history of CVD or moderate CKD but did have at least one of the following: microalbuminuria or proteinuria; hypertension with left ventricular hypertrophy; left ventricular systolic and diastolic dysfunction as defined by the investigator; or an abnormal ankle-brachial index of <0.9. The complete list of inclusion and exclusion criteria is found in Table I.

Randomized treatment regimen

After determining eligibility and obtaining written informed consent, patients were randomized to receive either IDeg or IGlar, both supplied by the trial sponsor (Novo Nordisk) in identical 100-U/mL, 10-mL vials. Commercially available IGlar (Lantus) vials were procured and the label removed. Identical empty vials and vial covers were also procured and filled with IDeg. Treatment was administered using 1-mL syringes. An interactive voice/web response system was used for randomization. The randomization code for a particular patient could be broken in the case of a medical emergency if knowing the treatment allocation would influence the clinical management of the patient. All patients continued their current pretrial antihyperglycemic therapy with the exception of basal insulin, which was discontinued. Patients self-administered the investigational product subcutaneously once daily between dinner and bedtime, starting on the day of randomization. For patients who were taking rapid-acting insulin before the trial, the investigator could decide on an individual basis to replace this with insulin aspart, which was provided free of charge by the trial sponsor. Premixed/biphasic insulin products were replaced by the investigational product according to treatment allocation, with

Table I. DEVOTE inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Type 2 diabetes	An acute coronary or cerebrovascular event in the previous 60 d
HbA_{1c} ≥7.0% or HbA_{1c} <7.0% and current insulin treatment corresponding to ≥20 U/d of basal insulin	Planned coronary, carotid or peripheral artery revascularization
Age ≥50 y at screening and at least 1 of the following conditions:	Chronic heart failure NYHA class IV
• Prior myocardial infarction	Current hemodialysis or peritoneal dialysis or eGFR <30 mL/min per 1.73 m^2 per CKD-EPI
• Prior stroke or prior TIA	*End-stage liver disease*, defined as the presence of acute or chronic liver disease and recent history of 1 or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥2.0 mg/dL, albumin level ≤3.5 g/dL, prothrombin time ≥4 s prolonged, international normalized ratio ≥1.7 or prior liver transplant
• Prior coronary, carotid, or peripheral arterial revascularization	Known or suspected hypersensitivity to trial products or related products
• >50% stenosis on angiography or other imaging of coronary, carotid, or lower-extremity artery	Female of child-bearing potential who is pregnant, breastfeeding or intends to become pregnant, or is not using adequate contraceptive methods as required by local law or practice
• History of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina pectoris with ECG changes	Expected simultaneous participation in any other clinical trial of an investigational medicinal product.
• Asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echocardiogram	Participation in a clinical trial with stent(s) is allowed
	Receipt of any investigational medicinal product within 30 d before randomization
	Brazil: receipt of any investigational medicinal product within 1 y before randomization, unless there is a direct benefit to the patient at the investigator's discretion
• Chronic heart failure NYHA class II-III	Current or past (within the last 5 y) malignant neoplasms (except basal cell and squamous cell skin carcinoma)
• Chronic kidney disease corresponding to glomerular filtration rate 30-59 mL/min per 1.73m^2 per CKD-EPI	Any condition that in the investigator's opinion would make the patient unable to adhere to the initial trial visit schedule and procedures
Age ≥60 y at screening and at least 1 of the following risk factors:	
• Microalbuminuria or proteinuria	
• Hypertension and left ventricular hypertrophy by ECG or imaging	
• Left ventricular systolic and diastolic dysfunction by imaging	
• Ankle/brachial index <0.9	

CKD-EPI, Chronic Kidney Epidemiology Collaboration; *ECG*, electrocardiogram; *eGFR*, estimated glomerular filtration rate; *NYHA*, New York Heart Association; *TIA*, transient ischemic attack.

the addition of rapid-acting insulin as needed to achieve glycemic targets. There was no maximum insulin dose prespecified. Intensification of therapy was determined by the site investigator based upon clinical judgment.

