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Meta-analysis of the association between new hypoglycemic agents and digestive diseases

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Abstract

Background: New hypoglycemic agents include sodium-glucose cotransporter-2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP1RAs), and dipeptidyl peptidase-4 inhibitors (DPP4is). The association between each class of these new hypoglycemic drugs and the risks of various digestive system diseases is unknown. We aimed to explore this relationship by performing a meta-analysis.

Methods: We included large randomized trials of SGLT2is, GLP1RAs, and DPP4is. Outcomes of interest were 91 kinds of digestive diseases including 75 kinds of gastrointestinal disorders and 16 kinds of hepatobiliary disorders. Meta-analysis was done to generate pooled risk ratio (RR) and 95% confidence interval (CI). Subgroup analysis was conducted according to 3 different drug classes.

Results: We included 21 large trials in this meta-analysis. Compared with placebo, GLP1RAs were associated with the higher risks of gastric ulcer hemorrhage (RR 2.68, 95% CI 1.07–6.68; P_{drug} = .035; I^2 = 0), pancreatitis (RR 1.48, 95% CI 1.02–2.15; P_{drug} = .041; I^2 = 0), cholangitis acute (RR 5.96, 95% CI 1.04–34.08; P_{drug} = .045; I^2 = 0), and cholecystitis acute (RR 1.52, 95% CI 1.08–2.15; P_{drug} = .017; I^2 = 1.5%), but were not significantly associated with the occurrences of the other 87 kinds of digestive diseases (P_{drug} ranged from .064 to .999). SGLT2is versus placebo were not significantly associated with the occurrences of 91 kinds of digestive diseases (P_{drug} ranged from .077 to .995). DPP4is versus placebo were not significantly associated with the occurrences of 91 kinds of digestive diseases (P_{drug} ranged from .085 to .999).

Conclusions: Neither SGLT2is nor DPP4is are associated with the occurrences of various kinds of digestive diseases, whereas GLP1RAs are associated with the higher risks of 4 kinds of digestive diseases, namely, gastric ulcer hemorrhage, pancreatitis, cholangitis acute, and cholecystitis acute. These findings seem to suggest that GLP1RAs are not applicable for patients at high risk of 4 specific digestive diseases, whereas SGLT2is and DPP4is are safe for patients susceptible to digestive diseases. However, our findings require to be further verified by future studies with sufficient statistical power.

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials,CI = confidence interval,DPP4is = dipeptidyl peptidase-4 inhibitors,GLP1RAs = glucagon-like peptide 1 receptor agonists,RR = risk ratio,SGLT2is = sodium-glucose cotransporter-2 inhibitors.

Keywords: cholangitis, cholecystitis, digestive diseases, gastric ulcer hemorrhage, GLP1RAs, hypoglycemic agents, pancreatitis, SGLT2is

1. Introduction

New hypoglycemic agents for the treatment of diabetes are divided into 3 classes: sodium-glucose cotransporter-2 inhibitors (SGLT2is) such as canagliflozin and empagliflozin, glucagon-like peptide 1 receptor agonists (GLP1RAs) such as liraglutide and semaglutide, and dipeptidyl peptidase-4 inhibitors (DPP4is) such as sitagliptin and linagliptin. SGLT2is and GLP1RAs can also exert the cardiovascular and renal protection effects except having the antihyperglycemic effects. Moreover, the cardiorenal benefits that SGLT2is exhibit have been confirmed not only in patients with type 2 diabetes[1–3] but also in patients with cardiac or renal failure without type 2 diabetes.[4]

Studies focusing on the efficacy of these new hypoglycemic agents are plentiful enough, whereas studies focusing on the safety of these drugs are relatively lacking. Previous meta-analyses reveal that SGLT2is[5] and DPP4is[6] are not associated with a higher risk of overall gastrointestinal adverse events, whereas GLP1RAs[7,8] are associated with that risk. However, there are no relevant meta-analyses that have evaluated whether these new drug classes lead to the higher

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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risks of various specific digestive diseases. In the absence of the trials that treated the occurrences of various digestive diseases as primary endpoints and meanwhile assessed the risks of these new hypoglycemic drugs in leading to various digestive diseases, we failed to include them to conduct a meta-analysis to evaluate the association between these hypoglycemic drugs and the risks of various digestive diseases. Fortunately, the occurrences of various digestive diseases were reported in detail as digestive adverse events among those large randomized trials which aimed to assess cardiorenal outcomes in patients receiving SGLT2is, GLP1RAs, or DPP4is. Hence, we aimed to, using these safety data relevant with digestive system, conduct a meta-analysis to define the association between each class of these new hypoglycemic drugs and 91 kinds of digestive system diseases.

2. Methods

2.1. Inclusion criteria and quality assessment

Studies that were eligible to be included in this meta-analysis were large randomized, placebo-controlled, cardiorenal outcome trials, which assessed any SGLT2i, GLP1RA, or DPP4i, enrolled at least 1000 participants in each study group, and reported the occurrences of various kinds of digestive system diseases. Outcomes of interest were 91 kinds of digestive diseases which consisted of 75 kinds of gastrointestinal disorders (ID 1-75 in **Table S1**, Supplemental Digital Content, http://links.lww.com/MD/H18, which shows the names of gastrointestinal and hepatobiliary disorders) and 16 kinds of hepatobiliary disorders (ID 76-91 in **Table S1**, Supplemental Digital Content, http://links.lww.com/MD/H18, which shows the names of gastrointestinal and hepatobiliary disorders). Relevant articles published before April 2021 were searched in 3 online databases, namely PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase. The search keywords we mainly used in this meta-analysis were "Empagliflozin", "Dapagliflozin", "Sotagliflozin", "Canagliflozin", "Ertugliflozin", "Gliflozins", "SGLT2 inhibitors", "Liraglutide", "Exenatide", "Lixisenatide", "Dulaglutide", "Semaglutide", "Albiglutide", "GIP-1 Receptor Agonists", "Linagliptin", "Sitagliptin", "Omarigliptin", "Alogliptin", "Saxagliptin", "DPP-4 Inhibitors", "Renal", "Cardiovascular", "Cardiorenal", and "Randomized controlled trial". The numbers of subjects developing digestive diseases of interest and the numbers of total subjects in active drug and placebo groups among included trials were extracted from the website of ClinicalTrials (https://clinicaltrials.gov/) respectively by 2 authors. Moreover, the 2 authors evaluated the quality of included trials according to the Cochrane' tool assessing risk of bias for randomized trials.[9] All the disagreements between them were examined and addressed by a third author.

