Comprehensive analysis of the safety of semaglutide in type 2 diabetes: a meta-analysis of the SUSTAIN and PIONEER trials

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Abstract. The PIONEER and SUSTAIN serial trials are designed to assess the efficacy outcomes with semaglutide in patients with type 2 diabetes, but are not powered to assess various safety outcomes. We sought to assess the risk of semaglutide in leading to various serious adverse events (SAEs) in patients with type 2 diabetes. Studies eligible for inclusion were the PIONEER and SUSTAIN trials of semaglutide. We conducted meta-analysis to generate pooled risk ratios (RRs) and 95% confidence intervals (CIs). Meta-analysis was performed using both random-effects and fixed-effects model to evaluate the robustness of pooled results. We implemented subgroup analysis according to drug dosages and routes of administration and type of comparators. Twenty-one trials were included. Semaglutide \textit{versus} control significantly reduced total SAEs (RR 0.92, 95% CI 0.87–0.97; \(I^2 = 0\)) and atrial fibrillation (RR 0.69, 95% CI 0.50–0.95; \(I^2 = 0\)), but significantly increased deep vein thrombosis (RR 3.66, 95% CI 1.09–12.25; \(I^2 = 0\)) and diarrhoea (RR 2.66, 95% CI 1.19–5.95; \(I^2 = 0\)). Semaglutide had no significant effects on 248 other kinds of SAEs. No statistically significant subgroup effects were observed. Semaglutide has a good safety profile in general and reduces atrial fibrillation by 31%, but increases diarrhoea by 166% and deep vein thrombosis by 266%. These findings may guide that semaglutide should be preferred or avoided in T2D patients with specific susceptibility factors.

Key words: Semaglutide, Safety, Type 2 diabetes, PIONEER, SUSTAIN

SEMAGLUTIDE, as a glucagon-like peptide-1 receptor agonist (GLP1RA), is one of the new antihyperglycemic agents, and can be used as once-daily oral semaglutide or once-weekly subcutaneous semaglutide. A series of PIONEER trials [1-10] have confirmed oral semaglutide with the distinct efficacy on control of glycated hemoglobin and reduction of body weight in patients with type 2 diabetes (T2D), while a series of SUSTAIN trials [11-21] have confirmed subcutaneous semaglutide with that efficacy. Furthermore, the PIONEER 6 trial [5] and the SUSTAIN 6 trial [16] have identified the benefits on the cardiovascular and renal endpoints respectively from oral semaglutide and subcutaneous semaglutide. Because these studies [1-21] are designed to assess the efficacy endpoints, none of them has the sufficient statistical power to assess the safety endpoints. Thus, we carried out this meta-analysis based on the PIONEER [1-10] and SUSTAIN [11-21] serial trials, using various serious adverse events (SAEs) related to various systems of the human body as study endpoints, to fully assess the safety of semaglutide in T2D patients.

Methods

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol for this meta-analysis is available at https://inplasy.com/inplasy-2020-11-0013.

We searched Embase, PubMed, and ClinicalTrials.gov for related studies published before October 20th, 2020. Studies eligible for inclusion were PIONEER trials and SUSTAIN trials assessing semaglutide in T2D patients.
The interventions of interest were semaglutide used at different dosages via different routes of administration: oral semaglutide (3 mg/day), oral semaglutide (7 mg/day), oral semaglutide (14 mg/day), subcutaneous semaglutide (0.5 mg/week), and subcutaneous semaglutide (1.0 mg/week). The comparators of interest were non-semaglutide GLP1RA antihyperglycemic drug, non-GLP1RA antihyperglycemic drug, and placebo. The endpoints of interest were various SAEs which were assessed in at least three of the SUSTAIN and PIONEER trials. Two authors independently assessed the quality of included trials according to the Cochrane risk of bias assessment tool, and independently extracted the original data from the ClinicalTrials.gov website or the full texts of included studies. Any disagreements between them would be resolved by discussion with a third author.

We performed meta-analysis using the study-level binary data (i.e., the numbers of events and subjects in the intervention group and in the control group) to generate pooled risk ratios (RRs) and 95% confidence intervals (CIs). Both random-effects meta-analysis and fixed-effects meta-analysis was conducted to examine the robustness of pooled results. I² statistic was calculated to assess heterogeneity. Subgroup analysis on all the endpoints of interest was conducted stratified by different drug dosages and routes of administration and different comparators. We detected subgroup effects by Cochran’s Q test. All statistical analyses were done in the Stata software (version 15.1).

Results

In this study we included a total of 21 randomized trials [1-21], consisting of 10 PIONEER trials [1-10] assessing oral semaglutide and 11 SUSTAIN trials [11-21] assessing subcutaneous semaglutide and involving a total of 12,260 semaglutide users and 14,176 comparators. All the studies included were with low risk of bias. SAEs which were assessed in at least three of the included trials were 252 kinds of SAEs, which are detailed in Supplementary Table 1. Thus, this study evaluated the risk of semaglutide in leading to the 252 kinds of SAEs.

