Glucagon-Like Peptide-1 Receptor Agonists Reduction in Stroke Type 2 DM Patients

Fatmah Salem Alhawyan[1]*, Mohammed Adel Althobaiti[2], Hashim Yahya Alnami[3], Hadeel Ibrahim Allahafi[4], Ayman Jamaan Almalky[2], Sultan Ahmed Al johani[2], Rokayah Hussain Shiban[5], Mohammed Ahmed Saddah[6], Hussam Mohammed Alamrah[6], Moayad Zeyad Aljuhani[7], Ebtehal Hamid Alfallaj[8]

[1] Department of Endocrinology, Armed Forces Hospital, Ministry of Defense, Abha, Saudi Arabia.
[2] College of Medicine, Taif University, Taif, Saudi Arabia.
[3] College of Medicine, King Khalid University, Abha, Saudi Arabia.
[4] Department of Nephrology, King Fahad Hospital, Jeddah, Saudi Arabia.
[5] College of Medicine, Medical University of Lodz, Lodz, Poland.
[6] College of Medicine, King Khalid University, Abha, Saudi Arabia.
[7] College of Medicine, Medical University of Warsaw, Warsaw, Poland.
[8] Department of Internal Medicine, King Abdulaziz Specialist Hospital, Sakaka Aljouf, Saudi Arabia.

ABSTRACT

Objectives: Diabetes mellitus is one of the most prevalent diseases worldwide. It is associated with a high mortality rate due to cardiovascular diseases and stroke. Prevention of cardiovascular disorders and stroke will greatly enhance the life quality of diabetic patients. Hence, we assess the efficacy of Glucagon-Like Peptide-1 Receptor Agonists to prevent stroke in diabetic patients. **Methods:** Six databases were searched using specific search terms. We included randomized controlled trials that assess the risk of stroke in diabetic patients having Glucagon-Like Peptide-1 Receptor Agonists and the prevalence of stroke in these groups of patients and different other outcomes reported in diabetic patients. The studies were assessed for the quality of evidence using the Cochrane quality assessment tool before being included for the review. **Results:** Seven studies fulfilled our inclusion criteria and passed the quality assessment to be included for the qualitative evidence synthesis. Based on these studies, Glucagon-Like Peptide-1 Receptor Agonists decreased the incidence and risk of cardiovascular diseases generally, and stroke, specifically. However, Dulaglutide, Albiglutide did not show significant improvements. **Conclusion**: Glucagon-Like Peptide-1 Receptor Agonists showed a significant decrease in the risk of stroke and different cardiovascular events. More studies are needed to identify the optimal dose and timing of administration of different agonists.

Key Words: *Stroke, Cerebrovascular diseases, Cardiovascular diseases, Dulaglutide, Albiglutide, Exenatide LAR, Semaglutide, Liraglutide, Lixisenatide, Diabetes mellitus, Glucagon-Like Peptide-1 Receptor Agonists.*

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INTRODUCTION

Diabetes Mellitus is considered a global health problem due to its high morbidities and mortality risks [1-5]. More than 250 million cases of diabetes are diagnosed in 2010 and the number is expected to increase to reach half a million in 2030 [6]. Diabetes mellitus is more prevalent in developing countries than in developed countries. This is attributed to an unhealthy lifestyle and obesity [7].

A syndrome called metabolic syndrome is usually associated with a high risk of diabetes as well as different cardiovascular complications [7]. It is associated with the occurrence of type II diabetes which is more common affecting 90% of cases. Diabetic patients have a higher risk of stroke, atherosclerosis, and arterial diseases [8].

The mortality of diabetes is rising and is considered the seventh leading cause of death and most of these cases die due to stroke or cardiovascular diseases or both [7].

Corresponding author: Fatmah Salem Alhawyan
Address: Department of Endocrinology, Armed Forces Hospital, Ministry of Defense, Abha, Saudi Arabia.
E-mail: dr-alhawayan @ hotmail.com
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A study found that diabetes is an independent risk factor for stroke. It was significantly associated with twice the risk for ischemic stroke and hemorrhagic stroke [9]. The risk for stroke in diabetics is associated with older age specifically around 50 years old and white adults. Usually, these patients are suffering from hypertension, myocardial infarction (MI), and high cholesterol [10].