2.2. Statistical analyses

We performed meta-analysis respectively based on trials of SGLT2is, trials of GLP1RAs, and trials of DPP4is. Meta-analysis was conducted respectively using random-effects model and fixed-effects model to synthesize risk ratio (RR) and 95% confidence interval (CI). I^2 was used to reflect heterogeneity magnitude. When I^2 was <50%, we selected fixed-effects results as the results of pooled analysis. Otherwise, we selected random-effects results as the results of pooled analysis. The robustness of pooled results was evaluated by the similarity between fixed-effects results and random-effects results. A P value of <.05 means statistical significance. We did all the statistical analyses in this study using the Stata 16.0 software.

2.3. Ethical statement

The data analyzed in this study were extracted from previously published studies, and thus ethical approval was not necessary.

3. Results

3.1. Characteristics of included trials

We finally included 21 large randomized trials for this meta-analysis after we performed study selection. The whole process of study selection is presented in **Figure S1** (Supplemental Digital Content, http://links.lww.com/MD/H19, which is the flow chart of study selection). The 21 included trials consisted of 9 SGLT2i trials (i.e., EMPA-REG OUTCOME [NCT01131676],[10] CANVAS [NCT01032629],[11] CANVAS-R [NCT01989754],[11] DECLARE–TIMI 58 [NCT01730534],[12] VERTIS CV [NCT01986881],[13] CREDENCE [NCT02065791],[14] DAPA-HF [NCT03036124],[15] DAPA-CKD [NCT03036150],[16] and EMPEROR-Reduced [NCT03057977][17]), 7 GLP1RA trials (i.e., ELIXA [NCT01147250],[18] SUSTAIN-6 [NCT01720446],[19] LEADER [NCT01179048],[20] EXSCEL [NCT01144338],[21] REWIND [NCT01394952],[22] Harmony Outcomes [NCT02465515],[23] and PIONEER 6 [NCT02692716][24]), and 5 DPP4i trials (i.e., SAVOR-TIMI 53 [NCT01107886],[25] TECOS [NCT00790205],[26] EXAMINE [NCT00968708],[27] CARMELINA [NCT01897532],[28] and OMNEON [NCT01703208][29]). The bias risk of all the included trials was assessed as low risk (**Figure S2**, Supplemental Digital Content, http://links.lww.com/MD/H20, which is the plot of quality assessment). Nine SGLT2i trials involved 33,124 patients receiving SGLT2is (versus 26,568 patients receiving placebo), 7 GLP1RA trials involved 27,942 patients receiving GLP1RAs (versus 27,980 patients receiving placebo), and 5 DPP4i trials involved 23,833 patients receiving DPP4is (versus 23,750 patients receiving placebo).

3.2. Meta-analyses

Table 1 shows the summary results for meta-analysis of 3 new classes of hypoglycemic agents and 91 kinds of digestive system diseases. Compared with placebo, GLP1RAs were associated with the higher risks of gastric ulcer hemorrhage (RR 2.68, 95% CI 1.07–6.68; P_{drug} = 0.035; I^2 = 0), pancreatitis (RR 1.48, 95% CI 1.02–2.15; P_{drug} = .041; I^2 = 0), cholangitis acute (RR 5.96, 95% CI 1.04–34.08; P_{drug} = .045; I^2 = 0), and cholecystitis acute (RR 1.52, 95% CI 1.08–2.15; P_{drug} = .017; I^2 = 1.5%), but were not significantly associated with the occurrences of the other 87 kinds of digestive diseases (P_{drug} ranged from .064 to .999), with RR (0.23–3.22), low limit of 95% CI of RR (0.04–0.95), upper limit of 95% CI of RR (1.07–28.89), and I^2 (most was 0). SGLT2is versus placebo were not significantly associated with the occurrences of 91 kinds of digestive diseases (P_{drug} ranged from 0.077 to 0.995), with RR (0.26–3.92), low limit of 95% CI of RR (0.04–0.82), upper limit of 95% CI of RR (1.07–35.51), and I^2 (most was 0). DPP4is versus placebo were not significantly associated with the occurrences of 91 kinds of digestive diseases (P_{drug} ranged from .085 to .999), with RR (0.18–5.94), low limit of 95% CI of RR (0.02–0.93), upper limit of 95% CI of RR (1.28–49.48), and I^2 (most was 0). The detailed results for meta-analysis on 91 outcomes of interest stratified by 3 drug classes are presented in **Figures S3 to S93** (Supplemental Digital Content, http://links.lww.com/MD/H21, which are the forest plots of meta-analysis on 91 outcomes), which suggested that the results from random-effects model were not substantially different with those from fixed-effects model.

Table 1

Summary results for meta-analysis of 3 new classes of hypoglycemic agents and 91 kinds of digestive system diseases.

