A Meta-Analysis Evaluating the Efficacy of Liraglutide in Reducing Cardiovascular Complications Among Patients with Type 2 Diabetes

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Background. The objective of this study was to determine the efficacy of liraglutide in reducing cardiovascular complications.

Methodology. Literature searches of electronic databases (PubMed and ScienceDirect) were performed to identify relevant studies. Relevant journals included were electronically searched for randomized controlled trials (RCTs) regarding the use of liraglutide versus placebo in reducing the rate of cardiovascular complications. Data extraction and quality assessment were done by independent reviewers. Statistical analysis of the study was accomplished using Cochrane Systematic Review Software Review Manager. Mean difference was used to analyze a data set which used mean and standard deviation from the studies. A p-value of less than 0.05 for the observed effect size was considered statistically significant.

Results. A total of two RCTs with 16,977 patients were included in this meta-analysis. The results showed that in the liraglutide group, there is a statistically lower rate of the major adverse cardiovascular events (risk ratio [RR] 0.86 [0.78, 0.95]), cardiovascular events (RR 0.75 [0.63, 0.89]), and all-cause mortality (RR 0.81 [0.70, 0.93), but it is not statistically significant when compared to the placebo group in terms of non-fatal myocardial infarction and non-fatal stroke. There is no significant difference in rates of severe adverse events in general ($p>0.05$). However, liraglutide caused significant reduction in rates of severe hypoglycemia as an independent secondary outcome ($p<0.05$).

Conclusion. Compared with placebo, liraglutide provided a significant reduction in MACE, cardiovascular events, all-cause mortality and severe hypoglycemia as an adverse event.

Keywords. *Liraglutide, GLP-1 agonist, Major adverse cardiovascular events, Type 2 diabetes, Cardiovascular complications*

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia. According to the Centers for Disease Control and Prevention Diabetes Surveillance System in 2022, approximately 11.3% of adults (37.3 million people) are affected by diabetes.[1,2] It proves to be a global public health burden, as this number is expected to rise by another 200 million by 2040, based on the statistics of the International Diabetes Federation.[3]

Diabetes mellitus is associated with several microvascular and macrovascular complications which lead to a 2-fold to 4-fold increased risk of cardiovascular diseases.[4] Major adverse cardiovascular events (MACE) remain the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) and is defined as the composite of total death, myocardial infarction, coronary artery revascularization, stroke, and hospitalization because of heart failure.[5,6] Hence, new and safe treatment modalities are being investigated.

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Glucagon-like peptide 1 (GLP-1) is a hormone secreted from the small intestine in response to food intake, as part of the incretin system. It delays gastric emptying and inhibits pentagastrin and acid secretion stimulated by food ingestion. It stimulates insulin production and inhibits glucagon excretion, thus reducing blood glucose.[7,8] GLP-1 actions do not only translate into improvement of well-known cardiovascular risk factors such as glycemic control, dyslipidemia, weight, or arterial hypertension but also show benefits on blood pressure, vascular endothelium, atherosclerosis progression and inflammation, myocardial ischemia, and heart failure.[8]

Liraglutide, a GLP-1 analogue, has been approved as treatment of T2DM and has shown significant reduction in glycated hemoglobin, whether given as monotherapy or in combination with other oral hypoglycemic agents.[9] It also proved its effectiveness among obese patients in decreasing body mass index and its benefits in both kidney and cardiovascular outcomes.[10] Among patients with chronic heart failure and ischemic heart failure, it has improved left ventricular ejection fraction, functional capacity, and quality of life.[11,12] Liraglutide may be given once daily by subcutaneous injection.[13]

The GLP-1 analogue liraglutide may significantly benefit cardiovascular outcomes in T2DM patients; however, meta-analysis of randomized control trials with a thorough evaluation of its effect in reducing MACE and their adverse effects in Diabetic patients is lacking. The present study investigates the effectiveness of Liraglutide in reducing MACE among patients with T2DM.

