Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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BRIEF ORIGINAL

Meta-analysis evaluating the risk of respiratory tract infections and acute respiratory distress syndrome with glucagon-like peptide-1 receptor agonists in cardiovascular outcome trials: Useful implications for the COVID-19 pandemic☆

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Abstract Patients with type 2 diabetes mellitus (T2DM) are at increased risk for severe coronavirus disease 2019 (COVID-19) and related mortality. Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) have significant cardiovascular and renal benefits for patients with T2DM and related comorbidities. Their anti-inflammatory properties could be beneficial in these patients. This work provides less-biased estimates regarding the risk for respiratory tract infections and acute respiratory distress syndrome by performing the first significant meta-analysis of cardiovascular outcome trials in the literature. Notably, GLP-1-RAs do not seem to increase the risk for respiratory tract infection, pneumonia, or acute respiratory distress syndrome in patients with T2DM and cardiovascular comorbidities.

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PALABRAS CLAVE
Agonistas del receptor del péptido similar al glucagón tipo 1;
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COVID-19;
Infección respiratoria;
Neumonía

Metaanálisis para evaluar el riesgo de infecciones respiratorias y síndrome de distrés respiratorio del adulto con los agonistas del receptor del péptido similar al glucagón tipo 1 en los ensayos de seguridad cardiovascular: consecuencias útiles para la pandemia de COVID-19

Resumen Los pacientes con diabetes mellitus tipo 2 (DMT2) presentan un mayor riesgo de sufrir una enfermedad grave por coronavirus 2019 (COVID-19) con un incremento de la mortalidad relacionada. Los agonistas del receptor del péptido similar al glucagón tipo 1 (AR-GLP-1) ejercen efectos cardiovasculares y renales beneficiosos en los pacientes con DMT2 de alto riesgo cardiovascular. Sus propiedades antiinflamatorias podrían resultar beneficiosas en estos pacientes. El presente estudio es un metaanálisis sobre el riesgo de infección respiratoria y distrés respiratorio del adulto causado por AR-GLP-1 utilizando como fuente los ensayos clínicos de seguridad cardiovascular publicados en la bibliografía. Hay que destacar que los AR-GLP-1 no parecen aumentar el riesgo de infección respiratoria, neumonía ni síndrome de distrés respiratorio del adulto en los pacientes con DMT2 y alto riesgo cadiovascular.

Introduction

Patients with type 2 diabetes mellitus (T2DM) experience an increased risk for severe coronavirus disease 2019 (COVID-19) infection, with obesity, cardiovascular disease, and chronic kidney disease representing independent risk factors for COVID-19 related mortality.[1,2] As shown in a recent meta-analysis of observational studies published in Primary Care Diabetes, patients with COVID-19 and diabetes have a two-fold increase in the risk for severe disease and related death.[3]

Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) provide significant cardiovascular and renal benefits for patients with T2DM and related co-morbidities. They have therefore been proposed as a second-line treatment option, according to recent recommendations.[4] However, their continuation among patients with COVID-19 infection has been argued due to their potential to lead to dehydration, mainly in the context of gastrointestinal adverse events.[5] Their anti-inflammatory properties could prove beneficial for those patients, even though there are no studies so far addressing their efficacy in COVID-19 patients.[6,7] GLP-1-RAs have been shown to upregulate angiotensin-converting enzyme 2 (ACE2); however, the clinical implications of this effect remain unclear.[8]

We sought to provide the less biased effect estimates regarding the impact of this antidiabetic drug class on major outcomes of interest, namely upper and lower respiratory tract infection, viral infection, influenza, and acute respiratory distress syndrome (ARDS), by pooling corresponding data from the relevant hallmark cardiovascular outcome trials.[9–15]

Methods

Two independent reviewers (D.P. and A.B.) extracted the data from the eligible reports (along with data provided in supplementary appendices and grey literature sources, mainly Clinicaltrials.gov) by using a pilot-tested data extraction form.

As we assessed only dichotomous variables, differences were calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel ((M-H)) random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0% and 25%, moderate if I^2 was between 25% and 50%, or high if I^2 was greater than 75%.[16] All analyses were performed at the 0.05 significance level while undertaken with RevMan 5.3 software.[17]

Two independent reviewers (D.P. and C.P.) assessed the quality of the included RCTs by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary safety outcomes, namely upper and lower respiratory tract infections.[18] Each domain was rated as low, unclear, or high risk of bias. The presence of adequate procedures in all domains rated a study as being of low risk of bias, while inadequate procedure in at least one domain rated a study as being of high risk of bias. Discrepancies between reviewers were solved by discussion, consensus, or arbitration by a third senior reviewer (M.D.).

