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Occurrence of Gastrointestinal Adverse Events Upon GLP-1 Receptor Agonist Initiation With Concomitant Metformin Use: A Post Hoc Analysis of LEADER, STEP 2, SUSTAIN-6, and PIONEER 6

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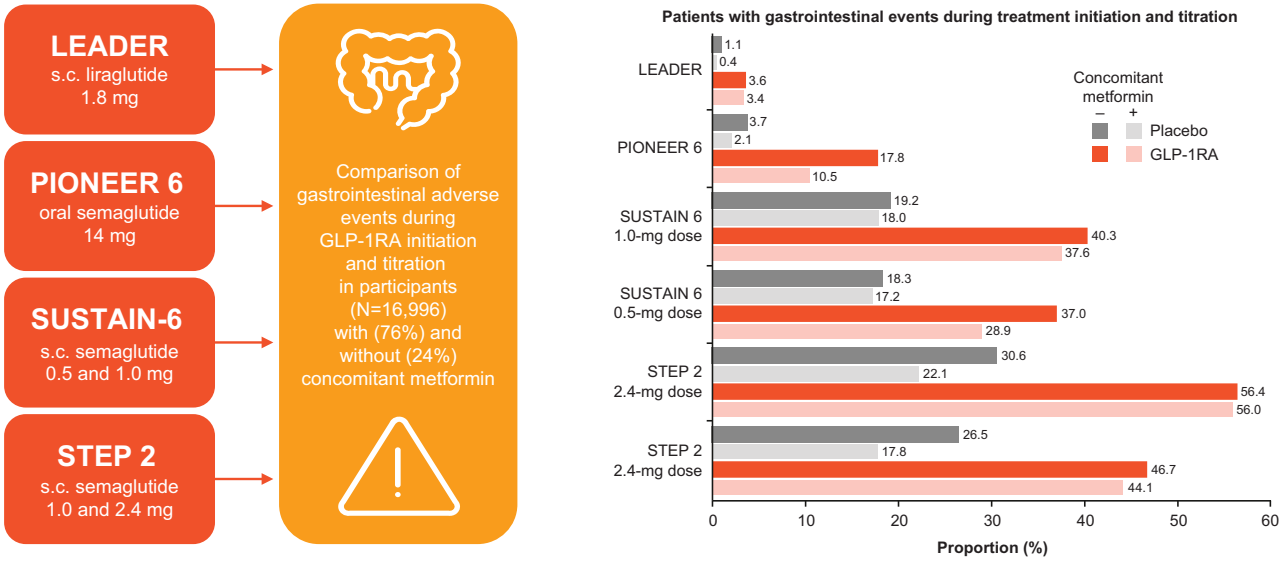

LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; STEP 2, Semaglutide Treatment Effect in People with Obesity; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; PIONEER 6, Peptide Innovation for Early Diabetes Treatment.

Concomitant metformin did not increase the frequency (primary end point) or severity of gastrointestinal adverse effects during GLP-1RA initiation or titration, and concomitant metformin did not increase GLP-1RA discontinuation

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Gastrointestinal (GI) symptoms are common adverse events reported with glucagon-like peptide 1 receptor agonists (GLP-1RAs) and metformin.
- **What is the specific question we wanted to answer?**
  Using four clinical trials evaluating GLP-1RAs (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], Semaglutide Treatment Effect in People with Obesity [STEP] 2, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], and Peptide Innovation for Early Diabetes Treatment [PIONEER] 6), we evaluated whether concomitant metformin use during GLP-1RA initiation and titration worsened GI symptoms.
- **What did we find?**
  Concomitant metformin use did not increase the occurrence or severity of GI adverse events during GLP-1RA initiation or titration. The percentage of participants randomized to a GLP-1RA who experienced GI adverse events and subsequently discontinued the study product was also similar regardless of metformin use.
- **What are the implications of our findings?**
  Metformin use during GLP-1RA initiation and titration is well tolerated, indicating that interruption of metformin prior to GLP-1RA initiation is unnecessary.

BRIEF REPORT

Occurrence of Gastrointestinal Adverse Events Upon GLP-1 Receptor Agonist Initiation With Concomitant Metformin Use: A Post Hoc Analysis of LEADER, STEP 2, SUSTAIN-6, and PIONEER 6

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OBJECTIVE

To assess the impact of concomitant metformin use on gastrointestinal adverse events during the initiation and titration of a glucagon-like peptide 1 receptor agonist (GLP-1RA).

