

Cardiovascular safety and lower severe hypoglycemia of insulin degludec versus insulin glargine U100 in patients with type 2 diabetes aged 65 years or older: Results from DEVOTE (DEVOTE 7)

BACKGROUND:

- As the incidence of diabetes continues to rise and patients living with diabetes are living longer, global burden of type 2 diabetes aged 65 years or older is projected to increase during the next few decades.
- Management of diabetes in patients aged 65 years or older has unique challenges such as drug metabolism, kidney and liver function, multiple co-morbidities, and adverse effects.
- Cardiovascular disease is the leading cause of mortality in this patient population and common among older individuals.

OBJECTIVE:

- To describe the risks of cardiovascular (CV) events and severe hypoglycemia with insulin degludec vs. insulin glargine 100 units/mL in patients with type 2 diabetes aged 65 years or older.

METHODS:

- **Study design:** multi-center, treat-to-target, randomized, double blind active-comparator trial; Designed to continue until 633 primary outcome events were confirmed.
- **Inclusion criteria:** Type 2 diabetes- ≥ 50 years with predefined previous cardiovascular disease or renal disease such as chronic kidney disease OR ≥ 60 with predefined cardiovascular risk factors (HbA1c $\geq 7\%$ or current insulin treatment at least 20 U of basal insulin per day); one or more antidiabetic agents.
- **Exclusion criteria:**
 - An acute coronary or cerebrovascular event in the previous 60 days
 - Planned coronary, carotid, or peripheral artery revascularization;
 - Chronic heart failure NYHA class IV-current or past (within 5 years)
 - Malignant neoplasms (except basal cell and squamous cell carcinoma),
 - End stage liver disease
 - Known or suspected hypersensitivity to trial products
 - Female of child-bearing age
 - Participation in another trial
 - Receipt of an investigational product within 1 year before randomization
- **Primary outcome measure:** time from randomization to first occurrence of a three-component major adverse cardiovascular event (MACE)
- **Secondary outcome measure:** the number of event adjudicated committee (EAC) confirmed events of severe hypoglycemia episodes.
- **DEVOTE trial: 7637 patients were enrolled**
 - Randomized 1:1 ratio
 - Patients would receive either degludec or glargine with each drug added to standard of care.
- Secondary analysis with DEVOTE trial: patients divided into three groups
 - 50-64 years (n=3682)
 - 65-74 years (n=3136)
 - ≥ 75 years (n=819)

RESULTS:

- **DEVOTE trial:**
 - The primary outcome occurred in 325 (8.5%) patients in the degludec group and 356 (9.3%) patients in the glargine group (HR 0.91; 95% CI 0.78-1.06; P<0.001).
 - A 91% power was estimated for 7500 patients followed-up with 633 events.
 - A total of 752 severe hypoglycemia events occurred: 280 events in 187 patients in the degludec group and 472 events in 353 patients in the glargine group.
 - In this trial, degludec was found to be similar to glargine in terms of cardiovascular events, but superior with regards to hypoglycemia risk. Degludec had a lower rate of both severe and nocturnal severe hypoglycemia.
- **Secondary analysis:**
 - Higher risks of MACE and non-fatal stroke across the age groups and a higher risk of CV death in the ≥75 year age group were non-significant (shown in Figure 1).
 - There was a significant lower risk of severe hypoglycemia with degludec vs. glargine in both the 50-64 and 65-74 year age group.
 - Risk of MACE after a severe hypoglycemic event in the two older groups was higher compared to before an event; significant in the 65-74 year age group (HR 1.69; CI 95% 1.03-2.77).

STRENGTHS:

- Double-blinded design
- Large enrollment of patients with a high CV risk
- High retention rate of patients in DEVOTE trial

LIMITATIONS:

- ≥75 year age group smaller than other age groups
- Reporting of hypoglycemic events in patients living alone due to this patient population may not recognize the signs and symptoms of hypoglycemia.
- Duration of the study (2 years).
- Concomitant at home antidiabetic medication dosages not reported.

CONCLUSION:

- This study demonstrated no difference in CV events between degludec versus glargine in patients with T2DM observed in the results of the DEVOTE trial up until age 74.
- The risk of severe hypoglycemia is lower with degludec compared with glargine.
- Future research: A trial should be done with a larger sample size in the ≥75 years age group in order to determine age outcomes on individuals.

REFERENCE:

Pratley, RE., Emerson, SS., Franek, E., Gilbert, MP., Marson, SP., McGuire, DK. et al. Cardiovascular safety and lower severe hypoglycemia of insulin degludec versus insulin glargine U100 in patients with type 2 diabetes aged 65 years or older: Results from DEVOTE (DEVOTE 7). *Diabetes Obes Metab.* Jul 2019;21(7):1625-1633.

Jessica Booth, PharmD Candidate