Medical Xpress

Benefit of glinides is not proven

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The benefit of glinides in the treatment of type 2 diabetes is not scientifically proven. Nor do they perform better than other antidiabetics available in tablet form, such as metformin and sulfonylureas. As a result, there is also no proof of additional benefit. Although repaglinide has been approved for 10 years and nateglinide for 8 years in Germany, there have been no relevant trials to date of longer duration than 14 months. This is the conclusion of a report by the German Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, which was published in June 2009 and for which an English-language summary is now available.

Therapy option for patients with diabetes mellitus type 2

Usually, treatment for diabetes mellitus type 2, formerly known as adult-onset diabetes, starts with non-drug therapies, such as dietary changes, weight loss and physical exercise. If this does not reduce glucose levels sufficiently, then drugs can be used as well.

In addition to insulin, these include the oral antidiabetics (OAD). Besides glinides, this group also contains sulfonylureas, metformin and glitazones, for example. The individual substances, however, differ in their mechanism of action. Glinides stimulate the production of insulin in the pancreas. A particular feature of glinides is their rapid effect: if taken before meals, glinides lower glucose levels comparatively rapidly after eating.

At present, two substances from the drug class of glinides are approved in Germany and are thus the subject of this IQWiG investigation: repaglinide (NovoNorm® from NovoNordisk) and nateglinide (Starlix® from Novartis). There is, however, a slight difference in the approval of the two substances: while repaglinide is approved both as a monotherapy and as a therapy in combination with metformin, here in Germany nateglinide may only be prescribed in combination with metformin.

No long-term trials available

The purpose of the investigation commissioned by the Federal Joint Committee (G-BA) was to assess the benefit of long-term use of glinides. IQWiG and its external experts identified a total of 10 relevant trials, 8 of them on repaglinide and 2 on nateglinide. Trials with a minimum treatment duration of 24 weeks were included. With this observation period, it is assumed that the patients are well-adjusted to the new drug.

None of the included trials lasted longer than 14 months. There were therefore no long-term trials on either repaglinide or nateglinide that were designed to investigate late complications of diabetes. This is surprising, particularly as both substances have been approved for over 8 years. Thus, the authors of the final report have come to the conclusion that, owing to a lack of trials, a benefit from glinides is not proven. It is suggested that research is needed and further trials are called for that investigate the long-term use of glinides.

No conclusions possible on important patient-relevant outcomes

Important questions remained unanswered even in the analysis of the available trials. This was particularly due to the fact that many of the

outcomes established in the Institute's report plan, such as avoiding late complications, health-related quality of life and patient satisfaction, were not investigated at all in the available trials.

The data on the investigated outcomes, moreover, did not permit a definite conclusion on whether patients profit from treatment with glinides. This was because some of the data were not presented with sufficient transparency or because the trials were susceptible to bias.

Thus, according to the conclusion drawn by IQWiG and its external experts, there is no proof of either benefit or additional benefit compared to other drug therapy options.

Comparison with other therapies was only partially possible

For the majority of therapy alternatives, no relevant trials were identified that compared other drugs with glinides. In particular, there is a lack of comparator trials with newer glucose-lowering agents such as, for example, exenatides or gliptins. No trials were found even for well-established antidiabetics such as insulin or glitazones. It was only possible to compare glinides with metformin and sulfonylureas.

Neither benefit nor harm could be determined in the case of cardiovascular events

Treatment with oral antidiabetics is currently being discussed among experts, particularly with reference to the possible occurrence of cardiovascular events, such as heart attacks. The authors of the report therefore also analysed the existing trials on glinides with reference to the occurrence of cardiovascular events. However, none of the trials were designed to investigate a benefit or harm from glinides for this

outcome. The only data on cardiovascular events appeared in analyses on adverse events. The low number of cases, however, do not permit any clear conclusion to be drawn concerning a benefit or harm from glinides with reference to cardiovascular events. Thus, for this aspect too, which is relevant in the selection of an antidiabetic, there is a lack of data. In this respect as well, IQWiG and its external experts see an urgent need for further research.

Source: Institute for Quality and Efficiency in Health Care