RESEARCH DESIGN AND METHODS

Using data from four clinical trials of liraglutide and semaglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], Semaglutide Treatment Effect in People with Obesity [STEP 2], Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], and Peptide Innovation for Early Diabetes Treatment [PIONEER] 6), we compared the incidence of gastrointestinal adverse events during GLP-1RA initiation and titration in participants with and without concomitant metformin use.

RESULTS

Of 16,996 participants, 12,928 (76%) were treated with metformin. Concomitant metformin use did not increase the percentage of participants who developed gastrointestinal adverse events or their severity during the observation window. Among participants experiencing gastrointestinal adverse events, metformin use did not increase study product discontinuation. Within treatment arms (GLP-1RA and placebo), a numerically higher percentage of metformin nonusers experienced gastrointestinal adverse events and discontinued the study product compared with metformin users.

CONCLUSIONS

Concomitant metformin use does not increase occurrence of gastrointestinal symptoms during GLP-1RA initiation or impact GLP-1RA discontinuation.

Gastrointestinal (GI) adverse events associate with both metformin and glucagon-like peptide-1 receptor agonists (GLP-1RAs), two first-line agents for the treatment of type 2 diabetes that are frequently prescribed in combination. GLP-1RAs are initiated at a

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low dose and titrated to minimize the occurrence of GI symptoms. Still, most treatment-related GI adverse events occur during the dose titration period. Few analyses have examined whether concomitant metformin use exacerbates GLP-1RA–associated GI symptoms, and real-world data and meta-analyses of randomized controlled trials are inconsistent (1–3). Regardless, some experts suggest metformin discontinuation or dose reduction during GLP-1RA initiation (4). The purpose of this study was to examine whether concomitant metformin use exacerbates GLP-1RA–induced GI adverse events or increases early GLP-1RA discontinuation. Using data from four clinical trials examining GLP-1RA in type 2 diabetes (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], Semaglutide Treatment Effect in People with Obesity [STEP 2], Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], and Peptide Innovation for Early Diabetes Treatment [PIONEER] 6), we compared the incidence of GI adverse events during the GLP-1RA titration period in participants with and without concomitant metformin use and evaluated whether concomitant metformin use impacted study product discontinuation.

RESEARCH DESIGN AND METHODS

The trial designs for LEADER, STEP 2, SUSTAIN-6, and PIONEER 6 have been previously published (5–8). All studies analyzed were large, randomized, double-blind, placebo-controlled clinical trials assessing the safety and efficacy of GLP-1RA in people with type 2 diabetes and did not require participants to be treated with metformin at baseline. Efficacy outcomes varied by trial.

In this post hoc analysis, we evaluated GI adverse events during GLP-1RA initiation and titration until the maintenance dose was achieved. We chose this period because GI adverse events commonly start during GLP-1RA initiation, continue through titration, and resolve after the maintenance dose is reached (9). We defined the observation window as the time from GLP-1RA initiation until the day of the last titration plus four half-lives of the GLP-1RA (estimated time to achieve final steady state). The observation windows are shown in Table 1. LEADER evaluated liraglutide (half-life: 0.5 days; target dose 1.8 mg). STEP 2 and SUSTAIN-6 evaluated subcutaneous semaglutide (half-life: 7 days; STEP 2: target doses 1.0 and 2.4 mg and SUSTAIN-6: target doses 0.5 and 1.0 mg). PIONEER 6 evaluated oral semaglutide (half-life: 7 days; target dose 14 mg).

The primary end point was the percentage of participants with at least one GI adverse event during the observation window stratified by metformin use at baseline. Repeat events were not analyzed. We also evaluated specific events of clinical interest, including nausea, vomiting, and serious GI adverse events. Finally, we examined the number of participants experiencing GI adverse events who subsequently discontinued the study product at any time. Sensitivity analyses that evaluated a consistent 140-day window for all trials are provided in the Supplementary Material.

