Original Investigation

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Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases

A Systematic Review and Meta-analysis of Randomized Clinical Trials

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Editorial Comment

Key Points

Question What is the association of glucagon-like peptide-1 receptor agonist (GLP-1 RAs) use with the risk of gallbladder or biliary diseases?

Finding This systematic review and meta-analysis of 76 randomized clinical trials found that use of GLP-1 RAs was associated with increased risk of gallbladder or biliary diseases, especially when used at higher doses, for longer durations, and for weight loss.

Meanings The findings of this systematic review and meta-analysis indicate that physicians and patients should be concerned about the risks of gallbladder or biliary diseases with using GLP-1 RAs for treatment in clinical practice; future studies should report on associated gallbladder and biliary diseases.

Abstract

Importance Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been widely recommended for glucose control and cardiovascular risk reduction in patients with type 2 diabetes, and more recently, for weight loss. However, the associations of GLP-1 RAs with gallbladder or biliary diseases are controversial.

Objective To evaluate the association of GLP-1 RA treatment with gallbladder and biliary diseases and to explore risk factors for these associations.

Data Sources MEDLINE/PubMed, EMBASE, Web of Science, and Cochrane Library (inception to June 30, 2021), websites of clinical trial registries (July 10, 2021), and reference lists. There were no language restrictions.

Study Selection Randomized clinical trials (RCTs) comparing the use of GLP-1 RA drugs with placebo or with non–GLP-1 RA drugs in adults.

Data Extraction and Synthesis Two reviewers independently extracted data according to the PRISMA recommendations and assessed the quality of each study with the Cochrane Collaboration risk-of-bias tool. Pooled relative risks (RRs) were calculated using random or fixed-effects models, as appropriate. The quality of evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework.

Main Outcomes and Measures The primary outcome was the composite of gallbladder or biliary diseases. Secondary outcomes were biliary diseases, biliary cancer, cholecystectomy, cholecystitis, and cholelithiasis. Data analyses were performed from August 5, 2021, to September 3, 2021.

Results A total of 76 RCTs involving 103 371 patients (mean [SD] age, 57.8 (6.2) years; 41 868 [40.5%] women) were included. Among all included trials, randomization to GLP-1 RA treatment was associated with increased risks of gallbladder or biliary diseases (RR, 1.37; 95% CI, 1.23-1.52); specifically, cholelithiasis (RR, 1.27; 95% CI, 1.10-1.47), cholecystitis (RR, 1.36; 95% CI, 1.14-1.62), and biliary disease (RR, 1.55; 95% CI, 1.08-2.22). Use of GLP-1 RAs was also associated with increased risk of gallbladder or biliary diseases in trials for weight loss (n = 13; RR, 2.29; 95% CI, 1.64-3.18) and for type 2 diabetes or other diseases (n = 63; RR, 1.27; 95% CI, 1.14-1.43; P <.001 for interaction). Among all included trials, GLP-1 RA use was associated with higher risks of gallbladder or biliary diseases at higher doses (RR, 1.56; 95% CI, 1.36-1.78) compared with lower doses (RR, 0.99; 95% CI, 0.73-1.33; P = .006 for interaction) and with longer duration of use (RR, 1.40; 95% CI, 1.26-1.56) compared with shorter duration (RR, 0.79; 95% CI, 0.48-1.31; P = .03 for interaction).

Conclusions and Relevance This systematic review and meta-analysis of RCTs found that use of GLP-1 RAs was associated with increased risk of gallbladder or biliary diseases, especially when used at higher doses, for longer durations, and for weight loss.

Invited Commentary

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