MACE are the leading cause of morbidity and mortality among patients with T2DM. The use of liraglutide as a new treatment modality may help in improving cardiovascular outcomes. However, based on the study of Marso et al., adverse events may also arise with the use of this medication, such as all-cause mortality, severe hypoglycemia, acute gallstone disease, cholelithiasis, cholecystitis, hypothyroidism, hyperthyroidism, diabetic foot ulcer, allergic reaction, injection-site reaction, nausea, vomiting, diarrhea, increased lipase level, decreased appetite, abdominal discomfort, acute or chronic pancreatitis, any benign neoplasm, any malignant neoplasm, pancreatic carcinoma, or medullary thyroid carcinoma.[14]

This study may help emphasize the benefit of liraglutide for the medical management of patients with T2DM, especially those at high risk of having cardiac complications. This study also shows the adverse events that may occur, thus helping to weigh benefits and risks of prescribing liraglutide. For patients, this would contribute to their treatment choices and may be given as an adjunct to insulin or oral hypoglycemic agents.

Objectives

The researchers aimed to determine the efficacy of liraglutide in reducing cardiovascular complications.

Outcome Measures

The primary outcome measure is rate of MACE: total death, myocardial infarction, coronary artery revascularization, stroke, and hospitalization because of heart failure. The secondary outcome measures are adverse events in general (e.g., all-cause mortality, severe hypoglycemia, acute gallstone disease, cholelithiasis, cholecystitis, hypothyroidism, hyperthyroidism, diabetic foot ulcer, allergic reaction, injection-site reaction, nausea, vomiting, diarrhea, increased lipase level, decreased appetite, abdominal discomfort, acute or chronic pancreatitis, any benign neoplasm, any malignant neoplasm, pancreatic carcinoma, medullary thyroid carcinoma) and severe hypoglycemia as independent secondary outcome.

Methodology

This study included randomized controlled trials (RCTs). The subjects enrolled included patients with T2DM who had either HbA1c >0.7% treated with any oral hypoglycemic agents, any prandial insulin, or basal insulin <20 units/day; or HbA1c <7% (53 mmol/mol) but were treated with ≥20 units/day of basal insulin (based on DEVOTE trial), ≥50 years old with at least one cardiovascular co-existing condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III), or an age ≥60 years with at least one cardiovascular risk factor as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index). They may have either not received drugs for this condition previously or been treated with one or more oral anti-hyperglycemic agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents. The intervention is the use of liraglutide, whereas the control is placebo.

A literature review and search were carried out using PubMed and ScienceDirect in June 2022. We used the following medical subject headings: Diabetes Mellitus, Type 2, Liraglutide, and Cardiovascular Diseases with interposition of Boolean operator "AND"/"OR". The authors screened through the titles and abstracts and excluded studies meeting the exclusion criteria, those with unavailable full text, or any paper that was unrelated to the study. Furthermore, references of each study, including previous systematic reviews and meta-analyses, were explored to identify other possible articles. The language of publication was restricted to English as well.

Selection Process

Studies were included if they met the following criteria: (1) RCTs; (2) patients were divided into experimental group, in which liraglutide was given, and control group, in which patients were assigned to receive placebo; and (3) outcomes included but were not limited to rate of MACE or time-to-event analysis, as well as adverse events. Studies that met the following criteria were not included in the study: (1) study design of lower quality and (2) publication not in the English language.

Data Extraction and Management

A total of two eligible studies were reviewed, and the following data were abstracted by the investigators: (1) first author's name; (2) year of publication; (3) study design; (4) number of participants in the intervention and control groups (i.e., liraglutide and placebo); and (5) outcomes. Upon extraction, these data were organized into a master table.

Assessment of Study Quality

Methodological quality for clinical trials was evaluated by the researchers using the Cochrane risk bias tool (Figure 1). The included randomized controlled trials were classified into low risk, high risk, or unclear risk using the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting bias (reporting bias), and other biases that may pose threats to validity. The quality of the studies was assessed by two authors. Any dispute was settled through discussion or with consultation with a third reviewer.