Results

GLP-1-RA treatment resulted in a non-significant decrease in the risk for upper respiratory tract infection, equal to 19% (RR = 0.81, 95% CI; 0.64–1.02, I^2 = 0%), as shown in Fig. 1 and a non-significant increase in the risk for lower respiratory tract infection, equal to 3% (RR = 1.03, 95% CI; 0.63–1.68, I^2 = 0%), as shown in Fig. 2.

All cardiovascular outcome trials except for the EXSCEL trial provided relevant numeric data concerning the incidence of upper and lower respiratory tract infections across the different treatment arms. Notably, GLP-1-RA treat-

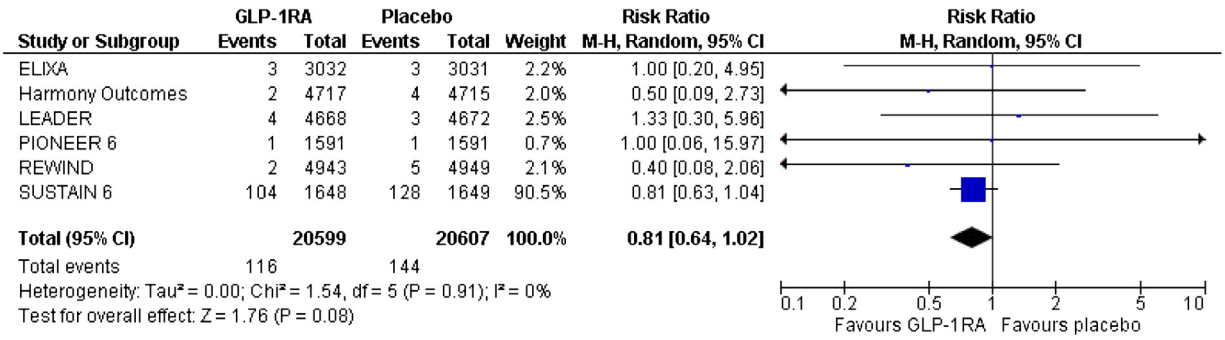

Figure 1 Effect of GLP-1-RA treatment compared to placebo on the risk for upper respiratory tract infection.

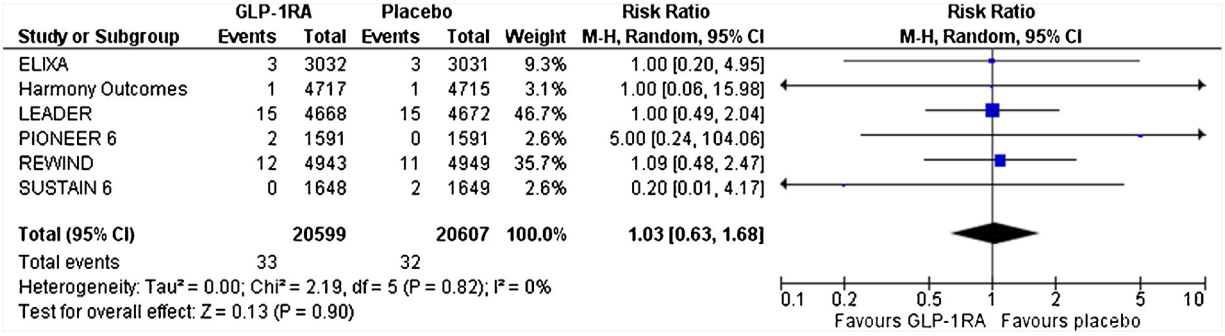

Figure 2 Effect of GLP-1-RA treatment compared to placebo on the risk for lower respiratory tract infection.

ment decreased the risk for influenza infection (RR = 0.60, 95% CI; 0.32–1.12, I^2 = 0%), pneumonia (RR = 0.89, 95% CI; 0.78–1.01, I^2 = 0%) and ARDS (RR = 0.51, 95% CI; 0.13–2.08, I^2 = 0%), although none of the observed effects reached statistical significance. Finally, GLP-1RA treatment led to a non-significant increase in the risk of viral infection (RR = 1.77, 95% CI; 0.65–4.80, I^2 = 0%).

The risk of bias for each assessed domain and overall risk of bias was low across all selected trials. Unfortunately, EXSCEL trial's rating was not applicable for the primary safety outcome since trialists did not provide numeric data regarding the incidence of upper and lower respiratory tract infections across the two treatment arms (exenatide and placebo).

Conclusion

Collectively, GLP-1-RAs do not seem to increase the risk for respiratory tract infection, pneumonia, or ARDS in patients with T2DM and cardiovascular co-morbidities. Therefore, they could be a safe treatment option for patients with COVID-19 disease.

Well-designed, prospective trials will elucidate their place in managing hospitalized COVID-19 patients and whether they could provide additional benefits besides maintaining adequate glycemia.

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Conflicts of interest

The authors declare no conflicts of interest.

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