ID	Outcome	Drug class	RR	LOW	UPPER	Studies	Events1	Patients1	Events0	Patients0	I^2 (%)	P_{drug}
1	Abdominal adhesions	SGLT2is	0.72	0.08	6.53	2	1	10,942	2	10,937	31.0	.771
1	Abdominal adhesions	GLP1RAs	1.14	0.19	7.01	3	2	15,318	2	15,353	0.0	.886
1	Abdominal adhesions	DPP4is	2.07	0.27	16.00	2	3	11,774	1	11,697	0.0	.487
2	Abdominal hernia	SGLT2is	0.84	0.40	1.80	6	19	26,693	15	20,140	0.0	.660
2	Abdominal hernia	GLP1RAs	0.93	0.49	1.77	5	19	24,703	21	24,740	0.0	.834
2	Abdominal hernia	DPP4is	0.75	0.30	1.85	4	9	21,132	12	21,071	0.0	.528
3	Abdominal pain	SGLT2is	1.00	0.64	1.57	9	47	33,124	36	26,568	0.0	.995
3	Abdominal pain	GLP1RAs	1.10	0.71	1.69	7	45	27,942	42	27,980	0.0	.678
3	Abdominal pain	DPP4is	1.30	0.75	2.25	5	29	23,833	22	23,750	0.0	.355
4	Abdominal pain lower	SGLT2is	1.45	0.29	7.20	4	3	18,365	1	16,002	0.0	.646
4	Abdominal pain lower	GLP1RAs	1.35	0.25	7.18	2	3	6316	2	6321	0.0	.725
4	Abdominal pain lower	DPP4is	0.62	0.08	5.03	2	1	10,981	2	10,891	0.0	.654
5	Abdominal pain upper	SGLT2is	1.00	0.37	2.67	7	14	28,607	8	22,051	2.9	.994
5	Abdominal pain upper	GLP1RAs	1.00	0.50	2.00	7	16	27,942	16	27,980	0.0	.998
5	Abdominal pain upper	DPP4is	1.75	0.53	5.82	4	9	21,741	4	21,650	0.0	.362
6	Abdominal wall hematoma	SGLT2is	0.94	0.23	3.95	5	3	14,759	2	10,566	0.0	.937
6	Abdominal wall hematoma	GLP1RAs	1.61	0.20	13.04	2	2	12,287	1	12,321	0.0	.658
6	Abdominal wall hematoma	DPP4is	0.71	0.13	3.95	3	2	19,040	4	18,971	0.0	.698
7	Anal fistula	SGLT2is	1.13	0.31	4.11	6	5	26,744	2	20,188	0.0	.858
7	Anal fistula	GLP1RAs	0.55	0.15	2.09	5	2	24,703	5	24,740	0.0	.383
7	Anal fistula	DPP4is	0.43	0.08	2.42	3	1	19,040	4	18,971	0.0	.339
8	Ascites	SGLT2is	1.61	0.54	4.76	6	11	26,912	4	20,359	0.0	.391
8	Ascites	GLP1RAs	1.02	0.32	3.24	5	6	23,320	6	23,357	0.0	.974
8	Ascites	DPP4is	0.70	0.21	2.37	3	4	19,040	6	18,971	0.0	.567
9	Chronic gastritis	SGLT2is	1.09	0.32	3.69	6	6	19,497	3	12,947	0.0	.891
9	Chronic gastritis	GLP1RAs	0.69	0.25	1.88	6	7	26,351	12	26,389	0.0	.467
9	Chronic gastritis	DPP4is	1.44	0.23	9.15	2	3	5586	2	5585	16.7	.698
10	Colitis	SGLT2is	0.67	0.32	1.41	8	16	30,756	17	24,200	0.0	.289
10	Colitis	GLP1RAs	1.04	0.53	2.03	7	18	27,942	17	27,980	0.0	.909
10	Colitis	DPP4is	1.06	0.38	2.94	4	8	21,132	7	21,071	0.0	.914
11	Colitis ischemic	SGLT2is	1.13	0.46	2.73	8	13	30,756	9	24,200	0.0	.793
11	Colitis ischemic	GLP1RAs	1.09	0.40	2.95	6	8	24,911	7	24,948	0.0	.861
11	Colitis ischemic	DPP4is	1.92	0.58	6.33	4	11	21,741	5	21,650	22.9	.284
12	Colitis ulcerative	SGLT2is	1.25	0.25	6.36	3	4	14,364	2	12,913	0.0	.784
12	Colitis ulcerative	GLP1RAs	3.22	0.87	11.89	5	8	23,320	1	23,357	0.0	.080
12	Colitis ulcerative	DPP4is	2.98	0.31	28.60	2	2	10,981	0	10,891	0.0	.345
13	Constipation	SGLT2is	1.25	0.64	2.43	9	30	33,124	16	26,568	19.2	.508
13	Constipation	GLP1RAs	1.26	0.69	2.31	7	24	27,942	19	27,980	0.0	.456
13	Constipation	DPP4is	1.03	0.46	2.31	5	13	23,833	13	23,750	0.0	.951
14	Diabetic gastroparesis	SGLT2is	0.82	0.20	3.40	5	3	23,103	3	17,993	0.0	.790
14	Diabetic gastroparesis	GLP1RAs	3.00	0.47	19.04	3	3	12,691	0	12,696	0.0	.244
14	Diabetic gastroparesis	DPP4is	0.67	0.17	2.60	4	3	16,567	5	16,476	0.0	.563
15	Diarrhea	SGLT2is	0.94	0.59	1.50	9	41	33,124	34	26,568	0.0	.801
15	Diarrhea	GLP1RAs	1.45	0.89	2.36	6	43	20,598	28	20,608	0.0	.133
15	Diarrhea	DPP4is	1.07	0.62	1.85	4	30	16,567	26	16,476	24.8	.805
16	Diverticular perforation	SGLT2is	3.92	0.43	35.51	2	3	5053	0	5052	0.0	.224
16	Diverticular perforation	GLP1RAs	0.83	0.25	2.73	4	5	19,986	6	20,025	0.0	.757
16	Diverticular perforation	DPP4is	1.00	0.17	5.77	3	2	17,638	2	17,586	0.0	.999
17	Diverticulum	SGLT2is	1.26	0.48	3.31	6	11	26,007	6	20,896	0.0	.645
17	Diverticulum	GLP1RAs	0.87	0.36	2.15	5	10	21,634	12	21,674	10.4	.771
17	Diverticulum	DPP4is	0.51	0.12	2.10	4	2	21,132	5	21,071	0.0	.351
18	Diverticulum intestinal	SGLT2is	0.52	0.17	1.58	7	6	22,687	7	16,136	0.0	.247
18	Diverticulum intestinal	GLP1RAs	2.53	0.88	7.24	5	12	23,320	4	23,357	0.0	.084
18	Diverticulum intestinal	DPP4is	0.74	0.14	3.93	3	2	19,040	3	18,971	0.0	.723
19	Diverticulum intestinal hemorrhagic	SGLT2is	1.06	0.34	3.31	6	7	23,670	5	19,469	0.0	.921
19	Diverticulum intestinal hemorrhagic	GLP1RAs	0.62	0.14	2.70	3	3	16,955	6	16,993	0.0	.524
19	Diverticulum intestinal hemorrhagic	DPP4is	1.60	0.31	8.30	3	4	13,461	2	13,438	0.0	.576
20	Duodenal ulcer	SGLT2is	0.87	0.43	1.75	8	19	30,756	15	24,200	0.0	.694
20	Duodenal ulcer	GLP1RAs	0.95	0.50	1.79	7	19	27,942	21	27,980	0.0	.864
20	Duodenal ulcer	DPP4is	0.79	0.35	1.77	5	11	23,833	15	23,750	0.0	.566
21	Duodenal ulcer hemorrhage	SGLT2is	0.93	0.32	2.68	6	9	26,226	7	21,115	0.0	.895
21	Duodenal ulcer hemorrhage	GLP1RAs	0.89	0.39	2.01	7	13	27,942	13	27,980	0.0	.776
21	Duodenal ulcer hemorrhage	DPP4is	0.99	0.23	4.37	3	3	18,247	3	18,165	0.0	.993
22	Duodenitis	SGLT2is	1.28	0.28	5.83	4	4	17,829	2	15,467	0.0	.752
22	Duodenitis	GLP1RAs	0.75	0.26	2.17	6	5	26,351	8	26,389	0.0	.594
22	Duodenitis	DPP4is	0.38	0.07	2.11	3	1	13,461	5	13,438	0.0	.269
23	Dyspepsia	SGLT2is	1.79	0.51	6.25	4	8	18,515	3	14,711	0.0	.360
23	Dyspepsia	GLP1RAs	0.90	0.34	2.42	6	8	26,294	9	26,331	0.0	.837
23	Dyspepsia	DPP4is	1.18	0.32	4.37	3	5	18,247	4	18,165	0.0	.804

