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The Influence of Liraglutide for Heart Failure: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: The efficacy of liraglutide to treat heart failure remains controversial. We conducted a systematic review and meta-analysis to explore the influence of liraglutide on heart failure.

Methods: We searched PubMed, EMbase, Web of Science, EBSCO, and Cochrane library databases through March 2018 for randomized controlled trials (RCTs) assessing the effect of liraglutide on cardiac function of heart failure. Meta-analysis is performed using the random-effect model.

Results: Four RCTs involving 629 patients are included in the meta-analysis. Overall, compared with the control group for heart failure, liraglutide treatment significantly can reduce NT-proBNP (Std. MD = -3.06; 95% CI = -5.78 to -0.34; *P* = .03), and improve 6MWT (Std. MD=1.10; 95% CI = 0.75 to 1.44; *P* < .00001), but has no remarkable influence on LVEF change (Std. MD=1.10; 95% CI = -1.97 to 3.98; *P* = 0.51), LVEDV change (Std. MD = 6.26; 95% CI = -1.45 to 13.97; *P* = .11), LVESV change (Std. MD = -13.47; 95% CI = -31.04 to 4.10; *P* = .13), hospitalization for heart failure (RR = 1.18; 95% CI = 0.88 to 1.58; *P* = .27), major adverse cardiovascular events (RR = 1.55; 95% CI = -0.24 to 9.89; *P* = .64), and cardiac death (RR = 1.11; 95% CI = 0.61 to 2.04; *P* = .72).

Conclusions: Liraglutide treatment has an important ability to reduce NT-proBNP and improve 6MWT for heart failure, but shows no important influence on LVEF, LVEDV, LVESV, hospitalization for heart failure, major adverse cardiovascular events, and cardiac death.

INTRODUCTION

Patients with heart failure have markedly impaired quality of life and high mortality [Matsushita 2018; Chatterjee 2018; Vanderpool 2018]. Angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone are widely used to reduce mortality and improve left ventricular ejection fraction (LVEF) [Pitt 1999; Bonsu 2018; Chanchai 2018]. Glucagon-like peptide-1 (GLP-1) is a hormone secreted from the small intestine in response to food intake as part of the incretion system and can reduce blood glucose through stimulating insulin production and inhibiting glucagon excretion [Drucker 2006; Nguyen 2018].

GLP-1 analogues also are reported to have beneficial cardiovascular properties with effects on myocardial metabolism, nitric oxide production, afterload, and cardiac contractility [Ussher 2014; Packer 2017; Hemmingsen 2017; Takahashi 2015]. GLP-1 analogue liraglutide has a favorable effect on the recovery of left ventricular function in patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI [Chen 2015; Chen 2016]. Clinically relevant LVEF improvement in chronic heart failure is observed with GLP-1 analogue [Munaf 2012]. In contrast, 48-h GLP-1 treatment fails to improve left ventricular function based on the results of one RCT [Halbirk 2010].

The use of GLP-1 analogue liraglutide on heart failure has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [Jorsal 2017; Nielsen 2017; Zhang 2017]. With accumulating evidence, we, therefore, perform a systematic review and meta-analysis of RCTs to investigate the efficacy of liraglutide treatment on heart failure.

MATERIALS AND METHODS

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [Moher 2009].

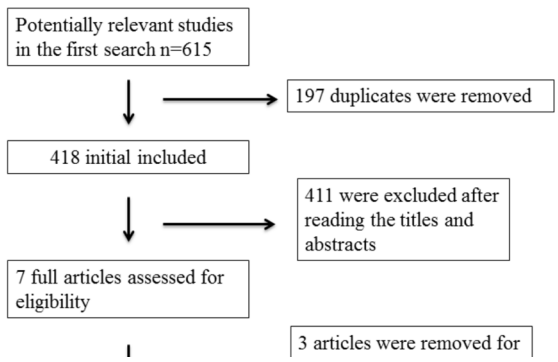

Figure 1. Flow diagram of study searching and selection process.

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Search strategy and study selection: Two investigators independently searched the following databases (inception to March 2018): PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library. The electronic search strategy was conducted using these keywords: liraglutide and heart failure. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria were as follows: (i) population: patients with heart failure; (ii) intervention: liraglutide treatment; (iii) comparison: placebo; (iv) study design: RCT.