Because baseline metformin use was not randomized, statistical comparison between participants with or without metformin within the treatment arms (GLP-1RA and placebo) could not be made. Instead, we used a logistic regression to evaluate the effect of the randomized treatment on GI adverse events within subgroups of metformin users or nonusers. The logistic model used GI adverse events as the binary outcome and GLP-1RA, metformin, and an interaction term as predictors. A Wald test was used to test for significance of the interaction within each trial.

Table 1—Observation windows

	Half-life (days)	Escalation period (days)	Observation window (days)
LEADER	0.5	14	16
STEP 2			
1.0 mg semaglutide	7	56	84
2.4 mg semaglutide	7	112	140
SUSTAIN-6			
0.5 mg semaglutide	7	28	56
1.0 mg semaglutide	7	56	84
PIONEER 6	7	56	84

RESULTS

Of 16,996 participants in these four trials, 12,928 (76%) were treated with metformin at baseline. STEP 2 had a higher proportion of metformin users (89.6%) among all trials (LEADER: 74.7%, SUSTAIN-6: 73.2%, and PIONEER 6: 77.3%). Baseline characteristics are provided in Table 2 and were similar between treatment arms within the trials, except for the estimated glomerular filtration rate (eGFR). Participants treated with baseline metformin had a higher eGFR compared with those not treated with metformin in all trials except in STEP 2, where the eGFR was equivalent (metformin users: 95.7 mL/min/1.73 m^2, metformin nonusers: 92.9 mL/min/1.73 m^2). Differences in characteristics among trials, such as duration of type 2 diabetes, age, and presence of chronic kidney disease, reflected the eligibility criteria and the primary outcome of the specific trial.

The primary outcome is shown in Table 3. Across all trials, participants randomized to a GLP-1RA experienced more GI adverse events. However, concomitant metformin use did not increase the percentage of participants who developed any GI adverse event during the observation window. The coefficient for interaction was not significant for any study except LEADER (Table 3). Sensitivity analyses that evaluated a consistent 140-day window for all trials demonstrated the same trends, but the coefficient of variation was no longer significant for the LEADER trial (Supplementary Table 1). Concomitant metformin use was not associated with an increased risk of serious GI adverse events, nausea, or vomiting in any trial (Supplementary Tables 2–4).

Finally, we examined rates of premature study product discontinuation in participants who experienced any GI adverse event during GLP-1RA initiation and titration. As shown in Table 4, concomitant metformin use did not associate with increased discontinuation of the study product at any point during the trial. Instead, in both randomized arms, GLP-1RA and placebo, a numerically higher percentage of participants who were not treated with concomitant metformin discontinued the study product. The same trend in discontinuation was observed during the GLP-1RA initiation and titration

Table 2—Demographics

	LEADER		STEP 2		SUSTAIN-6		PIONEER 6	
	Metformin	No metformin	Metformin	No metformin	Metformin	No metformin	Metformin	No metformin
Male, *n* (%)	4,540 (65.2)	1,450 (61.6)	533 (48.9)	60 (50.8)	1,463 (60.7)	531 (60.6)	1,693 (68.8)	482 (66.9)
Age, years	63.9 (7.0)	65.4 (7.8)	55.3 (10.5)	55.6 (11.6)	63.9 (7.0)	66.4 (8.0)	66.4 (8.0)	67.8 (7.6)
Duration of duration, years	12.5 (7.7)	13.9 (8.9)	8.2 (6.1)	7.0 (5.7)	13.3 (7.7)	15.5 (8.9)	14.3 (8.2)	16.8 (9.5)
BMI, kg/m^2	32.5 (6.1)	32.6 (6.9)	35.7 (6.3)	36.2 (6.3)	32.8 (5.9)	32.9 (7.0)	31.9 (6.3)	33.6 (7.0)
HbA_{1c}, %	8.6 (1.5)	8.9 (1.6)	8.1 (0.8)	8.0 (0.7)	8.6 (1.4)	8.9 (1.5)	8.1 (1.6)	8.3 (1.6)
eGFR, mL/min/1.73 m^2	83.0 (19.2)	67.6 (25.8)	95.7 (18.7)	92.9 (16.9)	81.3 (19.4)	61.0 (25.1)	77.5 (19.4)	62.9 (22.1)

Data are mean (SD) unless otherwise stated; *n* = number of subjects exposed. eGFR was calculated with Chronic Kidney Disease Epidemiology Collaboration equation.

observation window (Supplementary Table 5).