Figure 1. Risk of bias table

Brown-Frandsen 2018

Methods	RCT
Participants	7637
Interventions	Liraglutide
Outcomes	MACE vs Placebo
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Marso 2016

Methods	RCT
Participants	9340
Interventions	Liraglutide vs Placebo
Outcomes	MACE
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Statistical Analysis

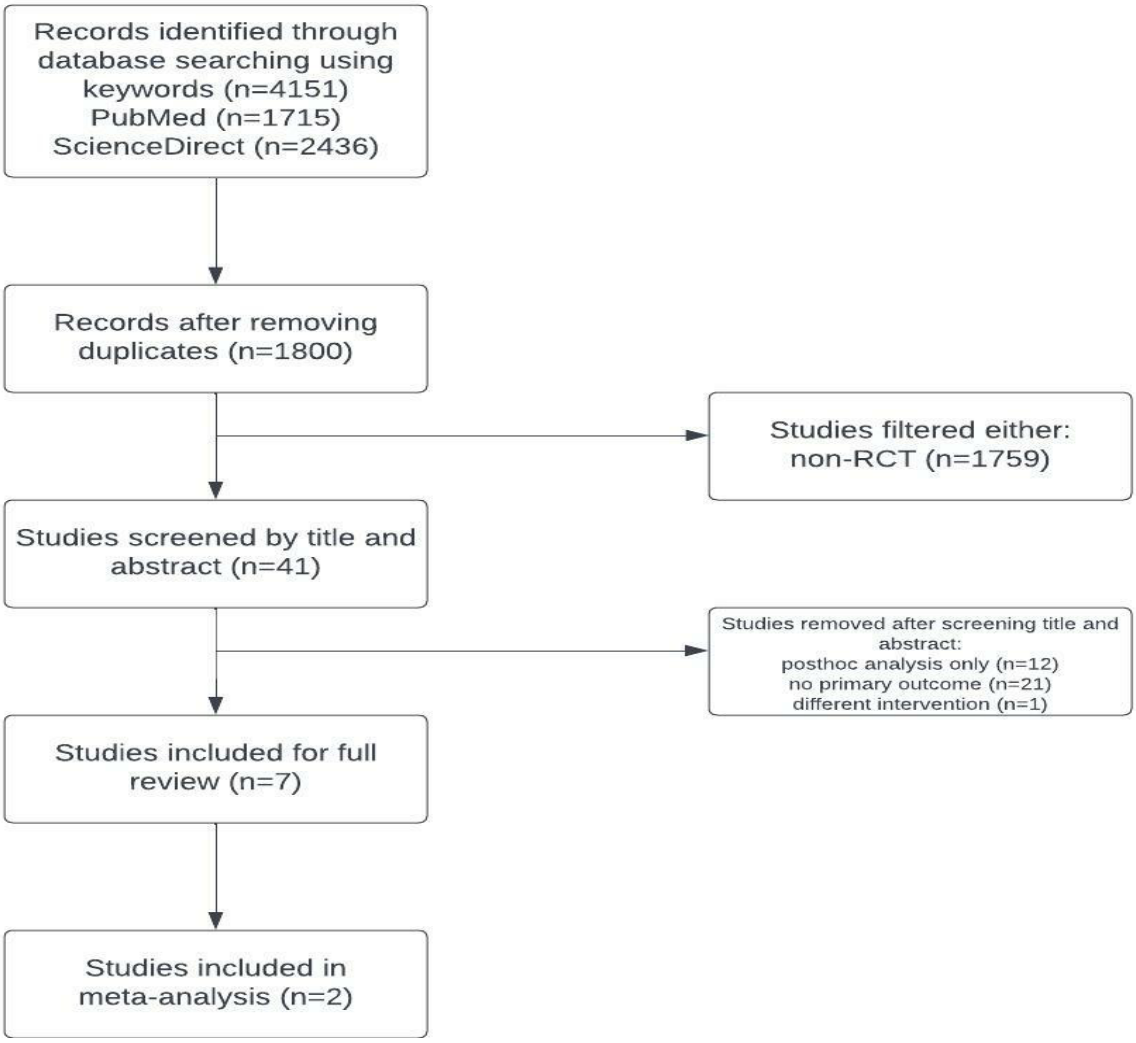
Statistical analysis of the study was accomplished using the Cochrane Systematic Review Software Review Manager. The analysis method used a random effects model for pooled data with significant inconsistencies; otherwise, a fixed effect model was applied. Risk ratio was used to analyze dichotomous data. Mean difference was used to analyze a data set which used mean and standard deviation from the studies. Forest plots were used to visually present the results, and overall effect was measured using the Z score. The heterogeneity of intervention effects was appraised visually by observing the overlapping of results in the forest plots. Lack of overlapping was interpreted as indicative of possible heterogeneity. The authors further estimated heterogeneity quantitatively using I^2 statistics. $I^2 \geq 50\%$ indicated significant heterogeneity. A $p<0.05$ for the observed effect size was considered statistically significant. Descriptive analysis includes the mean difference with 95% confidence intervals and the weight of the study.

