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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Pancreatitis Risk: Sitagliptin Risk Negligible in Study but Not for DPP-4i Class Drugs in a Meta-analysis

Sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i) that is now widely used as an oral antihyperglycemia drug, may not be significantly associated with increased risk of pancreatitis or pancreatic cancer. The conclusion follows an assessment of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial cohort outcomes with the suggestion that it should start to provide some clarity for prescribers and patients on the pancreatic safety of the drug. A number of previous reports have suggested an increase in risk of pancreatitis associated with using sitagliptin, although the association has been somewhat controversial. According to the analysis by Buse et al. (**p. 164**), the study focused on suspected cases of acute pancreatitis and pancreatic cancer that occurred in the 14,671 participants in the cohort over a follow-up time of three years. For both pancreatitis and pancreatic cancer, rates were low (<0.3% in all groups) and differences in both cases between treatment and placebo were considered not statistically significant. To then benchmark the outcomes, the authors performed a meta-analysis with two other recently reported safety trials on two similar DPP-4i drugs. In the case of pancreatitis, there was a statistically significant increase in risk associated with their use. Meanwhile, there was no reported effect for pancreatic cancer. The researchers state that overall rates of pancreatic disease in the trial were low and that this might limit the strength of the conclusions. However, the fact that three trials have now reported a small increase in risk associated with DPP-4i class drugs suggests that longer-term pharmacovigilance is still needed. Commenting more widely on the study, John B. Buse said: "Pancreatitis and pancreatic cancer were uncommon events in the TECOS trial and in the other cardiovascular outcomes trials of DPP-4 inhibitors. In the meta-analysis, the slight increase in pancreatitis is balanced by lower incidence of pancreatic cancer, providing reassurance of the pancreatic safety of this widely used, efficacious, and well-tolerated class of antihyperglycemic agents."

Buse et al. Pancreatic safety of sitagliptin in the TECOS study. Diabetes Care 2017;40:164–170

Hypoglycemia Hospitalization and Type 1 Diabetes in Denmark: Low Rates and Reductions in Incidence but Caution Needed

A longitudinal study in Denmark suggests that between 2006 and 2012 there was a steady decline in the already low rates of hypoglycemia in patients with type 1 diabetes. The study by Ishtiak-Ahmed et al. (**p. 226**) used data from the Danish Adult Diabetes Database (DADD), which took into account the records from 17,230 patients. According to the authors, there were 2,369 hypoglycemia events requiring hospitalization among 1,735 patients over a cumulative of ~70,000 patient-years. The crude incidence of hypoglycemia was 3.38 per 100 patient-years, but there was a steady linear decline in hypoglycemia over the period of 8.4% with incidence rates dropping from 5.1 to 2.8 per 100 patient-years over the study period. Due to the design of the study, it was also possible for the authors to examine potential predictors of hospitalization for hypoglycemia. In this case, previous occurrence of hypoglycemia, HbA1c, albuminuria, age, and diabetes duration were all risk factors for hypoglycemia events. The authors go on to discuss many reasons why these particular characteristics would predict incident hypoglycemia. While acknowledging some weaknesses in the study, they conclude that on the one hand it is encouraging that rates seem to be low and falling. However, they caution that with increasing rates of type 1 diabetes and falling mortality, the absolute rate of hypoglycemia will probably rise in the coming decades simply due to the larger number of people living with long-standing type 1 diabetes. According to author Marit E. Jørgensen: "The clear decline in hypoglycemia hospitalization is probably a consequence of a number of interventions, including the widespread use of analog insulins, pump therapy, and continuous glucose monitoring. In particular, it is satisfactory that this decline in hypoglycemia hospitalization actually happens parallel to a decline in mortality and morbidity in type 1 diabetes, while improvements—especially in glycemic control—could have been accompanied by an increase in rates of severe hypoglycemia."

