Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis

Highlights

- GLP-1 receptor agonists were associated with modest reduction on blood pressure.
- GLP-1 receptor agonists were associated with a slight increase in heart rate.
- GLP-1 receptor agonists are not associated with significant improvement in hypertension.

Abstract

Aims

To evaluate current evidence of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on blood pressure, heart rate, and hypertension in patients with type 2 diabetes.

Methods

Medline, Embase, the Cochrane library, and the website www.clinicaltrials.gov were searched on April 5th, 2014. Randomized-controlled trials with available data were included if they compared GLP-1RAs with placebo and traditional antidiabetic drugs in patients with type 2 diabetes with duration ≥ 12 weeks. Weighted mean difference for blood pressure and heart rate, odds ratio (OR) for hypertension were calculated by random-effect model. Network meta-analysis was performed to supplement direct comparisons.

Results

Sixty trials with 14 treatments were included. Compared with placebo, insulin, and sulfonylureas, GLP-1RAs decreased systolic blood pressure with range from −1.84 mmHg (95% CI: −3.48 to −0.20) to −4.60 mmHg (95% CI: −7.18 to −2.03). Compared with placebo, a reduction in diastolic blood pressure was detected significantly only for exenatide-10 μg-twice-daily (−1.08 mmHg, 95% CI: −1.78 to −0.33). Exenatide (2 mg once weekly), liraglutide 1.2 mg once daily), and liraglutide (1.8 mg once daily) increased heart rate by 3.35 (95% CI: 1.23–5.50), 2.06 (95% CI: 0.43, 3.74), and 2.35 (95% CI: 0.94–3.76) beats/min versus placebo. This effect was evident compared with active control (range: 2.22–3.62). No significant association between incident hypertension and GLP-1RAs was detected, except for the association between exenatide-10 μg-twice-daily and sulfonylureas (OR, 0.40, 95% CI: 0.16, 0.82)

Conclusions

GLP-1RAs were associated with modest reduction on blood pressure, a slight increase in heart rate, yet no significant association with hypertension. Further investigation to explore mechanisms is warranted.

Keywords

GLP-1 receptor agonists; Type 2 diabetes; Network meta-analysis; Blood pressure; Heart rate; Hypertension

Introduction

An increasing number of patients with type 2 diabetes mellitus (T2DM) are being treated with glucagon-like peptide-1 receptor agonists (GLP-1RAs), a new class of antidiabetic agents based on incretin therapy [1], [2]. GLP-1RAs are analogs of GLP-1, which could stimulate insulin secretion, improve insulin resistance and slow down gastrointestinal motility [3], [4], [5]. Exenatide (Byetta; Eli Lilly & Co.) and liraglutide (Victoz; Novo Nordisk), the two earliest GLP-1 RAs, were approved by the United States Food and Drug Administration (FDA) in 2005 and 2010, respectively. Albiglutide (Eperzan, GSK) and lixisenatide (Lyxumia, Sanofi) were approved by the European Medical Agency in 2013. Dulaglutide (Trulicity, Eli Lilly) was also approved by FDA for use in the United States in September 2014.

Among patients with T2DM, hypertension is a very common complication, affecting almost three-quarters of T2DM patients [6], [7], [8]. The combination of poorly controlled blood pressure and blood glucose would greatly increase the risk of cardiovascular complications such as heart failure, myocardial infarction, and stroke [9]. A reduction of approximately 5 mm Hg in systolic blood pressure was considered to be associated with decreased risk of major cardiovascular events and death [10]. On the other hand, the effect of heart rate on cardiovascular complications in patients with T2DM cannot be neglected either; relevant studies have shown that raised heart rate was potentially associated with a higher cardiovascular risk [11], [12], [13]. Therefore, it is important to better control these cardiovascular risk factors, including blood pressure and heart rate, for patients with T2DM to achieve favorable cardiovascular safety profiles. Indeed, several clinical trials and meta-analyses for GLP-1RAs have demonstrated the blood pressure lowering effect as well as raised heart rate, although the mechanisms are not very clearly understood [14], [15], [16], [17]. However, all of them evaluated head-to-head comparisons of different GLP-1RAs versus placebo or active comparators, and most of them only evaluated exenatide and liraglutide. So far, few studies included all GLP-1RAs simultaneously to assess if there are differences on blood pressure and heart rate between any two of them. Furthermore, none of the analyses evaluated the impact of different dosages on blood pressure and heart rate within each GLP-1RA.

This study aimed to evaluate current evidence of GLP-1RAs on blood pressure, heart rate, and hypertension in patients with T2DM. Additional network meta-analysis was conducted to assess the robustness of the pairwise meta-analysis, supplement missing evidence of head-to-head comparisons by combining both direct and indirect evidence and rank treatments in the evidence network.

Section snippets

Materials and methods

The protocol was registered in PROSPERO, registration number CRD42014009019. …

Study characteristics and evidence network

60 trials involving 14 treatments met the selection criteria. A total of 26,654 patients were included in the analysis. Flow chart of trials selection was shown in Fig. 1.

Discussion

In addition to adequate glycemic control, increasing attention is being paid to the cardiovascular protective effect of GLP-1RAs [16], [25], [26]. Our network meta-analysis suggested that liraglutide (LIR1.2 and LIR1.8), exenatide (EX10BID and EX2QW), and Albi30QW induced a small but significant reduction in SBP compared with placebo and active comparators. In terms of DBP reduction, EX10BID had a significant DBP lowering effect compared with either placebo or insulin. This was accompanied by a…

Conflict of interest

None declared.

Contributor statements

FS and SY designed the study and revised the manuscript. SSW, LSL, XCQ, and KY extracted the data, SSW, ZRY, YZ, and KY evaluated the RCTs quality. SXG and ZRY verified the data, FS and SSW analyzed the data and wrote the manuscript, LNJ and SYZ contributed to interpreting the results, draft reviewing, and finalizing the paper.

Study registration

PROSPERO Identifier, CRD42014009019.

Declaration of interests

The authors have nothing to disclose.

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