Results

Study Selection

Based on the literature search on online databases, a total of 4,151 studies were identified from PubMed (n=1,715) and ScienceDirect (n=2,436). After filtering for RCTs and research articles and removing non-English and duplicate studies, 41 articles remained. The authors then screened through the titles and abstracts and excluded all irrelevant studies, leaving seven articles for review, from which five studies without the primary and secondary outcomes were excluded. Only two articles were included in the meta-analysis, containing but not limited to rate of MACE or time-to-event analysis, and adverse events (Figure 2).

Figure 2. Flow Diagram of study selection



Study Characteristics

A total of 16,977 patients were included in the two studies. There were 5,291 patients in the experimental group and 11,686 patients in the control group. RCT was the sampling procedure of all the studies included. With regard to age, mean values were collated from all the studies, and for overall, the studies have a mean age of 64.59 (Table 1).

Effect of interventions

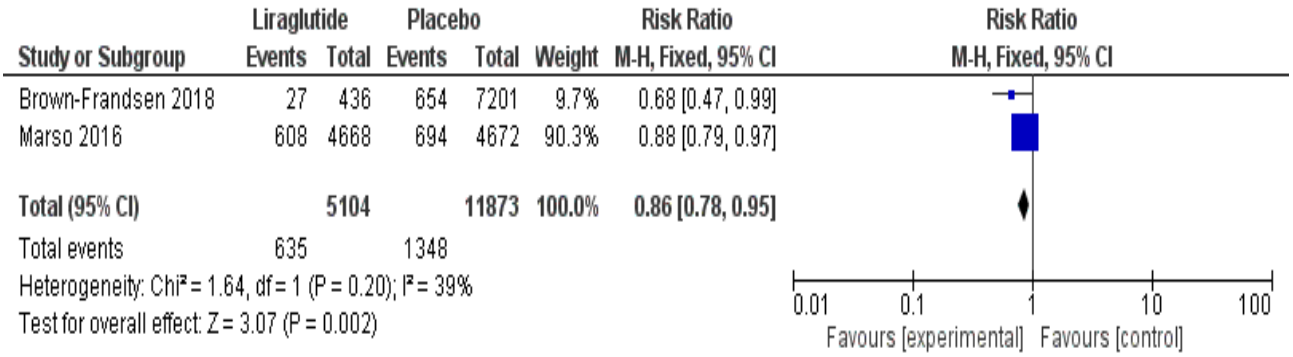
Fixed effects model was used to compare differences between the groups, due to low heterogeneity. Two studies showed risk less than 1, which favors the use of liraglutide with risk ratios (RRs) of 0.68 (0.47, 0.99) and 0.88 (0.79, 0.97), respectively. In general, the RR is 0.86 (0.78, 0.95), which means that in the combined studies, liraglutide significantly reduced MACE. This result is significant since p-value (p=0.002) is less than 0.05 at 95% significance level (Table 3).

population, as the inclusion criteria were not defined, and one did not describe the age and natal gender. Two articles posed a high risk of bias to its exposure and outcome measurements, since one article reported a concomitant neoplasm and the other based its outcome on cisgender females. Five articles had a high risk of outcome measurement, since the results were generalized with female-to-male transgender or there was no mention of proper reference for the recommendations stated. Despite these, most of the articles had low risk of bias when it came to adequate exposure (described MtF transgender and possible exposure), and outcome measurement (mentioned histologic confirmation or screening methods for breast cancer).

Table 1. Characteristics of included studies

Study and Year	Country	Study Design	Patients	Age, mean	Gender M:F	Intervention, liraglutide (n)	Control, placebo (n)
Brown-Frandsen et al., 2018	Denmark	RCT subanalysis	Medical	-	6003:3337	436	7,201
Marso et al., 2016	Massachusetts	RCT	Medical	-	6003:3337	4668	4,672

Figure 3. Forest plot comparison: efficacy of liraglutide vs placebo in reducing MACE



In terms of reducing cardiovascular events, the two studies showed risk less than 1, which favors the use of liraglutide with RRs 0.48 (0.24, 0.98) and 0.78 (0.65, 0.93), respectively. In general, the RR was 0.75 (0.63, 0.89) which means that in the combined studies, liraglutide significantly reduced cardiovascular events. This result is significant: p=0.001, which is less than 0.05 at 95% significance level (Figure 4).

