Dulaglutide and type 2 diabetes

No reduction in all-cause mortality or cardiovascular mortality

● In a randomised, placebo-controlled trial including about 10 000 patients with type 2 diabetes and a mean HbA1c of 7.3% at enrolment, addition of *dulaglutide* to their usual hypoglycaemic therapy did not reduce all-cause or cardiovascular mortality after a follow-up of about 5 years. Acute pancreatitis, pancreatic cancer and thyroid cancer were more frequent in the *dulaglutide* group.

In patients with type 2 diabetes, when the glycated haemoglobin (HbA1c) level remains too high despite *metformin* monotherapy, addition of a GLP-1 (glucagon-like peptide-1) receptor agonist, such as *liraglutide*, by subcutaneous injection, is an alternative to insulin, particularly when avoiding weight gain or hypoglycaemia is a priority (1,2). In placebo-controlled trials in patients at high cardiovascular risk with a mean HbA1c of 8.7% at enrolment, *liraglutide* reduced cardiovascular mortality, and *semaglutide* (another GLP-1 receptor agonist) appeared to reduce the risk of cardiovascular complications. However, for different reasons, these data constitute low-level evidence (3,4).

In 2016, the evaluation data that were available for *dulaglutide* (another GLP-1 receptor agonist) when marketing authorisation was granted, did not show any clinical benefit regarding complications of diabetes compared to other GLP-1 agonists (5). The evaluation was inadequate to establish potential cardiovascular risks, although an increased occurrence of sinus tachycardia and conduction disorders was observed (5).

The results of the Rewind trial were published in 2019. This trial compared the incidence of cardiovascular events after addition of *dulaglutide* or placebo to existing hypoglycaemic therapy (6). *Dulaglutide* was used at a dose of 1.5 mg per week. This randomised double-blind trial included 9901 patients with type 2 diabetes whose mean age was 66 years. Nearly one-third of them had had a previous cardiovascular event. At enrolment, the mean HbA1c level was 7.3%. About one-quarter of patients were receiving insulin, either alone or in combination with an oral glucose-lowering drug (6).

The primary outcome measure was the first occurrence of death from cardiovascular causes, or non-fatal myocardial infarction, or non-fatal stroke (**a**)(6).

After a median follow-up of 5.4 years, at least one event in the primary outcome occurred in 12% of patients in the *dulaglutide* group versus 13.4% of patients in the placebo group (p=0.026) (6). Among these components of the composite outcome, the only statistically significant reduction observed in the *dulaglutide* group was the incidence of non-fatal stroke: 2.7% versus 3.5% in the placebo group (p=0.017). All-cause mortality was similar in the two groups, about 11%, as was cardiovascular mortality, about 7% (6).

The adverse effects of GLP-1 receptor agonists such as *dulaglutide* are gastrointestinal disorders, particularly nausea and vomiting, excessive weight loss with a risk of gallstones, renal failure, pancreatitis, pancreatic cancer and thyroid cancer (2). In the Rewind trial, treatment discontinuation following an adverse event was more frequent in the *dulaglutide* group: 9.1% versus 6.3% in the placebo group (6). There was in increase in gastrointestinal disorders in the *dulaglutide* group compared to the placebo group: 47% versus 34%; supraventricular tachycardia or cardiac conduction disorders: 4.4% versus 3.9%; and gallstones: 2.8% versus 2.4% (6). Among the 4949 patients in the *dulaglutide* group, 23 patients developed acute pancreatitis, versus 13 out of 4952 patients in the placebo group; 19 patients developed pancreatic cancer, versus 12 in the placebo group; and 7 developed thyroid cancer versus 3 in the placebo group (6).

In practice In patients with type 2 diabetes who had a modest elevation of HbA1c, addition of *dulaglutide* to hypoglycaemic therapy slightly reduced the risk of stroke (2.7% versus 3.5% after about 5 years of treatment), but did not reduce either all-cause mortality or cardiovascular mortality. The increased risk of acute pancreatitis and pancreatic or thyroid cancer must be taken into account, as with any GLP-1 receptor agonist. The value of adding a GLP-1 receptor agonist to hypoglycaemic therapy has not been demonstrated in patients whose HbA1c is lower than 8.5%.

▶ Translated from *Rev Prescrire* **March 2020**
Volume 40 N° 437 • Pages 210-211

***a-** According to the trial protocol, deaths of unknown cause were considered as deaths from cardiovascular causes (ref 6).*

Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Glucose-lowering treatment of type 2 diabetes. Part II - Glucose-lowering options after metformin: a difficult choice based largely on adverse effects" *Prescrire Int* 2015; **24** (160): 130-135.

2- Prescrire Rédaction "Incrétinomimétiques agonistes GLP-1 : exénatide, liraglutide, etc." Interactions Médicamenteuses Prescrire 2020.

3- Prescrire Editorial Staff "Diabetes and liraglutide. Very tenuous results from the Leader trial" *Prescrire Int* 2017; **26** (186): 246-247.

4- Prescrire Rédaction "sémaglutide (Ozempic®) et diabète de type 2. Un autre agoniste du GLP-1 en injection hebdomadaire, sans plus" *Rev Prescrire* 2020; **40** (435): 7-9.

5- Prescrire Editorial Staff "Dulaglutide weekly in type 2 diabetes. Cardiovascular reactions should be better documented" *Prescrire Int* 2016; **25** (175): 236-237.

6- Gerstein HC et al. "Dulaglutide and cardiovascular outcomes in type 2 diabetes (Rewind): a double-blind, randomised placebo-controlled trial" *Lancet* 2019; **394**: 121-130 + annex: 320 pages.