The trial protocol provided an algorithm for basal insulin titration to achieve a fasting self-measured blood glucose (SMBG) of 71 to 90 mg/dL (4.0-5.0 mmol/L). Guidance on adjustment of rapid-acting insulin was also provided, aiming for premeal or bedtime SMBG values of 71 to 126 mg/dL (4.0-7.0 mmol/L). The trial leadership recognized that this level of glycemic control may not be appropriate in selected patients at higher cardiovascular risk, and that investigators might reasonably recommend a less stringent glycemic target. Therefore, an alternative fasting SMBG target of 91 to 126 mg/dL (5.0-7.0 mmol/L) was also an acceptable alternative target. The investigators were required to prespecify the glycemic target for individual patients before randomization. The option to reassess this prespecified glycemic target was possible throughout the trial duration. Titration adequacy was monitored centrally and feedback provided to encourage adherence to the protocol.

Planned follow-up

After randomization, patients were seen weekly for 2 weeks, monthly for 6 months, and then every 3 months for the remaining part of the trial. There was a planned end-of-treatment follow-up visit 30 days after investigational product discontinuation. At every trial visit, information regarding the use of concomitant medication, the occurrence of serious adverse events (AEs), severe hypoglycemic events, and investigational product compliance was obtained. After randomization, HbA_{1c} was measured at 7 days, 30 days, and then at every trial visit thereafter.

End point assessment

The primary end point was the time from randomization to the first occurrence of a 3-component MACE consisting of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The key secondary end point was *severe hypoglycemia*, defined according to contemporary American Diabetes Association criteria, as an episode requiring assistance from another person or an episode temporally associated with an accident, convulsion, or death.[6] Other secondary end points included the time from randomization to all-cause death, the frequency of serious AEs, and the frequency of AEs leading to discontinuation of the investigational product.

Additional end points were the change from baseline to the final assessment of HbA_{1c}, fasting plasma glucose, blood pressure, pulse rate, lipid profile, weight, body mass index, eGFR, as well as basal and bolus insulin dose at the end of the trial.

Event adjudication

Acute coronary syndrome, cerebrovascular events, fatal events, and severe hypoglycemic episodes were prospectively adjudicated by an independent Event Adjudication Committee (EAC). The EAC comprised 10 experts in cardiology, neurology, and endocrinology. The EAC members were blinded to treatment and were not involved in the design, conduct, or reporting of the clinical trial results. The EAC had access to relevant source documents and was empowered to request additional clinical information from sites to resolve uncertainty with event adjudication classification.

Identification of events for adjudication was performed using several processes. The investigators classified all documented AEs in the case report form as an acute coronary syndrome (unstable angina or acute myocardial infarction), a cerebrovascular event, a severe hypoglycemic event, a fatal event, or none of the above. All events except for "none of the above" triggered EAC adjudication. Further, AEs classified as "none of the above" were systematically screened by blinded sponsor employees to identify potentially missed events. Patients underwent a 12-lead ECG at baseline and at yearly intervals. All ECGs were forwarded to a central core ECG lab for formal reading. Any ECGs found to have changes suggestive of a new myocardial infarction were sent for adjudication to identify potentially silent myocardial infarctions. Lastly, blinded sponsor employees reviewed preselected standardized queries using the Medical Dictionary for Regulatory Activities (MedDRA) to identify events not otherwise triggered for EAC adjudication.

Nonfatal myocardial infarction

Acute coronary syndrome was triggered for EAC review if the patient experienced symptoms of myocardial ischemia that required hospitalization, periprocedural myocardial ischemia, or if there was evidence of a silent myocardial infarction. Both nonfatal myocardial infarctions and unstable angina requiring hospitalization underwent formal event adjudication. The latter was not a component of the primary end point.