The cause of stroke in diabetics is usually due to endothelial dysfunction, arterial stiffness, and systemic inflammation. All of these factors predispose to atherosclerosis which is, in turn, will increase the risk of stroke [7]. Diabetic patients have different stroke presentations than nondiabetic ones. Neuropathy and vasculopathy control the presentation. They have a higher risk for subcortical infarction and lower risk of intracerebral hemorrhage [11]. In addition, the high level of plasma glucose is associated with poor outcomes [7]. That is why the main method of prevention lies in the control of blood glucose levels [1].

Glucagon-Like Peptide-1 Receptor Agonists are a group of drugs used for the treatment of type II diabetes mellitus that showed great efficacy against cardiovascular disorders including stroke. They act through the augmentation of insulin secretion and suppressing glucagon secretion. The treatments act through the activation of the Glucagon-Like Peptide-1 Receptor [12]. It is found to inhibit the risk of cardiovascular diseases through its interaction with multiple metabolic pathways. It has also a significant effect on glucose homeostasis, inflammatory pathways, and thrombosis [13].

Randomized clinical trials have suggested a beneficial effect of Glucagon-Like Peptide-1 Receptor Agonists on the prevention of stroke [14-16]. However, a clinical trial found that it does not prevent the risk of cerebrovascular disease [17]. That is why we aim to stand on the real benefit and efficacy of Glucagon-Like Peptide-1 Receptor Agonists against cerebrovascular disorders in diabetics.

METHODS

Database Search

A comprehensive search approach was used to identify randomized controlled trials from six databases PubMed, Google Scholar, SCOPUS, ISI web of science, clinical trial.gov, and Cochrane Collaboration. The search terms used were (Diabetes OR Diabetes Mellitus OR Hyperglycaemia) AND (“cerebrovascular” OR “stroke” OR “cardiovascular”) AND (“lixisenatide” OR “liraglutide” OR “semaglutide” OR “exenatide” OR “dulaglutide” OR “albiglutide” OR “glucagon-likepeptide-1”).

Inclusion and Exclusion Criteria for Screening

Specific inclusion criteria are used to identify high quality and studies that fulfill the goals of this research. Inclusion criteria are i) randomized controlled studies that assess the efficacy of glucagon-like peptide-1 against cerebrovascular disorders, ii) studies that assess the incidence of stroke in diabetic patients before or after the treatment with glucagon-like peptide-1. Books, review articles, letters to the editor, editorial reports, case reports, and conference abstracts and duplicates are excluded.

Screening for Studies

The retrieved studies from each database were screened based on inclusion and exclusion criteria. First, Title/Abstract screening was conducted by three independent reviewers. The included studies were then screened thoroughly to make sure they fulfilled the target of this review. Each study was reviewed thoroughly to extract and build a qualitative review.

Quality Assessment of the Included Papers

The quality of included studies was evaluated by three reviewers using "The Cochrane Collaboration's tool for assessing the risk of bias” [18]. It had seven specific domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The answers were categorized as ‘low risk,’ ‘high risk,’ or ‘unclear risk’ of bias.

RESULTS

Search Results

The search performed on six databases yielded 849 studies, of which, only seven randomized clinical trials fulfilled the inclusion criteria and were used for qualitative evidence synthesis (Figure 1).

Risk of Bias

All trials had a low risk of bias, however, two studies had missing outcome bias (Figure 2). Other studies had high risk in specific domains in figure 3.