(Continued)

Table 1

(Continued)

ID	Outcome	Drug class	RR	LOW	UPPER	Studies	Events1	Patients1	Events0	Patients0	I^2 (%)	P_{drug}
24	Dysphagia	SGLT2is	0.94	0.28	3.13	4	6	18,296	6	14,492	34.0	.916
24	Dysphagia	GLP1RAs	1.58	0.53	4.72	5	9	24,703	5	24,740	0.0	.411
24	Dysphagia	DPP4is	0.88	0.22	3.46	4	4	21,741	5	21,650	0.0	.851
25	Enteritis	SGLT2is	0.50	0.18	1.39	7	4	24,727	10	20,920	0.0	.184
25	Enteritis	GLP1RAs	0.23	0.05	1.09	3	1	14,328	8	14,336	0.0	.064
25	Enteritis	DPP4is	4.07	0.67	24.60	3	5	14,475	0	14,376	0.0	.126
26	Enterovesical fistula	SGLT2is	0.62	0.08	5.07	2	1	10,774	2	10,766	0.0	.659
26	Enterovesical fistula	GLP1RAs	1.00	0.14	7.10	2	2	9611	2	9621	0.0	.999
26	Enterovesical fistula	DPP4is	1.00	0.20	4.95	4	2	21,132	2	21,071	0.0	.999
27	Fecaloma	SGLT2is	1.04	0.22	4.85	3	6	15,410	3	13,051	42.2	.962
27	Fecaloma	GLP1RAs	0.54	0.13	2.30	4	2	21,672	5	21,708	0.0	.404
27	Fecaloma	DPP4is	1.14	0.19	6.98	3	2	19,040	2	18,971	0.0	.890
28	Food poisoning	SGLT2is	0.89	0.31	2.53	6	7	23,400	6	19,592	0.0	.820
28	Food poisoning	GLP1RAs	1.00	0.17	5.78	3	2	12,642	2	12,653	0.0	.999
28	Food poisoning	DPP4is	0.67	0.11	4.12	2	2	10,372	3	10,312	0.0	.666
29	Gastric hemorrhage	SGLT2is	0.89	0.26	3.05	5	5	22,985	4	17,878	0.0	.854
29	Gastric hemorrhage	GLP1RAs	0.69	0.11	4.40	3	1	14,328	2	14,336	0.0	.698
29	Gastric hemorrhage	DPP4is	0.64	0.12	3.53	3	2	14,475	5	14,376	15.9	.611
30	Gastric polyps	SGLT2is	1.12	0.28	4.56	3	4	16,165	3	13,805	0.0	.872
30	Gastric polyps	GLP1RAs	0.89	0.30	2.63	5	6	21,634	7	21,674	0.0	.833
30	Gastric polyps	DPP4is	1.93	0.34	11.16	3	3	12,852	1	12,859	0.0	.461
31	Gastric ulcer	SGLT2is	0.90	0.47	1.69	8	21	30,220	18	23,665	0.0	.735
31	Gastric ulcer	GLP1RAs	0.94	0.50	1.77	7	19	27,942	20	27,980	0.0	.856
31	Gastric ulcer	DPP4is	0.77	0.36	1.62	5	13	23,833	17	23,750	0.0	.484
32	Gastric ulcer hemorrhage	SGLT2is	1.36	0.50	3.68	5	10	23,271	6	18,164	0.0	.546
32	Gastric ulcer hemorrhage	GLP1RAs	2.68	1.07	6.68	6	22	26,351	6	26,389	0.0	.035
32	Gastric ulcer hemorrhage	DPP4is	0.89	0.32	2.43	4	7	20,339	8	20,265	0.0	.814
33	Gastritis	SGLT2is	0.77	0.47	1.26	8	37	30,220	39	23,665	14.6	.294
33	Gastritis	GLP1RAs	0.82	0.55	1.23	7	46	27,942	57	27,980	3.2	.340
33	Gastritis	DPP4is	1.10	0.65	1.87	5	34	23,833	29	23,750	42.8	.715
34	Gastritis erosive	SGLT2is	1.92	0.63	5.81	5	12	22,985	4	17,878	0.0	.248
34	Gastritis erosive	GLP1RAs	0.53	0.23	1.25	5	9	24,703	18	24,740	0.0	.147
34	Gastritis erosive	DPP4is	0.56	0.19	1.64	5	5	23,833	11	23,750	0.0	.287
35	Gastritis hemorrhagic	SGLT2is	0.91	0.14	5.76	3	2	12,548	1	7446	0.0	.918
35	Gastritis hemorrhagic	GLP1RAs	2.16	0.36	12.84	3	4	9347	1	9353	0.0	.397
