Dipeptidyl Peptidase 4 Inhibitors and Risk of Inflammatory Bowel Disease Among Patients With Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials

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A recent retrospective cohort study found that new use of dipeptidyl peptidase 4 inhibitors (DPP4i) of 1.6 years was associated with an increased risk of inflammatory bowel disease (IBD) compared with other antidiabetes medications (hazard ratio 1.75 (95% CI 1.22, 2.49) (1). We previously demonstrated a weak association in an analysis of 86 prevalent and incident cases of IBD among DPP4i users using the U.S. Food and Drug Administration's Adverse Event Reporting System (2). In contrast, a cohort study suggested DPP4i initiation reduces risk of autoimmune diseases including IBD (3). Because the link between DPP4i and IBD remains uncertain, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate this potential association among patients with type 2 diabetes (T2D).

This meta-analysis is registered with the international prospective register of systematic reviews (PROSPERO) (no. CRD42018095206). We systematically searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to 28 April 2018 to identify DPP4i trials in T2D patients that explicitly reported IBD events. The large-scale cardiovascular trial for linagliptin (CARMELINA trial [4]) was published 7 months after our search; we therefore included this study. Two reviewers independently performed study selection, data extraction, and quality assessment. The primary outcome was IBD, including both Crohn disease (CD) and ulcerative colitis (UC). IBD events were strictly identified using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA version 21.0). We examined a secondary end point that included unspecified colitis in addition to CD and UC cases. Quality assessment was assessed by the Cochrane risk of bias tool.

We estimated relative risk (RR) with 95% CI using random-effects models. Statistical heterogeneity between studies was measured using the I^2 statistic and Cochran Q test. We conducted sensitivity analyses using person-years as the denominator and number of events as the numerator to test the robustness of our primary analysis and calculated the number needed to harm for the primary outcome. All analyses were performed using Stata 14.

Of the 4,669 studies retrieved from the electronic databases, 13 eligible RCTs (8 placebo-controlled and 5 active-controlled) involving 54,719 patients and 39 events were identified. The mean age, diabetes duration, baseline HbA_{1c}, and follow-up were 60.9 years, 9.3 years, 7.8% (62 mmol/mol), and 1.5 years, respectively. The risk of bias for included trials was judged as high because IBD was not a predefined outcome.

Overall, IBD risk was similar between DPP4i users and control subjects (RR 1.01 [95% CI 0.30, 3.41]) (Fig. 1). DPP4i use may reduce CD risk (RR 0.75 [0.21, 2.66]) and increase UC risk (RR 2.98 [0.31, 28.60]). For the composite end point, the RR was 1.24 (0.65, 2.36). No evidence for statistical heterogeneity across studies was observed ($I^2 = 0.0\%$, $P > 0.05$). The sensitivity analysis was consistent with primary analysis. The number needed to harm for IBD was 21,868 over an average of 2.3 years.

To our knowledge, this is the first meta-analysis of RCTs to evaluate the risk of IBD with DPP4i use. We used rigorous inclusion criteria to minimize misclassification bias and observed no association between DPP4i and IBD. The absolute IBD risk in the included trials was low; 21,868 patients had to be treated with DPP4i, over 2.3 years, to lead to one additional case of IBD. In