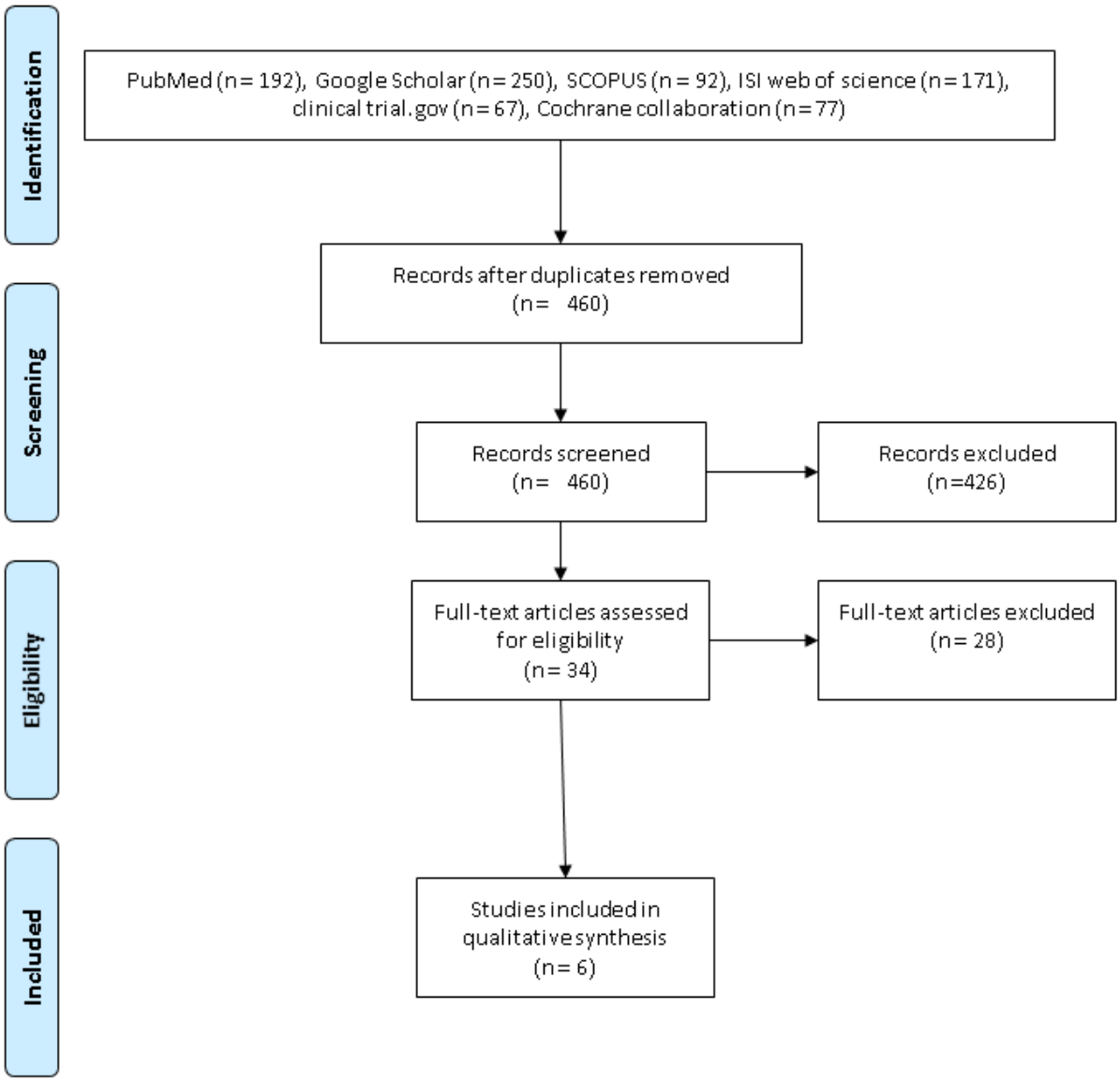
Patient Characteristics

Seven studies assessed the efficacy of different types of Glucagon-like peptide-1 analog in diabetic patients. One of the main outcomes assessed was a fatal and non-fatal stroke. The trials included 56 004 patients with 27 977 patients assigned to the treatment group and remaining patients to placebo (Table 1). The age of the participants ranged from 60.3 to 64.6 years old. The duration of diabetes ranged from 1.3 to 5.4 years. The follow-up duration for the patients ranged from 1.3 to 5.4 years in table 1.

Table 1. Characteristics of Patients in the Included Trials

Study	Treatment	Control	Patients n	Age (years)	Female %	Duration of Trial (Years)	Diabetes Duration (Mean; Years)	History of Stroke (%)
PIONEER-6 (2019)(Husain et al.)	Oralsemaglutide	Placebo	3183	66	31.6	1.3	14.9	NA
REWIND (2019)(Gerstein et al.)	Dulaglutide	Placebo	9901	66.2	46.4	5.4	10.5	31.5
HARMONY (2018)(Hernandez et al.)	Albiglutide	Placebo	9463	64.1	30.5	1.6	14.1	25
EXSCEL (2017)(Holman et al.)	ExenatideLAR	Placebo	14752	62	38	3.2	12	22.4
SUSTAIN-6 (2016)(Marso, Bain, et al.)	Semaglutide	Placebo	3297	64.6	39.3	2.1	13.9	11.6
LEADER (2016)(Marso, Daniels, et al.)	Liraglutide	Placebo	9340	64.3	35.7	3.8	12.8	16.1
ELIXA (2015)(Pfeffer et al.)	Lixisenatide	Placebo	6068	60.3	30.7	2.1	9.3	5.4

