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.