In terms of reducing non-fatal myocardial infarction, the two studies showed risk less than 1, which favors the use of liraglutide with RRs 0.83 (0.49, 1.40) and 0.88 (0.75, 1.04), respectively. In general, the RR was 0.87 (0.75, 1.02), which means that in the combined studies, liraglutide reduced non-fatal myocardial infarction. However, there was no significant difference between liraglutide and placebo in this aspect (p=0.10; Figure 5).

Figure 4. Forest plot comparison: efficacy of liraglutide vs placebo in reducing

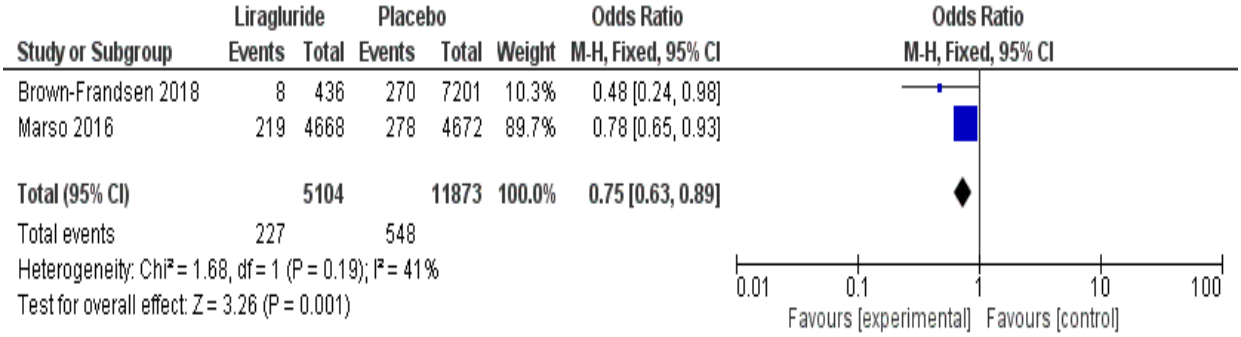
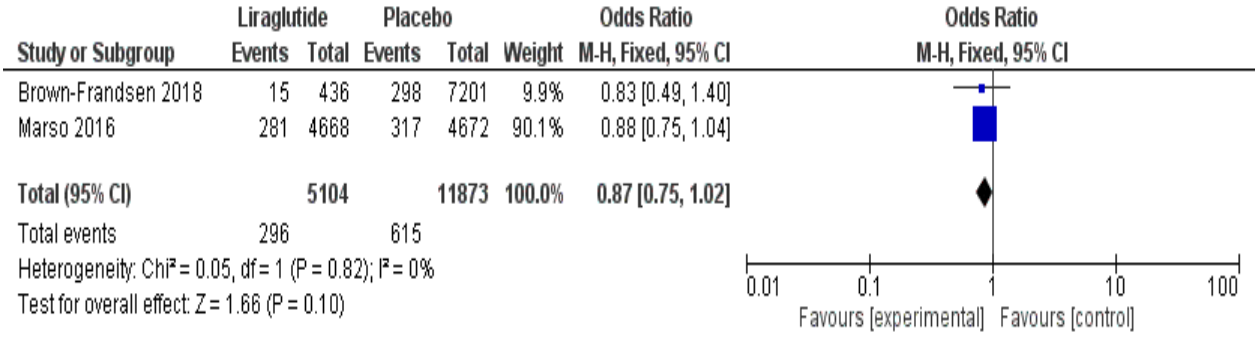


Figure 5. Forest plot comparison: efficacy of liraglutide vs placebo in reducing non-fatal myocardial infarction



In terms of reducing non-fatal stroke, the two studies showed risk less than 1, which favors the use of liraglutide, with RRs 0.56 (0.23, 1.38) and 0.90 (0.72, 1.11), respectively. In general, the RR was 0.87 (0.70, 1.07) which means that in the combined studies, liraglutide reduced non-fatal stroke. However, there was also no significant difference between liraglutide and placebo in this aspect (p=0.18; Table 6).