Figure 1. PRISMA Flowchart Summarizing the Search Process in This Study



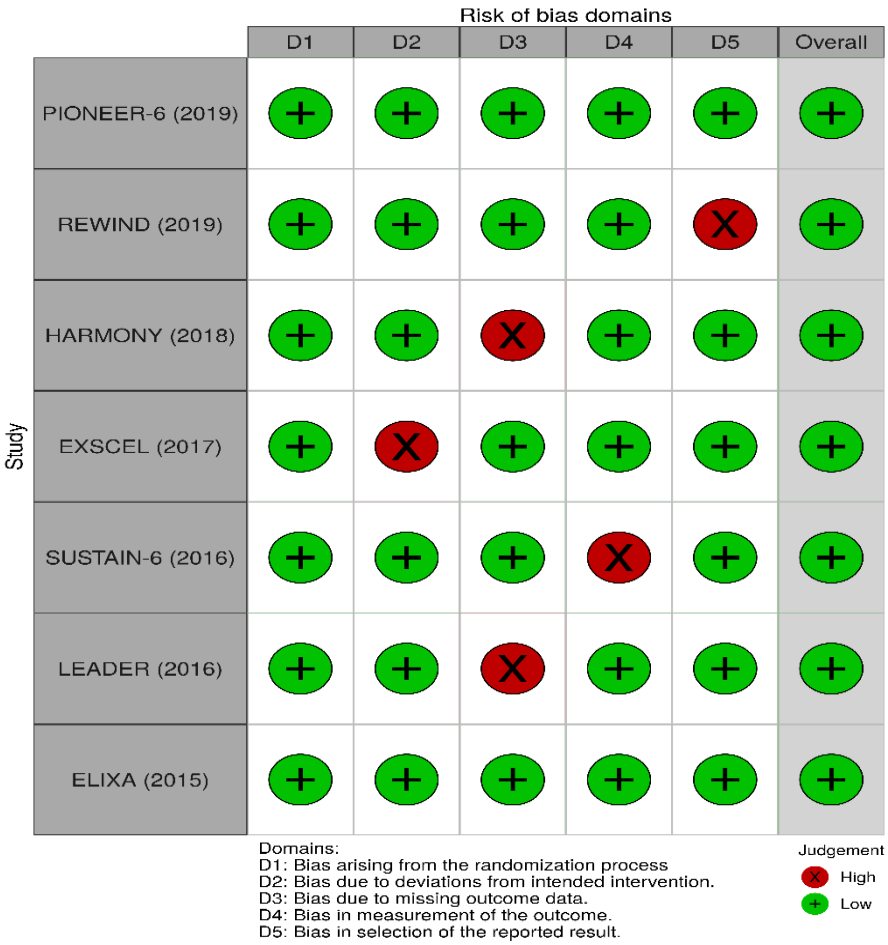


Figure 2. Risk of Bias Graph Indicating the Quality in Each Domain

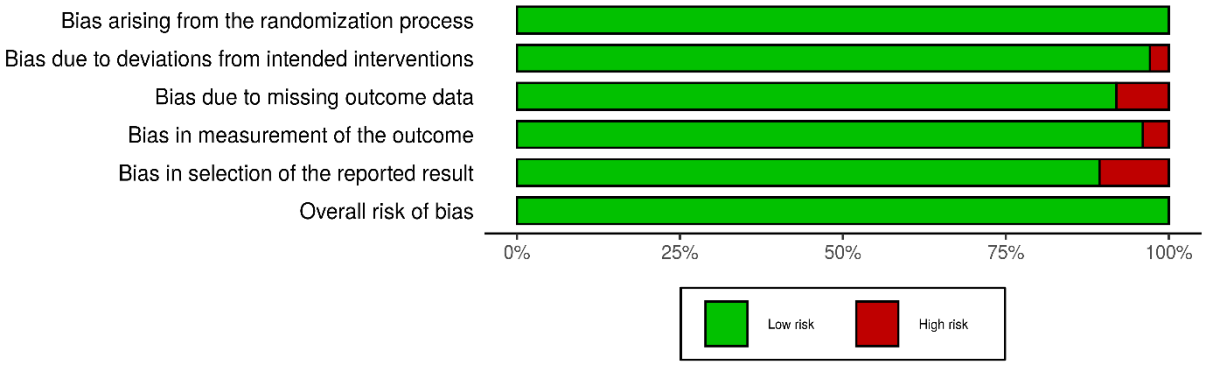


Figure 3. Risk of Bias Summary Summarizing the Overall Risk of Bias in Each Domain.

Efficacy of Different Types of Glucagon-like Peptide-1 Analog

Only six types of Glucagon-like peptide -1 analogs were tested in the clinical trials namely Dulaglutide, Albiglutide, Exenatide LAR, Semaglutide, Liraglutide, and Lixisenatide [14-17, 19-21].

Dulaglutide did not show promising results as there was no significant difference regarding stroke. Meanwhile, subgroup analysis showed that it only decreased the incidence of non-fatal stroke. Notwithstanding, it did not decrease the incidence of fatal stroke [17].

Albiglutide did not affect the incidence of cerebrovascular disease in diabetic patients. Subgroup analysis did not reveal any significant difference in the incidence between fatal or nonfatal stroke between the placebo and Albiglutide groups [19]. Lixisenatide did not affect the incidence of stroke in diabetic patients. Lixisenatide was assessed if it would decrease the incidence of non-fatal stroke or not; it did not decrease the incidence of non-fatal stroke [21]. Meanwhile, Liraglutide did not affect the

stroke incidence in diabetics for both fatal and non-fatal stroke. A transient ischemic attack was investigated in this study and was not decreased in the Liraglutide group [20]. Surprisingly, a single weekly dose of Exenatide decreased the risk of both fatal and non-fatal stroke in diabetics [14]. Two studies assessed the efficacy of Semaglutide; one used oral Semaglutide and the other used injections. Both oral and injectable Semaglutide decreased the risk of non-fatal stroke [15, 16].

Other Outcomes that Are Affected by Glucagon-like Peptide-1 Analog