Ishtiak-Ahmed et al. Incidence trends and predictors of hospitalization for hypoglycemia in 17,230 adult patients with type 1 diabetes: a Danish register linkage cohort study. Diabetes Care 2017;40:226–232

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Risk of Thromboembolism Due to Hormonal Contraceptives Is Low in Women With Diabetes

A study on thromboembolism and hormonal contraception use in women with either type 1 or type 2 diabetes suggests risk of thromboembolic events is low. According to O'Brien et al. (**p. 233**), the study was based on data from an administrative health claims database that contains millions of coded medical records, pharmacy claims data, laboratory data, and other relevant information from ~15 million U.S. individuals. After applying filters to identify women of reproductive age with a diagnosis of diabetes and evidence of diabetic medication or device use, the authors then examined the rate of contraceptive use and subsequently any thromboembolic events (e.g., myocardial infarction, stroke, venous thrombosis). The authors report that they identified just over 146,000 women with diabetes, and the women experienced 3,012 thromboembolic events. Approximately 72% of the population had no claims for any form of hormonal contraception. Of the 28% that did have such a claim, the majority received estrogen-containing oral contraceptives. Rates of thromboembolism remained below 17 events per 1,000 woman-years independent of the contraceptive used—a low rate according to the authors. However, rates according to type of contraception used did vary, with the contraceptive patch having the highest rates of thromboembolism and intrauterine/subdermal contraceptives recording the lowest rates. Other contraceptives identified included the vaginal ring and either oral estrogen or progestin or both. Overall, the authors state that risk of thromboembolism due to hormonal contraceptives is low but that choices are available to contain that risk even further. Author Sarah H. O'Brien told *Diabetes Care*: "Published studies have demonstrated that women with diabetes are less likely than their healthy peers to receive contraception counseling or to use hormonal contraception, when in fact it is even more important for women with diabetes to receive effective contraception so they can safely plan their pregnancies. We hope our study provides reassurance to prescribers and increases contraception counseling in this patient population."

O'Brien et al. Hormonal contraception and risk of thromboembolism in women with diabetes. Diabetes Care 2017;40:233–238

A Biomarker for Metformin: Growth Differentiation Factor 15

Gerstein et al. (**p. 280**) report this month in *Diabetes Care* that a potential nonglycemic biomarker for metformin use may exist: growth differentiation factor 15 (GDF15). As a consequence of identifying the relationship, the authors suggest that it might provide important clues about the mechanism(s) of action and the effects of the drug. The study is based on an extensive analysis of stored blood samples that were obtained at baseline in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial. Approximately 8,500 participants of the original study population provided blood samples, which were then screened for potential biomarkers previously identified as being related to cardiovascular disease and diabetes. The outcome (previously reported) was the identification of 237 biomarkers in 8,401 individuals. Of these, 2,317 participants were receiving metformin at the time the blood was drawn. According to the authors, after adjustment (particularly for multiple testing), 26 biomarkers were independently associated with metformin use. Of these, GDF15 stood out as having a very strong relationship with metformin. Mean GDF15 rose with metformin dose and vice versa, and after accounting for factors linked to the propensity to prescribe metformin, the authors report that a 1 SD increase in GDF15 level predicted a 188 mg higher metformin dose. Subsequent genotyping in a subset of samples identified two single nucleotide polymorphisms that were independently associated with GDF15 levels. Whereas the relationship cannot truly be defined as causal and will require further research, it highlights uncertainty regarding metformin's mechanism of action and might provide a new tool to explore the role of metformin in diabetes and possibly in other diseases. Author Hertzel C. Gerstein said: "Metformin is the most commonly prescribed diabetes drug and is being widely studied for its effects on serious health outcomes. The identification of a novel biomarker for metformin and the link between this biomarker and cardiovascular outcomes may lead to important new insights into metformin's health benefits."

Gerstein et al. Growth differentiation factor 15 as a novel biomarker for metformin. Diabetes Care 2017;40:280–283

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