CONCLUSIONS

GI adverse events are the most prevalent adverse effects associated with GLP-1RAs. Although largely temporary and mild-to-moderate in severity, GI adverse events lead to discontinuation of GLP-1RAs both in clinical trial programs and in the real world (5–8,10). Factors that modify the risk or severity of GI symptoms are not well established, but practical ways to mitigate GI adverse events and prevent GLP-1RA discontinuation are needed given the glycemic, weight loss, and cardiovascular benefits of GLP-1RAs that have made them a potential first-line therapy for type 2 diabetes and obesity (11–13). Although the mechanisms for GI intolerance are different, reasonable clinical concern exists that metformin use may exacerbate GLP-1RA–induced GI symptoms, as metformin alone can cause abdominal pain, cramps, and diarrhea (14). Whether metformin should be paused to promote successful GLP-1RA initiation remains an important clinical question. In this post hoc analysis of four large GLP-1RA trials in type 2 diabetes, we demonstrate that concomitant metformin use during GLP-1RA initiation does not associate with increased risk or severity of GI adverse events or premature discontinuation of study product. We did not evaluate simultaneous initiation of metformin and GLP-1RA.

Interestingly, in every study, the percentage of participants experiencing any GI adverse event was numerically higher in participants without concomitant metformin treatment, irrespective of randomization to GLP-1RA or placebo. We also found that of those who experienced GI adverse events, a higher percentage of participants without concomitant metformin treatment discontinued the study product in both treatment arms across all four studies. These data are consistent with real-world evidence from the U.K. suggesting metformin use associates with lower odds of GI adverse events or drug discontinuation among patients treated with GLP-1RA (2).

The reasons for this finding are likely multifactorial but may be due to increased baseline or susceptibility to GI symptoms. In LEADER, SUSTAIN-6, and PIONEER 6, people who were not treated with metformin had lower kidney function. As such, people without concomitant metformin treatment may reflect a sicker population with a greater symptom burden. Nonetheless, similar findings were seen in STEP 2, where the eGFR was equivalent between metformin users and nonusers. As metformin was considered the single first-line pharmacological therapy for type 2 diabetes when all four studies were enrolling (15), it is conceivable that participants who did not tolerate treatment with metformin may be more susceptible to GI adverse events independent of the study product. Techniques for mitigating GLP-1RA–induced GI symptoms, such as in-depth counseling and slow titration (4,9),

Table 3—Any GI adverse events

		GLP-1RA		Placebo		
Trial*	Total *n/N* (%)	Metformin *n/N* (%)	No metformin *n/N* (%)	Metformin *n/N* (%)	No metformin *n/N* (%)	*P* value for interaction
LEADER	188/9,321 (2.0)	117/3,447 (3.4)	43/1,210 (3.6)	15/3,520 (0.4)	13/1,144 (1.1)	0.026
STEP 2						
1.0 mg semaglutide	254/804 (31.6)	164/372 (44.1)	14/30 (46.7)	63/353 (17.8)	13/49 (26.5)	0.436
2.4 mg semaglutide	319/805 (39.6)	204/364 (56.0)	22/39 (56.4)	78/353 (22.1)	15/49 (30.6)	0.371
SUSTAIN-6						
0.5 mg semaglutide	543/2,467 (22.0)	178/615 (28.9)	77/208 (37.0)	207/1,202 (17.2)	81/442 (18.3)	0.191
1.0 mg semaglutide	615/2,463 (25.0)	223/593 (37.6)	91/226 (40.3)	216/1,202 (18.0)	85/442 (19.2)	0.894
PIONEER 6	233/3,182 (7.3)	128/1,221 (10.5)	66/370 (17.8)	26/1,241 (2.1)	13/350 (3.7)	0.942

n = number of subjects with event; *N* = total number of subjects exposed. *Differences in adverse event data collection explain the lower number of adverse events in the LEADER and PIONEER 6 trials. STEP 2 and SUSTAIN-6 evaluated two doses of semaglutide, which were analyzed separately. Doses are indicated in the table.