Dulaglutide showed significant improvement of the renal pathologies like macroalbuminuria, and chronic renal failure [17]. Albiglutide only decreased the incidence of fatal and non-fatal myocardial infarction. However, it did not decrease the mortality of any cardiac causes [19]. Lixisenatide significantly decreased the HbA1C which resulted in more incidence of hypoglycemia in the treated group; however, it was non-significant. Lixisenatide did not affect the incidence of angina, myocardial infarction. Lixisenatide also significantly decreased body weight and systolic blood pressure [21]. Like Dulaglutide, Liraglutide enhanced nephropathy symptoms and diseases like microalbuminuria [20]. Exenatide decreased the risk of fatal and non-fatal myocardial infarction [14].

Exenatide significantly lowered glycated hemoglobin levels, systolic blood pressure, low-density lipoprotein cholesterol, and triglycerides. However, it significantly increased diastolic blood pressure and heart rate [14].

The injectable Semaglutide significantly decreased retinopathy complications and nephropathy pathologies. It also decreased the glycated hemoglobin and the need of anti-hyperglycemic drugs in the placebo group. It also significantly decreased the body weight in diabetic patients. It also decreased systolic blood pressure but increased heart rate [16]. Similarly, Oral Semaglutide decreased systolic blood pressure. Moreover, it decreased low-density lipoprotein cholesterol and triglycerides increased the risk of nonfatal myocardial infarction [15].

Factors Affecting the Efficacy of the Glucagon-like Peptide-1 Analog

The effect of Dulaglutide did not differ when the analysis adjusted for different confounders. They found that a history of stroke or myocardial infarction did not affect the results. In addition, different HbA1C levels, ethnicity, or body mass index did not affect the results [17]. For Albiglutide, smoking was the only factor that affected the efficacy of the Albiglutide on the outcome as it had better results in former smokers and non-smokers. The duration of diabetes, HbA1C, history of cardiac, renal, or arterial diseases did not affect the efficacy of the Albiglutide [19].

For Lixisenatide, adjusted analysis for glycated hemoglobin did not affect the results or the efficacy [21].