Data extraction and outcome measures: We extracted the following information: author, number of patients, age, body mass index, female, New York Heart Association (NYHA) classes, and detail methods in each group, etc. Data independently was extracted by two investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain data, when necessary. No simplifications and assumptions were made. The primary outcome is the N-terminal pro-B-type natriuretic peptide (NT-proBNP) change. Secondary

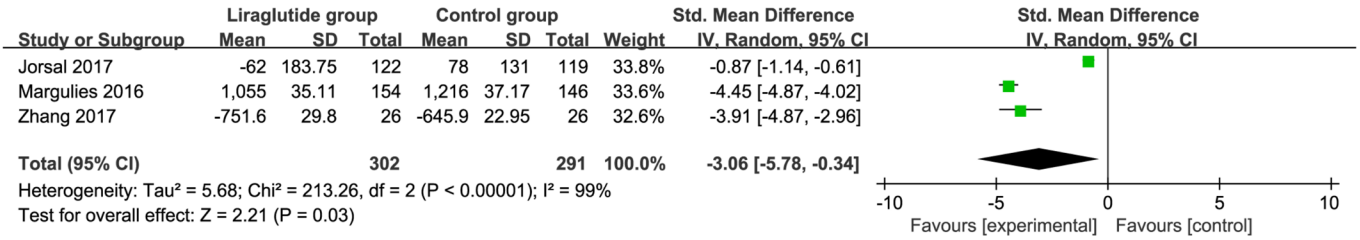

Figure 2. Forest plot for the meta-analysis of NT-proBNP change (pg/mL).

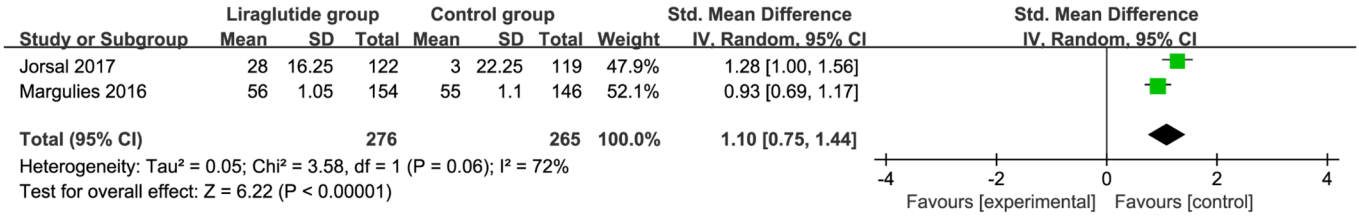

Figure 3. Forest plot for the meta-analysis of 6MWT change (m).

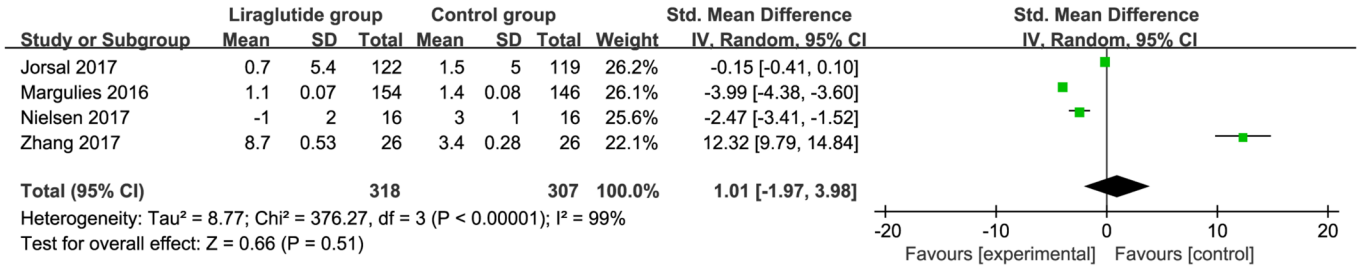

Figure 4. Forest plot for the meta-analysis of LVEF change (%).

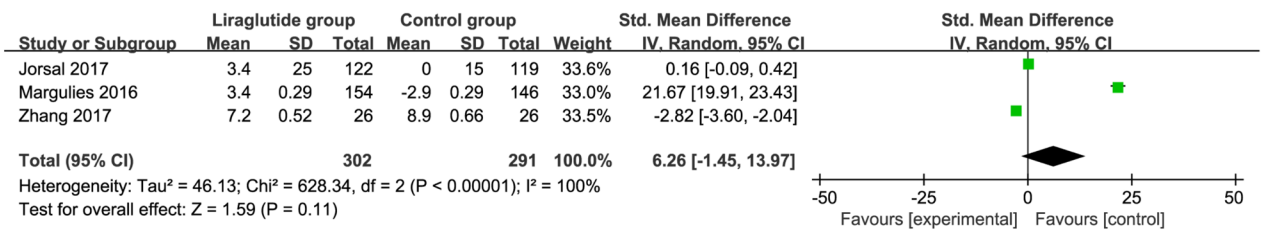

Figure 5. Forest plot for the meta-analysis of LVEDV change (mL).

outcomes include a 6-min walk test (6MWT) change, left ventricular ejection fraction (LVEF) change, left ventricular end-diastolic volume (LVEDV) change, left ventricular end-systolic volume (LVESV) change, hospitalization for heart failure, major adverse cardiovascular events, and cardiac death.