35	Gastritis hemorrhagic	DPP4is	1.34	0.25	7.15	3	3	19,040	2	18,971	0.0	.728
36	Gastrointestinal hemorrhage	SGLT2is	0.85	0.59	1.21	9	65	33,124	61	26,568	0.0	.361
36	Gastrointestinal hemorrhage	GLP1RAs	0.78	0.57	1.07	7	70	27,942	90	27,980	0.0	.129
36	Gastrointestinal hemorrhage	DPP4is	0.86	0.58	1.28	5	46	23,833	53	23,750	0.0	.468
37	Gastrointestinal necrosis	SGLT2is	0.70	0.11	4.30	3	2	13,323	2	11,873	22.8	.701
37	Gastrointestinal necrosis	GLP1RAs	1.35	0.25	7.18	3	3	14,328	2	14,336	0.0	.725
37	Gastrointestinal necrosis	DPP4is	1.00	0.14	7.09	2	2	10,760	2	10,759	0.0	.999
38	Gastrointestinal ulcer hemorrhage	SGLT2is	1.44	0.23	9.15	3	2	12,586	1	12,581	0.0	.698
38	Gastrointestinal ulcer hemorrhage	GLP1RAs	1.39	0.15	12.56	2	2	9611	1	9621	30.9	.771
38	Gastrointestinal ulcer hemorrhage	DPP4is	0.47	0.10	2.17	4	1	20,339	4	20,265	0.0	.330
39	Gastroesophageal reflux disease	SGLT2is	0.70	0.36	1.35	7	21	28,357	21	21,802	0.0	.289
39	Gastroesophageal reflux disease	GLP1RAs	1.19	0.73	1.96	7	38	27,942	30	27,980	0.0	.485
39	Gastroesophageal reflux disease	DPP4is	1.30	0.58	2.92	5	21	23,833	11	23,750	30.5	.520
40	Gingival bleeding	SGLT2is	0.26	0.04	1.68	3	0	15,124	3	12,765	0.0	.158
40	Gingival bleeding	GLP1RAs	3.01	0.31	28.89	2	2	10,375	0	10,404	0.0	.340
40	Gingival bleeding	DPP4is	0.99	0.10	9.53	2	1	10,981	1	10,891	0.0	.994
41	Hematemesis	SGLT2is	0.67	0.22	2.03	7	6	29,112	7	22,556	0.0	.477
41	Hematemesis	GLP1RAs	0.52	0.12	2.17	5	1	19,007	4	19,017	0.0	.367
41	Hematemesis	DPP4is	3.90	0.43	35.32	2	3	11,774	0	11,697	0.0	.226
42	Hematochezia	SGLT2is	0.63	0.16	2.47	5	4	22,985	4	17,878	0.0	.508
42	Hematochezia	GLP1RAs	0.80	0.22	2.89	4	5	18,546	7	18,584	22.3	.737
42	Hematochezia	DPP4is	0.86	0.20	3.73	3	3	19,040	4	18,971	0.0	.844
43	Haemorrhoidal hemorrhage	SGLT2is	0.45	0.16	1.33	7	4	28,357	8	21,802	0.0	.149
43	Haemorrhoidal hemorrhage	GLP1RAs	1.26	0.34	4.72	4	5	17,359	4	17,368	0.0	.730
43	Hemorrhoidal hemorrhage	DPP4is	0.18	0.02	1.57	2	0	10,981	5	10,891	0.0	.121
44	Hemorrhoids	SGLT2is	1.33	0.56	3.13	6	16	25,652	7	19,100	0.0	.519
44	Hemorrhoids	GLP1RAs	1.30	0.53	3.18	6	11	26,294	8	26,331	0.0	.572
44	Hemorrhoids	DPP4is	1.17	0.52	2.64	4	13	21,741	11	21,650	0.0	.707
45	Hiatus hernia	SGLT2is	1.12	0.33	3.79	3	6	16,147	4	12,343	0.0	.854
45	Hiatus hernia	GLP1RAs	1.31	0.44	3.88	5	12	23,320	11	23,357	45.7	.626
45	Hiatus hernia	DPP4is	1.21	0.18	7.93	2	3	11,774	2	11,697	26.1	.845
46	Ileus	SGLT2is	1.15	0.49	2.73	9	14	33,124	8	26,568	0.0	.747
46	Ileus	GLP1RAs	0.94	0.40	2.22	5	11	24,703	11	24,740	0.0	.892
46	Ileus	DPP4is	1.15	0.27	4.98	4	4	21,132	3	21,071	0.0	.849
47	Ileus paralytic	SGLT2is	0.51	0.16	1.65	6	4	25,871	6	19,319	0.0	.260