Supplementary Table 2 summarizes the results of all the meta-analysis and subgroup analysis. Fixed effects meta-analysis revealed, compared with control semaglutide significantly increased the risk of deep vein thrombosis (RR 3.66, 95% CI 1.09–12.25; I² = 0; p for drug effect = 0.036) and diarrhea (RR 2.66, 95% CI 1.19–5.95; I² = 0; p for drug effect = 0.018) whereas semaglutide significantly reduced the risk of atrial fibrillation (RR 0.69, 95% CI 0.50–0.95; I² = 0; p for drug effect = 0.025) and total SAEs (RR 0.92, 95% CI 0.87–0.97; I² = 0; p for drug effect = 0.005). Semaglutide showed the increased trend in the risk of dehydration (RR 2.16, 95% CI 0.94–5.00; I² = 0; p for drug effect = 0.071), intestinal obstruction (RR 4.23, 95% CI 0.85–20.94; I² = 0; p for drug effect = 0.077), and ventricular tachycardia (RR 2.18, 95% CI 0.87–5.43; I² = 3.4%; p for drug effect = 0.095); whereas semaglutide showed the reduced trend in the risk of cerebrovascular accident (RR 0.52, 95% CI 0.24–1.13; I² = 0; p for drug effect = 0.098), coronary artery bypass (RR 0.60, 95% CI 0.34–1.07; I² = 0; p for drug effect = 0.086), diabetes mellitus inadequate control (RR 0.54, 95% CI 0.28–1.05; I² = 0; p for drug effect = 0.070), and septic shock (RR 0.37, 95% CI 0.12–1.15; I² = 0; p for drug effect = 0.085). Semaglutide had a neutral effect on the occurrence of the other 241 kinds of SAEs (I² ranged from 0 to 40.9% with most of the I² values = 0, and p for drug effect ranged from 0.108 to 0.995). Random effects meta-analysis revealed the consistent results. The results of all the overall meta-analyses are detailed in Figs. S1-S252. The effects of semaglutide on the occurrence of the 252 kinds of SAEs were consistent across different drug dosages and routes of administration (P_subgroup ≥ 0.137) and across different comparators (P_subgroup ≥ 0.062). The results of all the subgroup analyses stratified by drug dosages and routes of administration are detailed in Figs. S253-S504, and those stratified by type of comparators are detailed in Figs. S505-S756.

Discussion

This study is the first one that performed a comprehensive analysis on the safety of semaglutide in T2D patients by meta-analysis of the effects of semaglutide on the occurrence of 252 kinds of SAEs. Accordingly, this study produces three key findings.

First, semaglutide versus control reduced the risk of total SAEs by 8% (RR 0.92) and atrial fibrillation by 31% (RR 0.69), and showed the reduced trend in the risk of septic shock; whereas semaglutide increased the risk of deep vein thrombosis by 266% (RR 3.66), and showed the increased trend in the risk of ventricular tachycardia. An updated meta-analysis [22] found that incorporates GLP1RAs did not increase the risk of atrial fibrillation, but failed to assess individual GLP1RAs. In this study we revealed a GLP1RA semaglutide with a 31% reduction in the risk of atrial fibrillation.

Second, semaglutide increased the risk of diarrhea by 166% (RR 2.66), and showed the increased trend in the risk of dehydration and intestinal obstruction. This finding suggests that, just like other GLP1RAs, when using semaglutide we should be concerned with the gastrointestinal adverse events.

Third, semaglutide showed the reduced trend in the
risk of cerebrovascular accident, coronary artery bypass, and diabetes mellitus inadequate control. This finding could be supported by the efficacy of semaglutide in reducing cardiovascular endpoints and control of glycated hemoglobin. Moreover, the present study also revealed that semaglutide had a neutral effect on the occurrence of 241 other kinds of SAEs including renal SAEs. Similarly, a recent study [23] based on a post-hoc analysis of the SUSTAIN 1–7 trials suggests no increase in the risk of kidney adverse events with semaglutide.

Since semaglutide was observed to increase the risk of both diarrhoea and deep vein thrombosis in this meta-analysis, and diarrhoea or dehydration can lead to the increase in blood viscosity, semaglutide increases the risk of deep vein thrombosis possibly due to increasing that of diarrhoea. Moreover, whether an increase in deep vein thrombosis is related to a decrease in body weight also needs to be further investigated. It is believed that a decrease in body weight contributes to a decrease in heart failure, which atrial fibrillation often leads to. Thus, semaglutide leads to a decrease in body weight, which probably leads to the decreases in atrial fibrillation and heart failure. According to the findings of included trials, compared with control semaglutide had a much better effect of glycemic control, which resulted in the reduced risks of relevant SAEs with semaglutide versus control. Therefore, our present meta-analysis identified the reduced risk of total SAEs with semaglutide versus control.

One of the strengths of this study is that most of the meta-analyses conducted in the study were with no heterogeneity and few of them were with mild to moderate heterogeneity. On the contrary, a limitation of this study is that a few endpoints were assessed with insufficient statistical power due to wide 95% CIs of RRs. Another limitation is that the present meta-analysis failed to address SAEs associated with long-term use of semaglutide since the follow-up duration of most trials included was 1 year or less.

In conclusion, semaglutide has a good safety profile in general and reduces atrial fibrillation by 31%, but increases diarrhoea by 166% and deep vein thrombosis by 266%. These findings may guide that semaglutide should be preferred or avoided in T2D patients with specific susceptibility factors.

**Figures**

Figures S1–S252 Meta-analysis of the effects of semaglutide on the occurrence of 252 kinds of serious adverse events

Figures S253–S504 Meta-analysis of the effects of semaglutide on the occurrence of 252 kinds of serious adverse events, stratified by drug dosages and routes of administration

Figures S505–S756 Meta-analysis of the effects of semaglutide on the occurrence of 252 kinds of serious adverse events, stratified by type of comparators

Figures S1–S756 are available at https://doi.org/10.6084/m9.figshare.13565084.

**Compliance with Ethical Standards**

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**Conflicts of interest**

All authors declare that they have no conflicts of interest.

**Ethical approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent**

Informed consent was not required because this article does not contain any studies with human participants performed by any of the authors.

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