Table 4—Participants with any GI adverse event during the observation window treated with and without metformin who discontinued study product at any time during the trial

		GLP-1RA		Placebo	
Trial*	Total *n*/*N* (%)	Metformin *n*/*N* (%)	No metformin *n*/*N* (%)	Metformin *n*/*N* (%)	No metformin *n*/*N* (%)
LEADER**	103/188 (54.8)	62/117 (53.0)	29/43 (67.4)	7/15 (46.7)	5/13 (38.5)
STEP 2					
1.0 mg semaglutide	38/254 (15.0)	24/164 (14.6)	4/14 (28.6)	5/63 (7.9)	5/13 (38.5)
2.4 mg semaglutide	44/319 (13.8)	28/204 (13.7)	2/22 (9.1)	8/78 (10.3)	6/15 (40.0)
SUSTAIN-6					
0.5 mg semaglutide	156/543 (28.7)	53/178 (29.8)	29/77 (37.7)	52/207 (25.1)	22/81 (27.2)
1.0 mg semaglutide	182/615 (29.6)	76/223 (34.1)	31/91 (34.1)	52/216 (24.1)	23/85 (27.1)
PIONEER 6	116/233 (49.8)	63/128 (49.2)	33/66 (50.0)	11/26 (42.3)	9/13 (69.2)

n = number of subjects with event; *N* = total number of subjects exposed with a GI adverse event within the observation window. *Differences in adverse event data collection explain the lower number of adverse events in the LEADER and PIONEER 6 trials. **Discontinuation in the LEADER trial is different from the other trials as it only captures drug withdrawn due to an adverse event. STEP 2 and SUSTAIN-6 evaluated two doses of semaglutide, which were analyzed separately. Doses are indicated in the table.

may be necessary in individuals with a low eGFR or those who did not tolerate metformin.

In all studies, we compared active treatment to placebo within the two metformin subgroups (metformin users and metformin nonusers) and demonstrated no statistical difference in three trials. Although there were few GI adverse events within the short observation window of liraglutide (16 days) and a numerically higher percentage of GI adverse events in metformin nonusers, the analysis suggested a statistically significant increase in GI adverse events in participants treated with metformin. The marked difference in pharmacokinetics between liraglutide and semaglutide could account for this difference. However, it is more likely that the statistical significance of this finding is due to the small sample size resulting from the method of adverse event collection. Accordingly, statistical significance was not observed in the sensitivity analysis that included more adverse events by extending the observation to 140 days. Consistently, although a prior meta-analysis suggested statistically significant increased GI-adverse events in people treated with concomitant metformin, this was largely mediated by short-acting GLP-1RAs (exenatide, lixisenatide), as no statistically significant increase in GI adverse events was seen with longer-acting GLP-1RAs like liraglutide (1).

Taken together, these data indicate that concomitant metformin use does not exacerbate GLP-1RA–induced GI symptoms and suggest that metformin discontinuation or dose reduction is unnecessary. Instead, although counseling about GI symptoms is necessary in all patients, increased counseling or slowed titration may be necessary in metformin nonusers.

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References

1. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. Diabetes Obes Metab 2017;19:336–347

2. Thong KY, Gupta PS, Blann AD, Ryder RE. The influence of age and metformin treatment status on reported gastrointestinal side effects with liraglutide treatment in type 2 diabetes. Diabetes Res Clin Pract 2015;109:124–129

3. Wu H, Lu Z, Chen R, et al. Factors associated with gastrointestinal side effects after liraglutide treatment for type 2 diabetes. Front Endocrinol (Lausanne) 2023;14:1098032

4. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with Glp-1 receptor agonists: a multidisciplinary expert consensus. J Clin Med 2022;12:145

5. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971–984

6. Husain M, Birkenfeld AL, Donsmark M, et al.; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–851

7. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

8. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–322

9. Wharton S, Davies M, Dicker D, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. Postgrad Med 2022;134:14–19

10. Sikirica MV, Martin AA, Wood R, Leith A, Piercy J, Higgins V. Reasons for discontinuation of GLP1 receptor agonists: data from a real-world cross-sectional survey of physicians and their patients with type 2 diabetes. Diabetes Metab Syndr Obes 2017;10:403–412

11. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes,

2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786
12. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Care in Diabetes—2023*. Diabetes Care 2023; 46(Suppl. 1):S140–S157
13. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet 2022;399: 394–405
14. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes Obes Metab 2017;19:473–481
15. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S111–S124