Stroke

Episodes of focal or global neurologic dysfunction caused by the brain, spinal cord, or retinal vascular injury as the result of hemorrhage or infarction were triggers for event adjudication. All types of strokes including ischemic, hemorrhagic, and undetermined were adjudicated.

Fatal events

All fatal events were triggers for event adjudication. The primary composite outcome included cardiovascular mortality. Cardiovascular death included deaths that are clearly cardiovascular and those that were undetermined by EAC review.

Severe hypoglycemia

All hypoglycemic events reported as an episode requiring the assistance of another person or fulfilling the definition of a serious AE were triggers for event adjudication. In addition, selected fatal events and events identified via the MedDRA search of "accidents and injuries (Standardized MedDRA Queries—narrow scope)" and "convulsions (Standardized MedDRA Queries—road scope)" were also triggers for adjudication.

Trial governance

DEVOTE was overseen by an executive Steering Committee composed of 4 experts in endocrinology, 3 in cardiology, 1 in biostatistics, and 4 employees of the trial sponsor (Novo Nordisk). The executive steering committee independently oversaw all aspects of the trial. The Global Expert Panel consisted of principal investigators from enrolling countries and designated employees of the sponsor. This panel provided advice and active implementation assistance for operational issues that naturally arise during the execution of a global clinical trial.

An independent external data monitoring committee (IDMC) was established to perform ongoing safety surveillance and data monitoring. The IDMC was comprised of permanent members who were recognized experts in the fields of cardiology, endocrinology, neurology, and statistics. The IDMC had access to complete, unblinded data and met at predetermined intervals, as well as on an ad hoc basis, to evaluate all relevant data and safety information that accumulated during the course of the trial. The IDMC could recommend terminating the trial prematurely. The IDMC also had access to unblinded data for all planned and interim data analyses.

Statistical considerations

The sample size estimate was based on the number of first MACE including cardiovascular death, nonfatal myocardial infarction, or stroke occurring after randomization. The estimates were based on an intention-to-treat principle and a log-rank test for a total of 633 first events. This number of events would provide 91% power to exclude an upper bound of a 95% CI exceeding 1.3 for the primary analysis of noninferiority, assuming the true HR was 1.0. To have a total of 633 first events with a trial duration of approximately 5 years, 3,750 patients would be needed for each randomized treatment arm with a 1:1 randomization scheme. This estimate was based on an annual event rate projected to be 2.1 per 100 patient-years in both treatment groups, with an assumed loss-to-follow-up rate of 1% per year throughout the trial. The primary end point was the time from randomization to the first positively adjudicated MACE, as determined by the EAC.

Interim analyses

DEVOTE used an interim analysis to assess the cardiovascular safety of IDeg using the data compiled when a total of 150 positively adjudicated primary end points were accrued. The interim analysis was prespecified to establish the noninferiority of IDeg relative to IGlar if the upper limit of the 2-sided 95% CI for the HR ($hazard_{IDeg}/hazard_{IGlar}$) was <1.8.

Final analysis of primary and secondary end points

The primary end point will be presented descriptively in a Kaplan-Meier plot according to randomized treatment, and analyzed using a Cox proportional hazard regression with treatment group as a factor using the full analysis set (FAS). The FAS will be defined according to the intention-to-treat principle. The HR and the corresponding 2-sided 95% CI will be estimated. The analyses done with the FAS will be considered confirmatory, whereas the analyses done with the per-protocol set will be considered supportive. The final noninferiority of IDeg will be established at the trial completion if the upper bound of the 95% CI is <1.3 and after the accumulation of at least 633 primary events.

