Sitagliptin and its long-term effects: not inferior to placebo

Almost ten years after the introduction of sitagliptin on the Dutch market, a manufacturer-sponsored study has been published on its long-term effects. The study had a median follow-up period of 3 years, which is longer than previous studies, but still relatively short for a drug that, in principle, needs to be used for life. The study found no significant differences between the two study groups as regards the primary and secondary outcome measures (apart from a slight decrease in estimated glomerular filtration rate). In other words, sitagliptin is not inferior to placebo. Among the individual components of the composite outcome measure, cardiovascular mortality was higher in the sitagliptin group (311 patients, 4.2%) than in the placebo group (291 patients, 4.0%), although the incidence of non-fatal myocardial infarction and non-fatal stroke, the other components of the composite outcome measure, was actually lower in the sitagliptin group. The use of composite outcome measures has its disadvantages, especially if the individual outcomes are not of equal importance, as is the case here with mortality, stroke and myocardial infarction.

Several previous studies have found an association between DPP-4 inhibitors and heart failure. The authors of the study described here are unable to adequately explain why they did not find such an association. There have also been studies which found an association between sitagliptin and acute pancreatitis. The study discussed here found an absolute but non-significant difference between the two groups, with almost twice as many cases in the sitagliptin group. Since acute pancreatitis is a very serious disorder, it remains important to be aware of this. DPP-4 inhibitors belong to a group of oral blood glucose lowering drugs whose long-term efficacy in preventing cardiovascular disorders among patients with diabetes mellitus has not been proven. All that has been proven is its efficacy in lowering blood glucose levels (an effect which was small in the present study) and there may be many (and sometimes serious) side-effects. In view of the doubts about the cardiovascular safety of this group of drugs, the registration authority has demanded additional research. The analysis with composite endpoints in the study discussed here, the first long-term study into the effects of sitagliptin on hard cardiovascular endpoints, found that the drug is non-inferior to placebo. However, the registration authorities should not accept safety assessment by means of a non-inferiority study, a type of research that assesses whether a particular drug is not inferior to an existing one. Since the existing drug in this case is a placebo, the conclusion is that sitagliptin is not inferior to placebo in terms of cardiovascular safety. The safety of sitagliptin ought to be examined in a superiority study, comparing it with the current standard of treatment. The manufacturer is already using the study discussed here in its advertising campaign, without stating that it is ‘not inferior to placebo’. Sitagliptin does not help to prevent macrovascular complications among patients with diabetes mellitus. The microvascular complications have not been studied, and the drug has no proven added value. Hence, out conclusion is that sitagliptin has no place in the treatment of type 2 diabetes mellitus. The drug is reimbursed by Dutch insurance companies, subject to certain conditions.

References*


*The literature refers to the Dutch text*