(Continued)

Table 1

(Continued)

ID	Outcome	Drug class	RR	LOW	UPPER	Studies	Events1	Patients1	Events0	Patients0	I^2 (%)	P_{drug}
47	Ileus paralytic	GLP1RAs	0.50	0.09	2.73	2	2	9611	4	9621	0.0	.424
47	Ileus paralytic	DPP4is	0.63	0.08	5.09	2	1	9358	2	9374	0.0	.661
48	Impaired gastric emptying	SGLT2is	0.88	0.23	3.31	4	5	18,314	4	15,954	0.0	.851
48	Impaired gastric emptying	GLP1RAs	1.16	0.41	3.26	7	9	27,942	7	27,980	0.0	.783
48	Impaired gastric emptying	DPP4is	2.04	0.34	12.32	3	4	13,073	1	12,991	0.0	.437
49	Inguinal hernia	SGLT2is	1.34	0.82	2.18	9	55	33,124	29	26,568	9.6	.245
49	Inguinal hernia	GLP1RAs	1.45	0.95	2.23	7	55	27,942	37	27,980	0.0	.085
49	Inguinal hernia	DPP4is	1.24	0.71	2.17	5	29	23,833	23	23,750	0.0	.439
50	Intestinal hemorrhage	SGLT2is	0.40	0.11	1.45	6	2	26,912	6	20,359	0.0	.164
50	Intestinal hemorrhage	GLP1RAs	1.22	0.35	4.28	4	5	16,966	4	17,002	0.0	.753
50	Intestinal hemorrhage	DPP4is	0.62	0.08	5.07	2	1	10,760	2	10,759	0.0	.659
51	Intestinal ischemia	SGLT2is	0.90	0.33	2.47	7	9	28,775	8	22,222	0.0	.839
51	Intestinal ischemia	GLP1RAs	1.84	0.60	5.63	5	9	15,881	4	15,893	0.0	.284
51	Intestinal ischemia	DPP4is	1.52	0.30	7.71	3	4	18,247	2	18,165	0.0	.612
52	Intestinal obstruction	SGLT2is	0.93	0.46	1.88	8	21	30,238	15	25,127	0.0	.848
52	Intestinal obstruction	GLP1RAs	0.74	0.40	1.39	6	19	26,351	25	26,389	7.4	.352
52	Intestinal obstruction	DPP4is	1.26	0.52	3.04	5	12	23,833	9	23,750	0.0	.607
53	Intestinal perforation	SGLT2is	1.25	0.30	5.14	5	4	23,322	2	18,212	0.0	.758
53	Intestinal perforation	GLP1RAs	3.00	0.61	14.88	4	4	18,652	0	18,685	0.0	.178
53	Intestinal perforation	DPP4is	0.23	0.04	1.39	3	0	19,040	5	18,971	0.0	.110
54	Intestinal polyp	SGLT2is	1.42	0.18	11.01	2	3	11,460	1	10,010	17.1	.736
54	Intestinal polyp	GLP1RAs	0.43	0.08	2.43	3	1	14,328	4	14,336	0.0	.341
54	Intestinal polyp	DPP4is	0.43	0.06	2.95	2	1	10,760	3	10,759	0.0	.392
55	Irritable bowel syndrome	SGLT2is	1.50	0.16	14.38	2	2	10,180	0	5078	0.0	.727
55	Irritable bowel syndrome	GLP1RAs	0.23	0.04	1.39	3	0	14,328	5	14,336	0.0	.111
55	Irritable bowel syndrome	DPP4is	1.34	0.25	7.13	3	3	14,475	2	14,376	0.0	.731
56	Large intestine perforation	SGLT2is	1.22	0.37	4.01	5	6	24,544	3	17,991	0.0	.748
56	Large intestine perforation	GLP1RAs	1.00	0.23	4.41	4	3	19,986	3	20,025	0.0	.998
56	Large intestine perforation	DPP4is	1.59	0.20	12.96	2	2	15,546	1	15,486	0.0	.662
57	Large intestine polyp	SGLT2is	1.31	0.72	2.41	8	31	30,220	17	23,665	0.0	.379
57	Large intestine polyp	GLP1RAs	1.02	0.59	1.76	7	28	27,942	32	27,980	6.3	.942
57	Large intestine polyp	DPP4is	1.29	0.49	3.44	3	11	12,852	9	12,859	37.9	.606
58	Lower gastrointestinal hemorrhage	SGLT2is	1.70	0.62	4.70	7	11	26,574	4	22,372	0.0	.304
58	Lower gastrointestinal hemorrhage	GLP1RAs	0.97	0.51	1.85	7	20	27,942	21	27,980	0.0	.922
58	Lower gastrointestinal hemorrhage	DPP4is	0.63	0.24	1.68	5	6	23,833	13	23,750	0.0	.356
59	Mallory-Weiss syndrome	SGLT2is	1.48	0.22	10.10	2	3	6550	1	4196	0.0	.689
59	Mallory-Weiss syndrome	GLP1RAs	2.85	0.43	18.71	2	4	7699	1	7704	0.0	.276
59	Mallory-Weiss syndrome	DPP4is	2.87	0.57	14.56	3	5	18,247	1	18,165	0.0	.203
60	Melaena	SGLT2is	2.00	0.55	7.20	6	7	26,226	1	21,115	0.0	.291
60	Melaena	GLP1RAs	0.87	0.31	2.39	6	7	26,351	8	26,389	0.0	.783
60	Melaena	DPP4is	5.94	0.71	49.48	2	5	10,760	0	10,759	0.0	.100
61	Nausea	SGLT2is	0.93	0.38	2.31	6	12	25,134	9	20,027	0.0	.881
61	Nausea	GLP1RAs	1.04	0.52	2.07	6	17	20,598	17	20,608	0.0	.922
61	Nausea	DPP4is	2.82	0.38	21.03	2	5	11,774	1	11,697	12.1	.313
62	Esophageal varices hemorrhage	SGLT2is	1.12	0.21	5.94	2	3	11,460	2	10,010	0.0	.897
62	Esophageal varices hemorrhage	GLP1RAs	1.53	0.38	6.05	5	6	23,263	3	23,299	8.4	.548
62	Esophageal varices hemorrhage	DPP4is	0.33	0.05	2.11	3	0	19,040	3	18,971	0.0	.242
63	Esophagitis	SGLT2is	0.96	0.18	4.97	3	3	18,754	2	13,647	0.0	.960
63	Esophagitis	GLP1RAs	0.77	0.27	2.18	6	6	26,294	8	26,331	0.0	.627
63	Esophagitis	DPP4is	2.65	0.65	10.87	4	9	16,567	2	16,476	0.0	.175
64	Pancreatic cyst	SGLT2is	0.35	0.07	1.68	4	1	19,102	4	14,904	0.0	.189
64	Pancreatic cyst	GLP1RAs	0.83	0.23	2.92	4	4	18,603	5	18,642	0.0	.768
64	Pancreatic cyst	DPP4is	0.97	0.16	5.89	3	2	8287	3	8264	22.0	.978
65	Pancreatitis	SGLT2is	1.21	0.70	2.08	9	38	33,124	22	26,568	0.0	.493
65	Pancreatitis	GLP1RAs	1.48	1.02	2.15	7	70	27,942	48	27,980	0.0	.041
65	Pancreatitis	DPP4is	1.54	0.87	2.70	4	31	16,567	20	16,476	0.0	.135
66	Pancreatitis acute	SGLT2is	1.16	0.74	1.82	9	53	33,124	35	26,568	0.0	.511
66	Pancreatitis acute	GLP1RAs	1.04	0.65	1.66	6	37	20,598	36	20,608	8.9	.876
66	Pancreatitis acute	DPP4is	1.05	0.49	2.26	4	15	16,567	14	16,476	0.0	.903
67	Pancreatitis chronic	SGLT2is	0.81	0.27	2.44	6	6	25,134	6	20,027	0.0	.703
67	Pancreatitis chronic	GLP1RAs	1.17	0.35	3.92	5	5	18,950	4	18,959	0.0	.799
67	Pancreatitis chronic	DPP4is	0.63	0.22	1.80	4	6	16,567	10	16,476	0.0	.391
68	Peptic ulcer	SGLT2is	1.04	0.38	2.85	7	9	28,893	6	22,337	0.0	.943
68	Peptic ulcer	GLP1RAs	1.21	0.47	3.07	5	11	23,320	8	23,357	0.0	.693
68	Peptic ulcer	DPP4is	0.98	0.27	3.48	5	5	23,833	5	23,750	0.0	.969
69	Rectal hemorrhage	SGLT2is	1.44	0.70	2.96	6	25	25,703	11	19,148	0.0	.317
69	Rectal hemorrhage	GLP1RAs	1.27	0.63	2.53	5	18	24,703	14	24,740	0.0	.506
69	Rectal hemorrhage	DPP4is	0.59	0.20	1.75	5	5	23,833	10	23,750	0.0	.342
70	Rectal polyp	SGLT2is	0.72	0.15	3.47	3	3	10,061	3	7310	0.0	.679
70	Rectal polyp	GLP1RAs	1.88	0.54	6.50	4	7	21,672	3	21,708	0.0	.319