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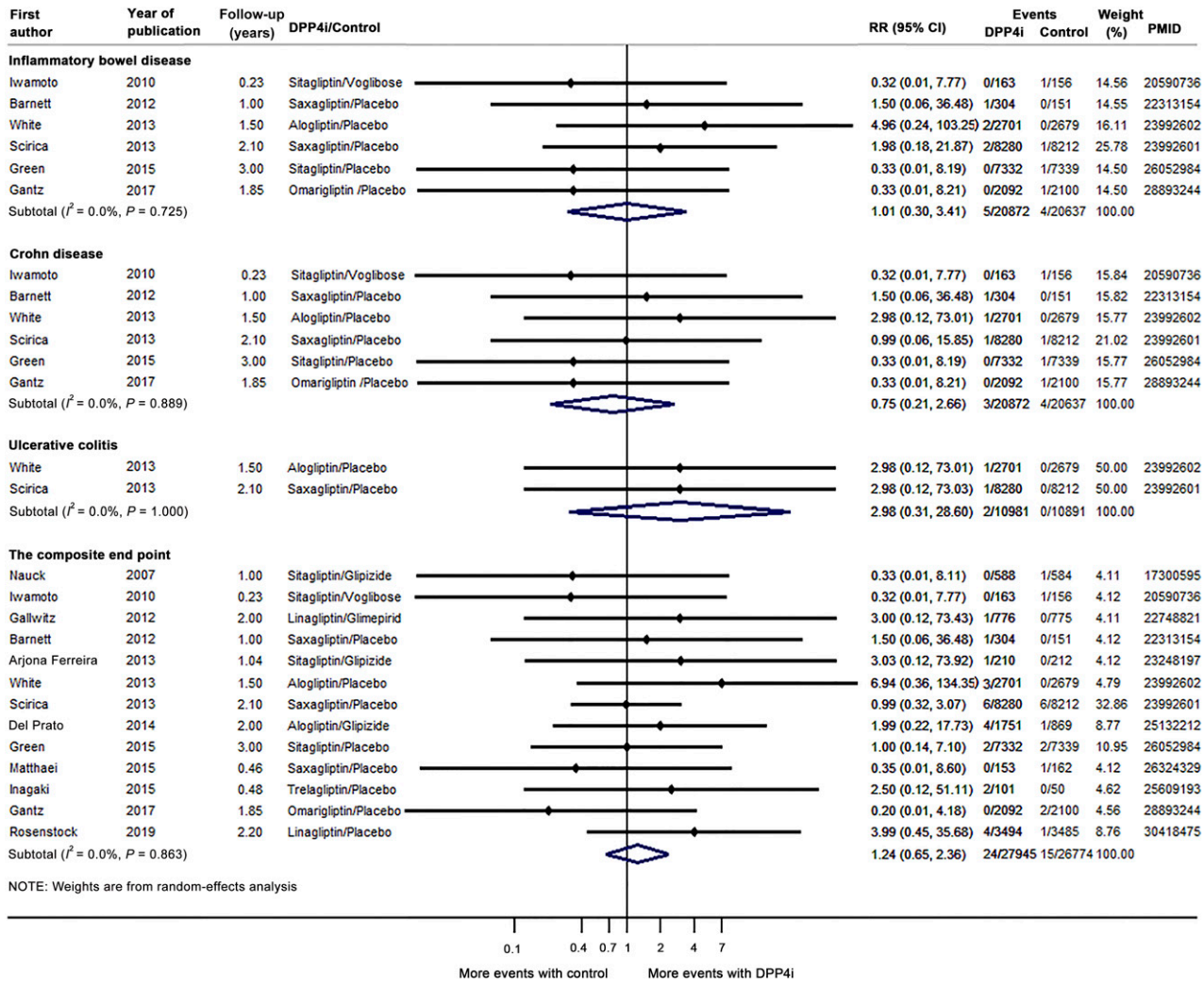

Figure 1—Results of the meta-analysis of DPP4i use on the risk of IBD. The results of the CARMELINA randomized clinical trial were published in November 2018 (4). We incorporated data from this large trial, and our final analysis included 13 studies (4,5,7–17).

contrast, only 12 T2D patients require treatment with DPP4i, over 2.1 years, for one patient to achieve the HbA_{1c} <7% (53 mmol/mol) goal (5); thus, the potential benefits of DPP4i treatment appear to outweigh any associated IBD risk. However, while we identified no significant association between DPP4i and IBD, we acknowledge that this analysis may have been underpowered to detect such an association due to the limited number of included trials and events and the statistical imprecision of our effect estimates.

Several experimental studies have shown that DPP4i may decrease IBD activity through inhibition of T-cell proliferation and cytokine production and decrease IBD severity through the restoration of gut mucosal damage (6). However, human studies have reported lower DPP4 concentrations in tissue and plasma from patients with IBD versus healthy subjects, suggesting that lower DPP4 concentrations may be associated with higher IBD activity (6). Hypothesized mechanisms for this link might relate to DPP4's immunoregulatory function, including signal transduction, chemotaxis, and T-cell activation (6). More work is needed to explore the association and possible mechanisms linking DPP4i and IBD.

In conclusion, our meta-analysis of 13 RCTs found no association between DPP4i use and IBD risk among T2D patients. However, given the relatively low number of trials and events as well as potential trial bias, we cannot definitively exclude the possibility of a weak association. Additional real-world studies are needed to investigate IBD risk among DPP4i users.

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G.L. and T.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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