Quality assessment in individual studies: Methodological quality of the included studies was independently evaluated using the modified Jadad scale [Jadad 1996]. There are 3 items for the Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of the Jadad scale varies from 0 to 5 points. An article with Jadad score ≤2 is considered to be of low quality. If the Jadad score ≥3, the study is thought to be of high quality [Kjaergard 2001].

Statistical analysis: We estimated the standard mean difference (Std. MD) with 95% confidence interval (CI)

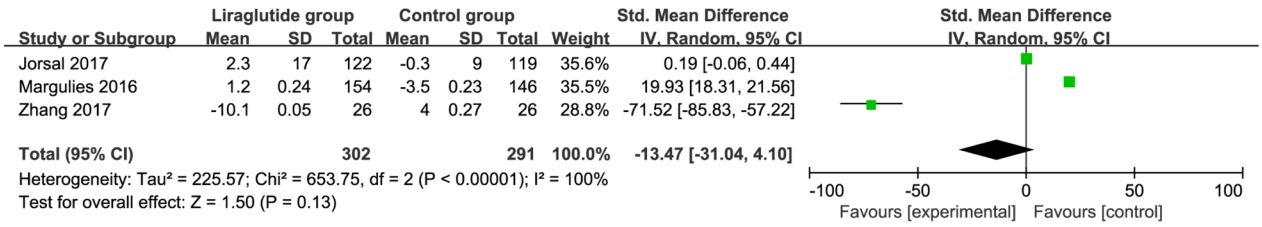

Figure 6. Forest plot for the meta-analysis of LVESV change (mL).

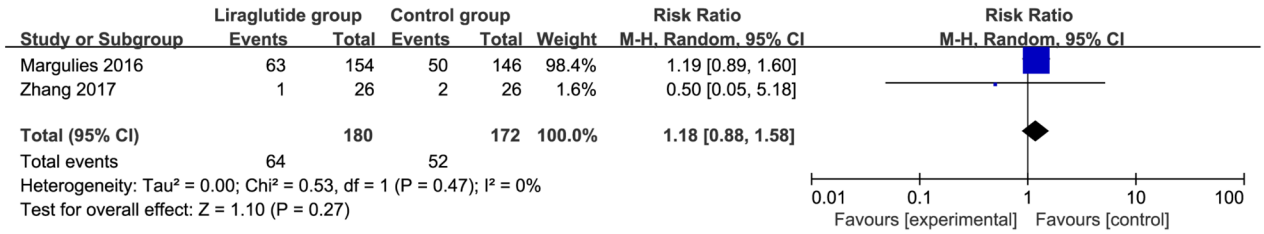

Figure 7. Forest plot for the meta-analysis of hospitalization for heart failure.

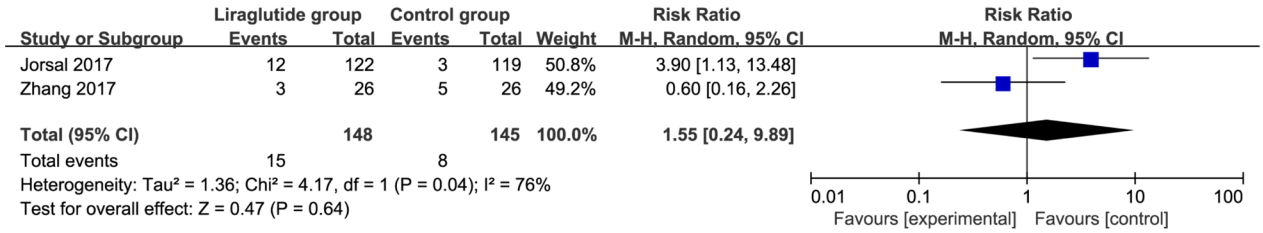

Figure 8. Forest plot for the meta-analysis of major adverse cardiovascular events.