In terms of reducing all-cause mortality, the two studies showed risk less than 1, which favors the use of liraglutide with RRs 0.51 (0.29, 0.89) and 0.84 (0.73, 0.97), respectively. In general, the RR was 0.81 (0.70, 0.93), which means that in the combined studies, liraglutide significantly reduces all-cause mortality. This result was significant (p=0.002; Table 7).

Figure 6. Forest plot comparison: efficacy of liraglutide vs placebo in reducing non-fatal stroke

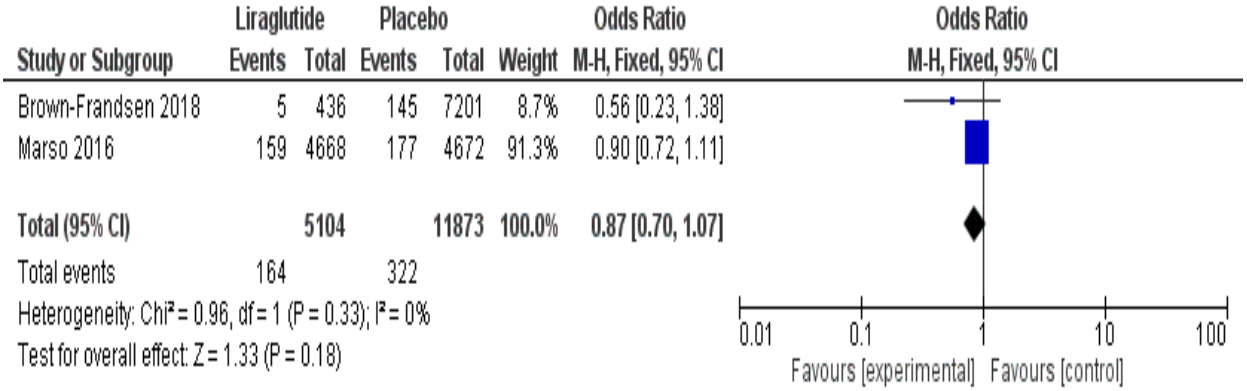
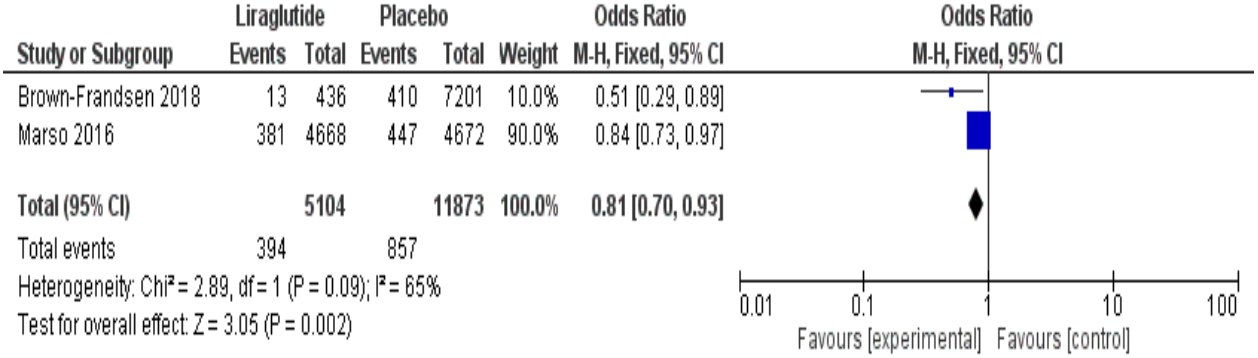


Figure 7. Forest plot comparison: efficacy of liraglutide vs placebo in reducing all-cause mortality



In terms of rates of adverse events, the study by Brown-Frandsen had RR 0.85 (0.75, 0.96), which means that there was a higher number of adverse events among those who used placebo than liraglutide. In contrast, the study by Marso had RR 1.03 (0.99, 1.06), which means there was a higher number of adverse events among those who used liraglutide. In general, there was no significant difference between liraglutide and placebo in terms of rate of adverse events (Figure 8).

With regard to rates of severe adverse events in general, the study by Brown-Frandsen had RR 0.79 (0.64, 0.97), which means there was a higher number of adverse events among those who used placebo. In contrast, the study by Marso had RR 1.03 (0.92, 1.10), which means there was a higher number of adverse events among those who used liraglutide. In general, there is no significant difference between liraglutide and placebo in terms of rate of severe adverse events, not including severe hypoglycemia (Figure 9).

