Type 2 diabetes

Cardiovascular assessment of dapagliflozin: no advance

● **A randomised, double-blind trial of *dapagliflozin* versus placebo included more than 17 000 patients with type 2 diabetes, half of whom were followed for at least 4 years. In this trial, *dapagliflozin* did not reduce the rate of cardiovascular complications of diabetes, or death.**

Gliflozins, such as *empagliflozin* and *dapagliflozin* (hypoglycaemic drugs), carry a risk of serious adverse effects, including amputations and ketoacidosis, whereas their potential preventive action on the complications of diabetes is very uncertain. In one trial, *empagliflozin* appeared to reduce mortality by preventing cardiovascular disorders other than those due to diabetes, such as heart failure, in patients with a history of cardiovascular events, perhaps through its diuretic action (1-4).

In early 2019, the results of a very large randomised, double-blind trial were published. The trial compared the effect of *dapagliflozin* versus placebo on cardiovascular outcomes in 17 160 patients with type 2 diabetes (1,5).

No reduction in the cardiovascular complications of diabetes compared to placebo. In this trial, all patients included were considered to be at increased risk of a cardiovascular event, either because of a history of cardiovascular event or peripheral artery disease (about 40% of patients), or because they were at least 55 years of age and had at least one cardiovascular risk factor in addition to diabetes (hypercholesterolaemia, hypertension, smoking). The mean glycated haemoglobin (HbA1c) level at baseline was 8.3% (5). Patients continued to receive other hypoglycaemic and cardiovascular drugs, as well as *dapagliflozin* or placebo.

After a median follow-up of 4.2 years, there was no difference between the groups as regards the rate of death from any cause (about 6.5%), cardiovascular death (2.9%), or the incidence of a composite outcome combining the occurrence of at least one of the following events: myocardial infarction, stroke or cardiovascular death (9%) (5).

Another outcome measure combined hospitalisation for heart failure and cardiovascular death. At least one of these two events occurred in 4.9% of patients in the *dapagliflozin* group compared to 5.8% of those in the placebo group (p=0.005). The observed difference was due solely to a lower rate of hospitalisation for heart failure in the *dapagliflozin* group: 2.5% versus 3.3% in the placebo group (5).

Another composite outcome measure was the occurrence of various renal events (decrease in glomerular filtration rate, new end-stage renal disease, or death from renal or cardiovascular causes). At least one of these events was reported in 4.3% of patients in the *dapagliflozin* group versus 5.6% of those in the placebo group (a statistically significant difference). This composite was a secondary outcome measure which only allows the hypothesis to be generated that *dapagliflozin* may reduce renal risk, but does not demonstrate it (5).

Adverse effects: ketoacidosis, genital infections, etc. The incidence of serious adverse effects was about 35% in both groups. About 8% of patients in the *dapagliflozin* group stopped treatment due to an adverse event, compared to about 7% in the placebo group (p=0.01). Ketoacidosis was slightly more frequent in the *dapagliflozin* group than in the placebo group (0.3% versus 0.1%), as were genital infections (0.9% versus 0.1%), myocardial infarction (2.7% versus 2.3%) and hypotension (0.3% versus 0.1%) (5).

In practice A randomised trial of *dapagliflozin* versus placebo including several thousand patients with type 2 diabetes did not show any reduction in the cardiovascular complications of diabetes. Given the risk of serious adverse effects with gliflozins, as of 2019, the harm-benefit balance of *dapagliflozin* is unfavourable.

▶ Translated from *Rev Prescrire* **October 2019**
Volume 39 N° 432 • Page 769

Literature search up to 16 July 2019

1- Prescrire Editorial Staff "Dapagliflozin. A hypoglycaemic drug causing disproportionate harm, especially to kidneys" *Prescrire Int* 2014; **23** (147): 61-64.
2- Prescrire Editorial Staff "Empagliflozin. Type 2 diabetes: no rush to use this drug" *Prescrire Int* 2016; **25** (172): 145-148.
3- Prescrire Editorial Staff "Type 2 diabetes. Canagliflozin: minimal cardiovascular benefit and an increase in amputations and ketoacidosis" *Prescrire Int* 2018; **27** (196): 219-220.
4- Prescrire Rédaction "Gliflozines (anti-SGLT2)" Interactions Médicamenteuses Prescrire 2019.
5- Wiviott SD et al. "Dapagliflozin and cardiovascular outcomes in type 2 diabetes" *N Engl J Med* 2019; **380** (4): 347-357 + annexes: 55 pages.