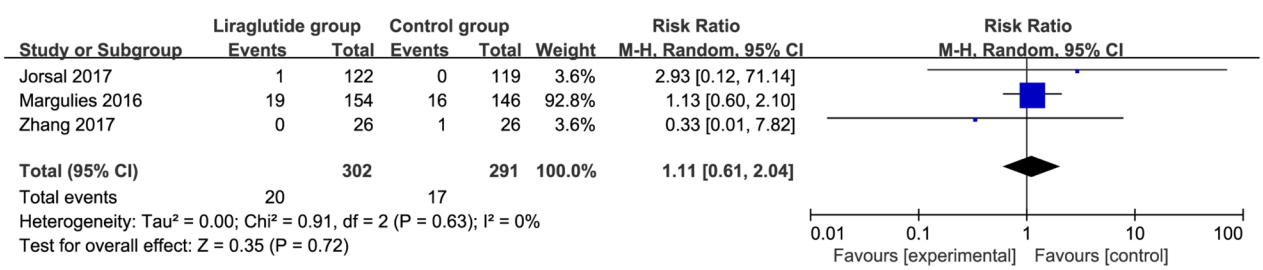

Figure 9. Forest plot for the meta-analysis of cardiac death.

for continuous outcomes (NT-proBNP change, 6MWT change, LVEF change, LVEDV change, LVESV change) and risk ratio (RR) with 95% CIs for dichotomous outcomes (hospitalization for heart failure, major adverse cardiovascular events, cardiac death). A random-effects model was used regardless of heterogeneity. Heterogeneity is reported using the I2 statistic, and I2 > 50% indicates significant heterogeneity [Higgins 2002]. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias was not evaluated because of the limited number (<10) of included studies. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

Literature search, study characteristics, and quality assessment: A detailed flowchart of the search and selection results is shown in Figure 1. There were 615 potentially relevant articles initially identified. Finally, 4 RCTs that met our inclusion criteria were included in the meta-analysis [Jorsal 2017; Nielsen 2017; Zhang 2017; Margulies 2016].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in Table 1. The six studies were published between 2016 and 2017, and sample sizes ranged from 36 to 300, with a total of 629. The initial dose of liraglutide is 0.6 mg/day and is gradually increased to 1.8 mg daily in 2 RCTs [Jorsal 2017; Zhang 2017]. The remaining 2 RCTs report 1.8 mg liraglutide daily [Nielsen 2017; Margulies 2016].

Characteristics of included studies

		Liraglutide Group						Control Group						
No.	Author	Number	Age (years)	Female (N)	Body Mass Index (kg/m^2)	NYHA classes (III/IV)	Methods	Number	Age (years)	Female (N)	Body Mass Index (kg/m^2)	NYHA classes (III/IV)	Methods	Jada scores
1	Zhang 2017	26	59.1 ± 11.8	6	25.3 ± 3.4	9/8	0.6 mg liraglutide once daily for 2 days, 1.2 mg liraglutide for another 2 days, and then 1.8 mg liraglutide for 3 days	26	58.7 ± 11.4	7	24.8±3.8	10/7	Matched placebo	4
2	Nielsen 2017	18	66 ± 7	1	26.3 ± 3.1	0/0	1.8 mg once daily	18	69 ± 9	1	27.3 ± 4.0	1/0	Matched placebo	3
3	Jorsal 2017	122	65 ± 9.2	13	28.0 ± 3.8	17/4	Initial dose of 0.6 mg/day, increased to 1.2 mg/day after 1 week and to 1.8 mg/day thereafter	119	65 ± 10.7	13	29.8±4.6	16/4	Matched placebo	4
4	Margulies 2016	154	62(52-68), median (IQR)	31	31(26-36), median (IQR)	93/8	a dosage of 1.8 mg/d during the first 30 days as tolerated and continued for 180 days	146	61(51-67), median (IQR)	33	33(25-38), median (IQR)	96/6	Matched placebo	5

*IQR, interquartile range

Among the 4 studies included here, 3 studies report NT-proBNP change [Jorsal 2017; Zhang 2017; Margulies 2016], two studies report 6MWT change [Jorsal 2017; Margulies 2016], four studies report LVEF change [Jorsal 2017; Nielsen 2017; Zhang 2017; Margulies 2016], three studies report LVEDV change and LVESV change [Jorsal 2017; Zhang 2017; Margulies 2016], two studies report hospitalization for heart failure [Zhang 2017; Margulies 2016], two studies report major adverse cardiovascular events [Jorsal 2017; Margulies 2016], and three studies report cardiac death [Jorsal 2017; Zhang 2017; Margulies 2016]. Jadad scores of the 4 included studies vary from 3 to 5, and all 4 studies are considered to be high-quality ones according to quality assessment.