Figure 8. Forest plot comparison: liraglutide vs placebo, rates of severe adverse events

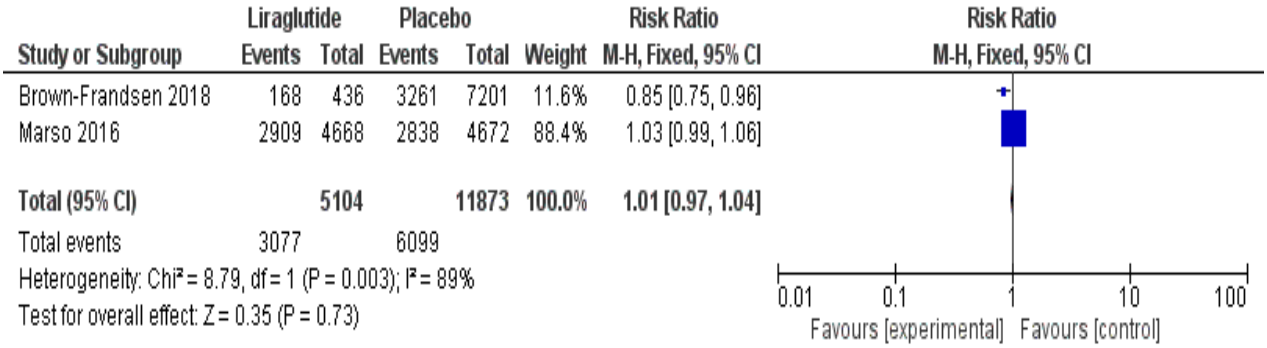
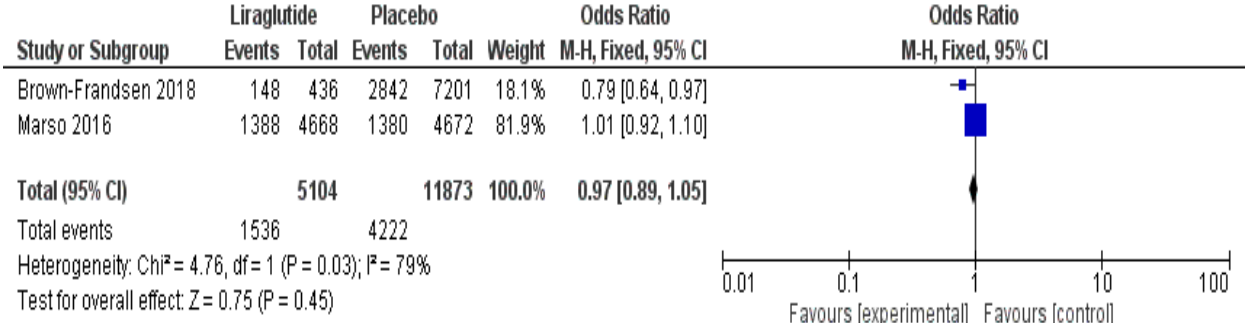


Figure 9. Forest plot comparison: liraglutide vs placebo, rates of severe adverse events other than hypoglycemia



The two studies had risk less than 1, which favors the use of liraglutide with RRs 0.78 (0.49, 1.23) and 0.74 (0.58, 0.95), respectively. In general, the RR was 0.75 (0.60, 0.93), which means that in the combined studies, liraglutide significantly reduced severe hypoglycemia. This result is significant (p=0.009; Table 10).

Risk of Bias Across Studies

Based on the Modified Cochrane Collaboration Tool, the included studies had low risk of random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. There is unclear risk for blinding of participants and personnel, since it was not mentioned in the respective studies (Figure 11).