If noninferiority for the primary end point is established, then the number of positively adjudicated severe hypoglycemic episodes will be considered as secondary confirmatory end points and analyzed using a negative-binomial regression model with log-link function, and the logarithm of the duration of the exposure time as offset. The model will include treatment group as a fixed factor and fitted using the final analysis set. Superiority will be considered confirmed if the upper limit of the 2-sided 95% CI for the ratio is <1.0. A hierarchical testing strategy will be applied, meaning that there will be no penalty on the α level for the statistical test. There will be no adjustment of the α level for the final statistical testing.

Data access management

The interim analysis was submitted in March 2015 by the trial sponsor and used in the approval of IDeg by the FDA for its use in the United States. The executive Steering Committee, in collaboration with the sponsor, developed a rigorous data access management plan to mitigate the risk of performing an interim analysis on the overall integrity of the clinical trial. This data access management plan tightly restricted the numbers of individuals who had access to the unblinded data and put in place very strict standards on how these data were accessed, reviewed, shared with others, analyzed, and stored to protect the overall integrity, blinding, and confidentiality of DEVOTE. Three groups of individuals had access to the unblinded data: (1) an external, independent statistical team (Statistics Collaborative, Inc, Washington, DC) with the sole responsibility of analyzing the interim data; (2) a Novo Nordisk interim reporting team, responsible for reviewing, interpreting, and creating the clinical report to submit to the FDA; and (3) the IDMC. No other individuals, including the DEVOTE Steering Committee and Novo Nordisk employees (including the Novo Nordisk executive management and internal safety committee), had access to these unblinded interim data.

The number of individuals in the Novo Nordisk interim reporting team was limited and each person had a vital role in the group. This team was granted sole authority to decide whether or not to submit the interim analyses results to the FDA. They were solely responsible for generating the report of the interim data for the FDA submission and all communication with the FDA regarding the interim data or additional data requests. These individuals signed a strict nondisclosure agreement, were identified prospectively, and were physically separated—with separate security access—from other employees of Novo Nordisk. The interim reporting team received formal training regarding the importance of keeping interim data confidential and they worked on a secured network separate from the Novo Nordisk network. A separate and secure IT infrastructure was created for handling the unblinded data within Novo Nordisk and an institutional firewall was established to support these functions.

Study population

DEVOTE enrolled 7,637 patients (n = 6,506 in the "prior CVD/CKD" cohort; n = 1,131 in the "no prior CVD" cohort) between October 2013 and November 2014 at 436 sites in 20 countries. A total of 8,205 patients were screened, of whom 561 were ineligible, primarily as a result of not meeting HbA_{1c} criteria (26%), not meeting