(Continued)

Table 1

(Continued)

ID	Outcome	Drug class	RR	LOW	UPPER	Studies	Events1	Patients1	Events0	Patients0	I^2 (%)	P_{drug}
70	Rectal polyp	DPP4is	0.50	0.12	2.13	3	2	19,040	6	18,971	0.0	.345
71	Small intestinal obstruction	SGLT2is	1.31	0.70	2.47	9	30	33,124	16	26,568	0.0	.397
71	Small intestinal obstruction	GLP1RAs	0.92	0.54	1.57	5	27	23,320	30	23,357	5.9	.753
71	Small intestinal obstruction	DPP4is	1.14	0.55	2.36	5	16	23,833	14	23,750	0.0	.719
72	Umbilical hernia	SGLT2is	1.01	0.49	2.08	7	26	29,112	15	22,556	40.4	.988
72	Umbilical hernia	GLP1RAs	0.69	0.38	1.25	7	20	27,942	30	27,980	0.0	.218
72	Umbilical hernia	DPP4is	1.15	0.43	3.06	3	9	19,040	9	18,971	14.2	.783
73	Upper gastrointestinal hemorrhage	SGLT2is	0.89	0.53	1.49	9	37	33,124	31	26,568	0.0	.648
73	Upper gastrointestinal hemorrhage	GLP1RAs	0.87	0.54	1.39	6	33	26,351	38	26,389	0.0	.560
73	Upper gastrointestinal hemorrhage	DPP4is	0.86	0.48	1.53	5	23	23,833	27	23,750	0.0	.610
74	Varices esophageal	SGLT2is	1.49	0.44	5.01	4	7	18,296	3	14,492	0.0	.517
74	Varices esophageal	GLP1RAs	1.94	0.34	11.17	3	3	17,004	1	17,036	0.0	.460
74	Varices esophageal	DPP4is	0.72	0.08	6.50	2	1	15,546	2	15,486	31.4	.769
75	Vomiting	SGLT2is	0.51	0.24	1.07	8	15	30,220	23	23,665	0.0	.077
75	Vomiting	GLP1RAs	1.59	0.92	2.74	6	37	20,598	21	20,608	0.0	.098
75	Vomiting	DPP4is	1.68	0.62	4.54	4	13	16,567	7	16,476	11.8	.303
76	Bile duct stone	SGLT2is	0.87	0.45	1.70	9	22	33,124	20	26,568	0.0	.684
76	Bile duct stone	GLP1RAs	1.27	0.61	2.63	6	17	20,598	13	20,608	0.0	.523
76	Bile duct stone	DPP4is	0.67	0.25	1.76	5	6	23,833	10	23,750	0.0	.412
77	Biliary colic	SGLT2is	0.71	0.16	3.08	4	3	19,120	4	16,366	0.0	.651
77	Biliary colic	GLP1RAs	2.10	0.71	6.27	5	10	23,320	4	23,357	0.0	.182
77	Biliary colic	DPP4is	0.65	0.15	2.89	4	3	21,741	6	21,650	12.1	.576
78	Cholangitis	SGLT2is	1.17	0.59	2.31	9	19	33,124	14	26,568	0.0	.657
78	Cholangitis	GLP1RAs	1.22	0.44	3.45	4	9	14,290	7	14,302	6.6	.701
78	Cholangitis	DPP4is	0.36	0.08	1.60	4	1	16,567	6	16,476	0.0	.178
79	Cholangitis acute	SGLT2is	1.19	0.44	3.23	7	8	22,944	6	21,490	0.0	.735
79	Cholangitis acute	GLP1RAs	5.96	1.04	34.08	3	8	11,202	0	11,212	0.0	.045
79	Cholangitis acute	DPP4is	0.99	0.17	5.73	3	2	14,475	2	14,376	0.0	.994
80	Cholecystitis	SGLT2is	0.87	0.58	1.29	9	58	33,124	51	26,568	0.0	.482
80	Cholecystitis	GLP1RAs	1.26	0.83	1.89	6	54	20,598	45	20,608	14.4	.277
80	Cholecystitis	DPP4is	1.66	0.93	2.94	5	32	23,833	19	23,750	0.0	.085
81	Cholecystitis acute	SGLT2is	0.96	0.68	1.34	9	80	33,124	64	26,568	0.0	.802
81	Cholecystitis acute	GLP1RAs	1.52	1.08	2.15	6	84	20,598	56	20,608	1.5	.017
81	Cholecystitis acute	DPP4is	1.47	0.90	2.40	4	40	16,567	27	16,476	0.0	.122
82	Cholecystitis chronic	SGLT2is	0.81	0.33	2.01	8	12	30,220	12	23,665	0.0	.654
82	Cholecystitis chronic	GLP1RAs	1.54	0.71	3.37	6	17	20,598	11	20,608	0.0	.277
82	Cholecystitis chronic	DPP4is	0.48	0.12	1.84	4	3	16,567	8	16,476	0.0	.284
83	Cholelithiasis	SGLT2is	0.90	0.65	1.24	9	93	33,124	74	26,568	0.0	.509
83	Cholelithiasis	GLP1RAs	1.17	0.90	1.53	6	119	20,598	101	20,608	20.6	.242
83	Cholelithiasis	DPP4is	0.98	0.66	1.45	5	48	23,833	49	23,750	0.0	.904
84	Drug-induced liver injury	SGLT2is	0.87	0.22	3.42	5	4	21,184	3	16,986	0.0	.839
84	Drug-induced liver injury	GLP1RAs	0.47	0.14	1.59	6	2	26,294	7	26,331	0.0	.224
84	Drug-induced liver injury	DPP4is	0.72	0.08	6.50	2	1	15,546	2	15,486	31.4	.769
85	Hepatic cirrhosis	SGLT2is	0.80	0.44	1.45	9	22	33,124	22	26,568	0.0	.458
85	Hepatic cirrhosis	GLP1RAs	0.90	0.46	1.75	7	17	27,942	19	27,980	0.0	.761
85	Hepatic cirrhosis	DPP4is	0.57	0.22	1.48	5	7	23,833	14	23,750	18.9	.247
86	Hepatic failure	SGLT2is	0.88	0.33	2.38	6	7	22,527	7	18,723	0.0	.803
86	Hepatic failure	GLP1RAs	0.74	0.18	2.99	4	4	15,976	6	15,985	23.4	.674
86	Hepatic failure	DPP4is	1.64	0.51	5.32	3	7	19,040	4	18,971	0.0	.410
87	Hepatitis	SGLT2is	0.56	0.09	3.45	3	1	12,805	3	12,800	0.0	.534
87	Hepatitis	GLP1RAs	1.00	0.10	9.62	2	1	6534	1	6540	0.0	.999
87	Hepatitis	DPP4is	1.59	0.20	12.96	2	2	15,546	1	15,486	0.0	.662
88	Hepatitis acute	SGLT2is	2.38	0.38	15.10	3	3	16,435	0	13,682	0.0	.358
88	Hepatitis acute	GLP1RAs	1.14	0.19	7.00	3	2	12,416	2	12,419	0.0	.887
88	Hepatitis acute	DPP4is	1.00	0.10	9.58	2	1	9967	1	9953	0.0	.997
89	Ischemic hepatitis	SGLT2is	0.48	0.10	2.40	4	1	17,829	3	15,467	0.0	.375
89	Ischemic hepatitis	GLP1RAs	0.71	0.20	2.61	5	3	19,007	5	19,017	0.0	.610
89	Ischemic hepatitis	DPP4is	0.33	0.03	3.19	2	0	11,774	2	11,697	0.0	.339
90	Jaundice	SGLT2is	0.45	0.07	2.76	3	1	16,435	3	13,682	0.0	.389
90	Jaundice	GLP1RAs	1.29	0.28	6.00	4	3	18,603	2	18,642	0.0	.745
90	Jaundice	DPP4is	1.14	0.19	6.98	3	2	13,866	2	13,797	0.0	.889
91	Portal vein thrombosis	SGLT2is	0.32	0.07	1.39	3	2	16,953	5	12,755	0.0	.128
91	Portal vein thrombosis	GLP1RAs	1.39	0.27	7.20	3	3	16,955	2	16,993	0.0	.696
91	Portal vein thrombosis	DPP4is	2.98	0.31	28.68	2	2	11,774	0	11,697	0.0	.344

