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Adding Dapagliflozin to Usual Diabetes Drugs May Improve Control

REUTERS HEALTH INFORMATION

By Lorraine L. Janeczko | April 24, 2014

NEW YORK (Reuters Health) - Adding dapagliflozin to conventional drugs for type 2 diabetes may improve glycemic control without significant weight gain, especially when glycemic control has been inadequate, according to a new meta-analysis.

Add-on dapagliflozin improved glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels, accompanied by good weight control, the authors reported online April 7 in BMJ Open.

"This study is the first meta-analysis to focus on the efficacy and weight gain issue of dapagliflozin versus placebo in synergy with antidiabetic drugs (not only metformin)," they wrote.

RCTs "are often discrepant in results," said principal investigator Dr. Siu-wai Leung of the University of Macau in China, and of the School of Informatics of the University of Edinburgh in Scotland, in an email to Reuters Health. "The consistency found in this study strengthens our confidence in the available medical evidence."

Dr. Leung added, "The findings surprised us because dapagliflozin was not so effective when used alone to treat type 2 diabetes mellitus (T2DM) and because all the eligible RCTs were sponsored by pharmaceutical companies."

"While the randomized controlled trials (RCTs) looked all right, their results and conclusions should be interpreted carefully for potential competing interest," Dr. Leung cautions.

The authors reviewed RCTs involving adults with T2DM who received dapagliflozin plus conventional antidiabetic drugs and were followed for at least eight weeks. Control groups had to take a combination of placebo plus conventional drugs (not just placebo); trial outcomes had to include HbA1c, FPG and body weight.

Of the 380 RCTs they considered, they found 12 eligible studies involving close to 4,000 patients. They analyzed the results with a random effects model, using meta-regression on the follow-up durations to determine dapagliflozin's long-term (>24 weeks) effects on controlling fasting plasma glucose and body weight. They excluded low-quality studies and those with interim stages from sensitivity analysis. Follow-ups ranged from 12 to 104 weeks.

The overall effect size of HbA1c (i.e., the adjusted mean difference) was 0.52% ($Z= 13.56$, $p<0.001$). The effect size of FPG was 1.13 mmol/L ($Z= 11.12$, $p<0.001$). The effect size of body weight was 2.10 kg ($Z= 18.77$, $p<0.001$).

Excluding low-quality and interim RCTs changed the overall mean differences to 0.56%, 1.11 mmol/L, 2.23 kg and 0.50%, 1.08 mmol/L, 2.08 kg, respectively. The sensitivity analysis, evaluating differences between overall results and results from the studies with low risk of bias, showed robustness of the meta-analysis on HbA1c, FPG and body weight.

Dr. Lawrence Phillips of Emory University School of Medicine in Atlanta, Georgia, told Reuters Health in a phone interview, "This is a well-done meta-analysis that tells us that, in general, these drugs, when given to people at various stages in their natural history as judged by using different kinds of drugs, are beneficial to lower glucose levels."

As to whether industry-funded trials are less reliable than independent trials, Dr. Phillips, who was not involved in the study, pointed out another issue. "It's not so much whether it's done by industry or not, because we've gotten better at requiring universal reporting and quality of design," he said.

"The problem is that sometimes in industry-supported trials, patients are paid to take part. In some countries, paying

people to take part can be a big deal, so patients are very reluctant to drop out because of side effects that might be a problem in other circumstances," he said.

"These are very good drugs that are generally well tolerated. Patients often lose a bit of weight when taking them. Their major side effects are yeast infections in women and, much less frequently, fungus genital infections in men," he said.

"This new class of drugs works in almost every setting of diabetes. And that's different from some other diabetes drugs," he said. "This works early in the natural history, it works late in natural history, and it works when people are taking any of the different diabetes pills or insulin," he added.

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