Table II. Baseline demographics

	Prior CVD/CKD n = 6506	No prior CVD n = 1131	Total population n = 7637
Age (y)	64.8 ± 7.7	66.2 ± 5.3	65.0 ± 7.4
Men	4179 (64.2)	599 (53.0)	4778 (62.6)
Ethnicity			
Hispanic or Latino	893 (13.7)	244 (21.6)	1137 (14.9)
Not Hispanic or Latino	5613 (86.3)	885 (78.2)	6498 (85.1)
Race			
White	4961 (76.3)	814 (72.0)	5775 (75.6)
Asian	649 (10.0)	127 (11.2)	776 (10.2)
Black	690 (10.6)	142 (12.6)	832 (10.9)
Other	206 (3.2)	48 (4.2)	254 (3.3)
Weight (kg)	96.8 ± 22.8	92.3 (22.9)	96.1 ± 22.9
BMI (kg/m^2)	33.7 ± 6.9	33.1 (6.8)	33.6 ± 6.9
Hyperlipidemia	5517 (84.8)	803 (71.0)	6320 (82.8)
Smoking			
Current	734 (11.3)	118 (10.4)	852 (11.2)
Previous	2937 (45.1)	416 (36.8)	3353 (43.9)
Prior myocardial infarction	2601 (40.0)	–	2601 (34.1)
Heart failure	947 (14.6)	–	947 (12.4)
Cerebrovascular disease	1236 (19.0)	–	1236 (16.2)
Diabetes duration (y)	16.1 ± 8.9	15.2 ± 8.2	16.0 ± 8.8
HbA_{1c} (%)	8.4 ± 1.6	8.6 ± 1.7	8.4 ± 1.7
Oral agents			
1 oral agent	2647 (40.7)	508 (45.0)	3155 (41.3)
2 oral agents	1482 (22.8)	359 (31.8)	1841 (24.1)
3+ oral agents	346 (5.3)	68 (6.0)	414 (5.4)
GLP-1 RA treatment	521 (8.0)	78 (6.9)	599 (7.8)
Insulin naïve	950 (14.6)	236 (20.9)	1186 (15.5)
Insulin treated			
Premix	639 (9.8)	97 (8.6)	736 (9.6)
Short acting	2510 (38.6)	297 (26.3)	2807 (36.8)
Intermediate acting*	917 (14.1)	196 (17.3)	1113 (14.6)
Long acting	3996 (61.4)	598 (52.9)	4594 (60.2)
eGFR (mL/[min SSA])	66.3 ± 21.8	76.4 ± 16.6	67.8 ± 21.4
Total cholesterol (mg/dL)	164.1 ± 47.3	170.4 ± 43.1	165.0 ± 46.7
LDL (mg/dL)	84.5 ± 36.7	90.6 ± 35.2	85.4 ± 36.5
HDL (mg/dL)	43.9 ± 12.7	47.4 ± 13.4	44.4 ± 12.9
Triglycerides (mg/dL)	187.2 ± 160.4	166.1 ± 102.4	184.1 ± 153.4
Medications			
Aspirin	4229 (65.0)	535 (47.3)	4764 (62.4)
Other anti-platelet medications	1577 (24.2)	22 (1.9)	1599 (20.9)
Statins	5240 (80.5)	732 (64.7)	5972 (78.2)
Other lipid medications	277 (4.3)	71 (6.3)	348 (4.6)
Any HTN medication	6168 (94.8)	1005 (88.9)	7173 (93.9)
β-blockers	4016 (61.7)	354 (31.3)	4370 (57.2)
Calcium channel blockers	2093 (32.2)	367 (32.4)	2460 (32.2)
Renin system blockers	5118 (78.7)	900 (79.6)	6018 (78.8)

Data listed are number (proportion [percentage]) or mean (SD)
Hyperlipidemia was defined as those patients on lipid-modifying agents.
BMI, body mass index; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *eGFR*, estimated glomerular filtration rate; *GLP-1 RA*, glucagon-like peptide-1 receptor agonist; *HDL*, high-density lipoprotein; *HTN*, hypertension; *LDL*, low-density lipoprotein; *NPH*, neutral protamine Hagedorn; *SD*, standard deviation; *SSA*, square surface area.
* Intermediate-acting insulin cover human insulin, NPH, and unknown types of insulin. A treatment in the insulin category is included if the patient has initiated the treatment before randomization.

age criteria (25%), being unable to adhere to trial visits and schedules (17%), and current or past malignant neoplasms (14%). The baseline demographics are shown in Table II. The majority of patients were male (64.2%) and Caucasian (76.3%). The mean (SD) age was 65.0 (± 7.4) years with a mean duration of diabetes of 16.0 (±8.8) years. The mean body mass index was 33.6 (±6.9) kg/m^2 and 82.8% had hyperlipidemia (those patients on lipid-modifying agents). The mean HbA_{1c} was 8.4% (± 1.7) at baseline and 41.3% of patients were on oral monotherapy, 24.1% were receiving oral dual therapy, and 5.4% were receiving oral triple therapy, whereas only 15.5% were insulin naïve. In terms of CVD, 34.1% had a history of myocardial infarction, 16.2% had a prior stroke or TIA, while 12.4% had chronic heart failure (NYHA class II-III). In addition, 31.2% of the total population had

moderate CKD at baseline. Aspirin was used by 62.4% of patients, 78.2% received lipid-lowering therapy, and 93.9% were treated with antihypertensive agents. The trial is expected to be completed in Q4 of 2016 and results will be communicated thereafter.