Figure 10. Forest plot comparison: liraglutide vs placebo, rates of severe hypoglycemia as an independent secondary outcome

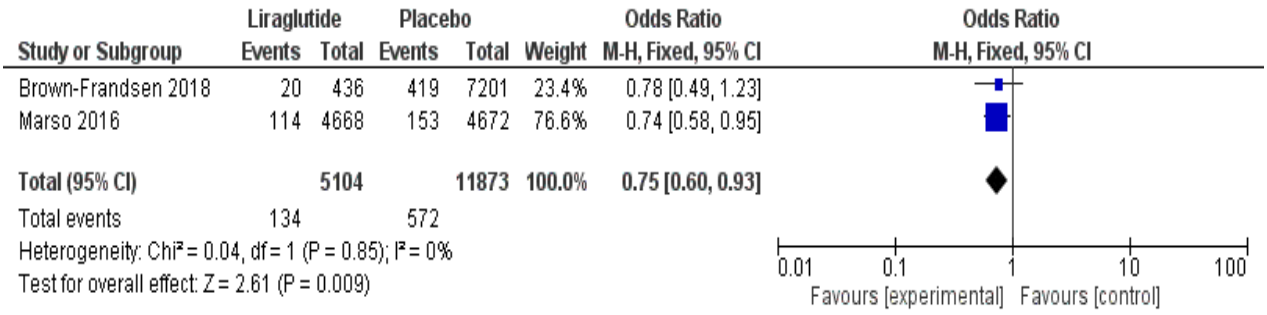


Figure 11. Risk of bias summary of included studies

Discussion

In the present meta-analysis, patients in the liraglutide group had significantly lower rates of MACE, which is the primary composite outcome. This emphasized the role of GLP-1 agonists in reducing morbidity and mortality among patients with T2DM; several studies have postulated how they intervene with the pathophysiology of diabetes and MACE: improving left ventricular function, increasing ejection fraction, adjusting levels of natriuretic peptides, and reducing visceral and ectopic fat deposition, to name a few.

Looking into the specific categories of MACE common between the two studies, we found that liraglutide caused a significant reduction in rates of cardiovascular events and all-cause mortality, while in non-fatal myocardial infarction and non-fatal stroke, there was no noted significant difference. Taking into account the specific classifications of MACE and in which classification this medication would be more effective would help in tailoring our management to each of our patients.

Liraglutide is not exempted from having adverse effects. Hence, we need to take into consideration the possible consequences of using this medication. Some patients develop hypoglycemia, acute gallstone disease, cholelithiasis, cholecystitis, hypothyroidism, hyperthyroidism, diabetic foot ulcer, allergic reaction, injection-site reaction, nausea, vomiting, diarrhea, increased lipase level, decreased appetite, abdominal discomfort, acute or chronic pancreatitis, any benign neoplasm, any malignant neoplasm, pancreatic carcinoma, or medullary thyroid carcinoma.[14,15] For the secondary outcome of this study, we found that liraglutide significantly reduces severe hypoglycemia, but there is no significant difference between liraglutide and placebo with regard to severe adverse events in general. Weighing benefits and risks would be important when deciding whether to add this medication to the treatment regimen of patients with T2DM.

This meta-analysis shows that liraglutide can be a primary consideration in terms of safety and efficacy. Initiating GLP-1 agonists can cause reductions in the composite outcomes. Hence, intensifying diabetic treatment regimens with liraglutide could be beneficial both in the short-term and the long-term goals among patients with T2DM.

Limitations

The limitation in this study would be the unclear risk of blinding participants and personnel, hence increasing performance bias. Also, since there are only two studies included, there may be overestimation of the actual magnitude of the effect.

Recommendations

For future research, it is recommended that there also be analysis of the different components of MACE and various adverse events (all-cause mortality, severe hypoglycemia, acute gallstone disease, cholelithiasis, cholecystitis, hypothyroidism, hyperthyroidism, diabetic foot ulcer, allergic reaction, injection-site reaction, nausea, vomiting, diarrhea, increased lipase level, decreased appetite, abdominal discomfort, acute or chronic pancreatitis, any benign neoplasm, any malignant neoplasm, pancreatic carcinoma, or medullary thyroid carcinoma). Future studies may include other recent research and other GLP-1 analogs as intervention.

Conclusion

Compared with placebo, liraglutide significantly decreased the rate of MACE among patients with T2DM. Specifically, it reduced cardiovascular death and all-cause mortality. There was no significant reduction in rates of non-fatal myocardial infarction and non-fatal stroke. There was also no significant difference in terms of severe adverse events in general. However, liraglutide helped in decreasing rates of severe hypoglycemia in patients with T2DM. Hence, in the clinical settings, clinicians are guided both by theoretical knowledge, experience, and sound judgment on which modality is applicable and beneficial to their patients.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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