CI = confidence interval, DPP4is = dipeptidyl peptidase-4 inhibitors, Events0 = the number of events in the control group, Events1 = the number of events in the intervention group, GLP1RAs = glucagon-like peptide 1 receptor agonists, LOW = the low limit of 95% CI of RR, Patients0 = the number of patients in the control group, Patients1 = the number of patients in the intervention group, $P_{drug} = P$ for drug effect, RR = risk ratio, SGLT2is = sodium-glucose cotransporter-2 inhibitors, Studies = the number of included studies, UPPER = the upper limit of 95% CI of RR.

4. Discussion

Two previous meta-analyses[5,6] identified that SGLT2is[5] and DPP4is[6] did not lead to the higher risk of overall gastrointestinal adverse events, whereas our meta-analysis further identified that these 2 new classes of hypoglycemic agents were not significantly associated with the occurrences of 91 kinds of specific digestive diseases. Two another meta-analyses[7,8] identified that GLP1RAs led to the higher risk of overall gastrointestinal adverse events, whereas our meta-analysis further identified that this new class of hypoglycemic agents was significantly associated with the higher risks of 4 kinds of digestive diseases (i.e., gastric ulcer hemorrhage, pancreatitis, cholangitis acute, and cholecystitis acute). In this meta-analysis, GLP1RAs was observed with the higher risks of cholangitis acute and cholecystitis acute, which is probably because GLP1RAs could increase the risk of cholelithiasis[30,31] and therefore led to the higher risks of cholangitis and cholecystitis. On the other hand, GLP1RAs was observed with the higher risk of gastric ulcer hemorrhage in this meta-analysis, which is probably associated with the fact that GLP1RAs has higher risk of gastrointestinal adverse events such as vomiting.[32,33] On the contrary, previous studies[33–35] did not show the significant association between use of GLP1RAs and risk of pancreatitis, whereas our meta-analysis showed this significant association. The reason for this is probably that our meta-analysis included more large sample randomized trials. However, further research is needed to determine this issue.

Because the trials which considered the occurrences of various digestive diseases as primary endpoints and meanwhile compared SGLT2is, DPP4is, or GLP1RAs with placebo or compared a new hypoglycemic drug with another were lacking, we conducted this meta-analysis by incorporating those trials which considered the occurrences of cardiorenal events as primary endpoints and conversely reported the occurrences of various digestive diseases as digestive adverse events. Thus, patients among the included trials had a high risk of developing cardiorenal events but did not have a high risk of various digestive diseases. This led to the very low incidences of various digestive diseases among included trials. Each study group among included trials had at least 1000 participants, which suggested the included trials with large sample sizes. However, the limited numbers of occurrences of various digestive diseases, to a large extent, attenuated the statistical power of this meta-analysis. This is the main limitation of this meta-analysis. On the contrary, only low risk of bias observed among included trials, no heterogeneity observed in most of the meta-analyses conducted in this study, and the robustness of meta-analysis results revealed by the similarity between fixed-effects results and random-effects results are the 3 main advantages of this study.

In general, neither SGLT2is nor DPP4is are associated with the occurrences of various kinds of digestive diseases, whereas GLP1RAs are associated with the higher risks of 4 kinds of digestive diseases, namely, gastric ulcer hemorrhage, pancreatitis, cholangitis acute, and cholecystitis acute. These findings seem to suggest that GLP1RAs are not applicable for patients at high risk of 4 specific digestive diseases whereas SGLT2is and DPP4is are safe for patients susceptible to digestive diseases. However, our findings require to be further verified by future studies with sufficient statistical power.

Author contributions

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Analysis: Jin-Hao Lin.
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All authors approved the manuscript.

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