Primary outcome: NT-proBNP change. This outcome data was analyzed with the random-effects model, and the pooled estimate of the 3 included RCTs suggested that compared with the control group for heart failure, liraglutide treatment can significantly reduce NT-proBNP (Std. MD = -3.06; 95% CI = -5.78 to -0.34; P = .03), with significant heterogeneity among the studies (I2=99%, heterogeneity P < .00001) (Figure 2).

Sensitivity analysis: Significant heterogeneity is observed among the included studies for the primary outcome. As shown in Figure 2, the study conducted by Jorsal [Jorsal 2017] showed results that are almost out of range with the others and probably contribute to the heterogeneity. After excluding this study, the results suggested that compared with the control group, liraglutide treatment is associated with a significant NT-proBNP reduction for heart failure (Std. MD=-4.36; 95% CI = -4.74 to -3.97; P < .00001), and no heterogeneity remains (I2 = 0%, heterogeneity P = .32).

Secondary outcomes: Compared with the control group for heart failure, tranexamic acid is associated with substantially improved 6MWT (Std. MD=1.10; 95% CI = 0.75 to 1.44; P < .00001; Figure 3), but shows no significant influence on LVEF change (Std. MD=1.10; 95% CI = -1.97 to 3.98; P = .51; Figure 4), LVEDV change (Std. MD=6.26; 95% CI = -1.45 to 13.97; P = .11; Figure 5), LVESV change (Std. MD = -13.47; 95% CI = -31.04 to 4.10; P = .13; Figure 6), hospitalization for heart failure (RR = 1.18; 95% CI = 0.88 to 1.58; P = .27; Figure 7), major adverse cardiovascular events (RR = 1.55; 95% CI = -0.24 to 9.89; P = .64; Figure 8), and cardiac death (RR = 1.11; 95% CI = 0.61 to 2.04; P = .72; Figure 9).

DISCUSSION

Plasma glucose, blood pressure, and lipids serve as important factors to exert a dose-dependent effect on cardiovascular risk [Santulli 2012; Sorensen 2016; Tang 2014; Zhang 2013]. GLP-1, an incretion hormone, is reported to decrease glucose levels and cardiovascular risk and enhance the recovery of cardiac function [Chen 2016; Packer 2018; Bethel 2018]. Inflammation and oxidative stress are significantly observed in heart failure, and GLP-1 can ameliorate inflammation [Packer 2017; Dokken 2011; Scheen 2017]. GLP-1 analogue liraglutide has been reported to reduce inflammation and increase left ventricular contractile function for heart failure [Chang 2013; Nauck 2017].

The influence of GLP-1 on the cardiovascular system has been studied. Pretreatment with GLP-1 decreases the accumulation of lactate and pyruvate in ischemic myocardium of pigs but does not affect functional parameters [Kavianipour 2003]. GLP-1 analogue liraglutide results in significantly improved cardiac output in mice and LVEF for heart failure [Zhang 2017; Noyan-Ashraf 2009]. Our meta-analysis suggests that liraglutide treatment can substantially reduce NT-proBNP and improve 6MWT for heart failure, but has no important influence on LVEF, LVEDV, LVESV, hospitalization for heart failure, major adverse cardiovascular events, and cardiac death.

When performing sensitivity analysis, there is significant heterogeneity. No heterogeneity is observed after excluding one study conducted by Jorsal [Jorsal 2017], and the remaining RCTs conclude that liraglutide treatment is associated with a significant NT-proBNP reduction for heart failure. Several reasons may explain this heterogeneity. First, patients in included RCTs without diabetes may have different responses to liraglutide treatments. Second, included patients include chronic heart failure and acute heart failure (or caused by acute myocardial infarction). Third, the duration of liraglutide treatment ranges from 7 days to 3 months, and liraglutide doses differ from 0.6 mg/day to 1.8 mg/day (or indifferent methods of increase). Finally, β-blockers, angiotensin-converting inhibitors, angiotensin- II receptor agonists, and diuretics are the cornerstone in heart failure treatment, and some patients do not receive an optimal dose of β-blockers or angiotensin-converting inhibitors.

This meta-analysis has several potential limitations that should be taken into account. First, our analysis is based on only 4 RCTs and 2 of them have a relatively small sample size (N < 100). More RCTs with large samples should be conducted to confirm this issue. Next, there is significant heterogeneity when performing sensitivity analysis, different doses and methods of liraglutide treatment and patient populations may influence the pooling results. Finally, some unpublished and missing data may lead to bias to the pooled effect.

CONCLUSION

Liraglutide treatment can provide some benefits to heart failure patients.

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