Discussion

Diabetes affects approximately 1 in 11 adults or 415 million people worldwide.[7] Approximately 90% of individuals with diabetes have T2D, which is associated with a heightened risk of cardiovascular complications and decreased lifespan.[8]

T2D is a progressive disorder characterized by a combination of insulin resistance and diminished insulin secretion as well as other metabolic abnormalities. Glycemic control is often suboptimal and many patients ultimately require treatment with insulin to achieve optimal glycemic control. The addition of basal insulin therapy is widely regarded as appropriate for many patients, whether early or late in the course of the disease. Given that β-cell function declines as T2D duration progresses, basal insulin may not be adequate to control the rise in glucose after meals, so the need for a basal-bolus strategy may be required. Administration of a basal insulin with a more stable kinetic profile would allow a patient to safely target a fasting glucose level by providing consistent glucose-lowering over a 24-hour period with a flat pharmacokinetic profile, and decreasing the likely occurrence of hypoglycemia.

Insulin degludec was engineered to achieve improved pharmacokinetic and pharmacodynamic properties such as a long duration of action and reduced intrapatient variability.[9,10] There is a single amino acid deletion of threonine at B30 and a dicarboxylic fatty acid addition to lysine at position B29. With subcutaneous injection, IDeg forms soluble, stable multihexamers. Bioactive IDeg monomers dissociate slowly from the subcutaneous space and diffuse into the circulation, yielding a duration of action of approximately 40 hours.[11] In several phase 3 clinical trials, IDeg was noninferior to insulin comparators in reducing HbA_{1c} in insulin-naïve T2D, insulin-treated T2D, and type 1 diabetes patients.[12-14] The observed reductions in HbA_{1c} range from 1.1% to 1.6% with IDeg and 1.2% to 1.4% reduction with the insulin comparator arm during the first 12 to 16 weeks. Glycemic control persisted through 52 weeks of follow-up, with an end-of-trial HbA_{1c} that approximated 7% in the T2D basal-only therapy trials.[15-18] A meta-analysis of the phase 3 trials demonstrated that treatment with IDeg is associated with a lower risk of hypoglycemia, particularly nocturnal confirmed hypoglycemia, compared with IGlar at a similar level of glycemic control. IGlar was selected as the comparator in DEVOTE as it is the most commonly prescribed insulin globally and its cardiovascular safety was established in the ORIGIN clinical trial.[19]

ORIGIN randomly assigned 12,537 people with impaired fasting glucose and impaired glucose tolerance or T2D to either IGlar or standard of care. The primary outcome included nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. At 7 years of follow-up, there was no difference in the frequency of the primary end point between the IGlar and standard-of-care cohorts (HR 1.02 [95% CI, 0.94-1.11]), nor were there any differences in the components of the composite between the 2 study groups. ORIGIN also demonstrated that the early use of basal insulin to normalize fasting plasma glucose was not associated with cancer, but was associated with a reduced frequency in the diagnosis of diabetes and an increased risk of both hypoglycemia and weight gain.

Conclusion

DEVOTE is a phase 3b, randomized, double-blind, active comparator-controlled clinical trial that aims to evaluate the cardiovascular safety of IDeg relative to IGlar in patients with T2D at a heightened risk of cardiovascular complications. It is expected that DEVOTE will provide conclusive data regarding the cardiovascular safety and efficacy of IDeg. Methodologically, it is the first double-blind, active-comparator, cardiovascular outcome trial of a specific antihyperglycemic therapy.

Author contributions

All authors confirm that they meet the International Committee of Medical Journal Editors uniform requirements for authorship. All authors contributed to drafting/critically revising the article, approval of the final manuscript and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication.

Conflicts of interest for authors

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