Liraglutide efficacy was affected by renal function, age, and cardiovascular events. The Liraglutide had a better outcome when it was administered in patients with a good glomerular filtration rate [20]. It also performed better in younger ages and patients with cardiovascular risk factors versus older age with established cardiovascular events. Exenatide efficacy was affected by age; it had better results in older ages [14].

Unlike previous drugs, the efficacy of injectable Semaglutide was not increased nor decreased by any patients' characteristics nor the history of other diseases [16]. The study also compared the dose of injectable Semaglutide; they used 0.5 mg and 1 mg single dose weekly. There was no significant difference between the two doses; however, the higher dose showed better results [16].

Mortality

For fatal stroke, Dulaglutide did not show any significant difference from placebo despite lower numbers. It also did not decrease the non-cardiovascular death event. Overall, it did not affect the survival rate in diabetic patients [17]. Albiglutide did not significantly influence the overall mortality rate in diabetic patients. Furthermore, it did not affect the mortality from cardiac or non-cardiac causes [19]. Lixisenatidehas not decreased mortality from heart failure or any other causes [21]. Liraglutide decreased the death rate either from cardiovascular events or non-cardiovascular diseases [20].

Exenatide decreased the risk of mortality from cardiovascular events in diabetics. Cardiovascular events included sudden cardiac death, acute myocardial infarction, heart failure or cardiogenic shock, cardiovascular procedure, stroke, and other cardiovascular causes. It also decreased the risk of death from non-cardiac causes such as pulmonary, renal, gastrointestinal, infection, non-infectious, malignancy, accidental/trauma, hemorrhage, not intracranial, suicide, non-cardiovascular system organ failure, non-cardiovascular surgery, pancreatitis, and other non-cardiovascular [14].

The injectable Semaglutide did not decrease the mortality either from cardiovascular events or any other causes. However, oral Semaglutide decreased the risk of death from cardiovascular causes or any cause [15, 16].

Incidence of Hospitalization

Dulaglutide did not significantly improve the incidence of hospital admission either for heart failure, angina, or any urgent cardiovascular events including stroke [17]. Albiglutide was not assessed for the hospitalization risk [18]. Lixisenatide did not decrease the hospitalization due to heart failure compared to placebo. However, it was not

assessed for the rate of hospitalization due to other causes [21].

Liraglutide non-significantly decreased the incidence of hospitalization for heart failure or unstable angina [20]. Exenatide decreased the risk of hospitalization for heart failure, however, it increased hospitalization for the acute coronary syndrome [14].

Injectable Semaglutide did not significantly decrease hospitalization for cardiovascular emergencies or any other emergencies. Oral Semaglutide had the same results as injectable Semaglutide because it increased the risk of unstable angina that resulted in increased hospitalization; however, it decreased the incidence of hospitalization related to heart failure [15, 16].

Side Effects

Dulaglutide had many side effects; however, the only significant adverse reaction was immune reactions. Reported side effects were more prominent in the treatment group. It is reported that it caused more acute pancreatitis, thyroid cancer, pancreatic cancer, severe hypoglycemia, and supraventricular tachycardia [17]. Albiglutide was found to increase the risk of pancreatitis, injection site reactions, hematological neoplasia, pancreatic cancer, and hepatobiliary disorder compared to placebo [19].

Lixisenatide was significantly associated with gastrointestinal side effects. Other reported non-significant side effects included cardiac events, eye events, infection side effects, and vascular side effects [21].

Liraglutide significantly caused serious adverse effects and severe adverse effects. Both adverse effects were defined based on the *Medical Dictionary for Regulatory Activities*. Liraglutide significantly increased the incidence of nausea, vomiting, diarrhea, abdominal pain, discomfort, and decreased appetite. Besides, Liraglutide injections had injection site reactions. It also increased the incidence of acute gall stone disease. Frankly, it was associated with severe hypoglycemia but still less than the placebo [20].

Lipase and amylase levels were significantly higher in the Semaglutide group [16]. Similarly, cardiac disorders, acute pancreatitis, gall bladder disorders, and acute renal failure were also highly significant. In addition, there were more frequent attacks of hypoglycemia in the treatment group. There was no difference between different doses of injectable Semaglutide [16]. Oral Semaglutide had the same side effects; however, it was infrequent. Meanwhile, most patients stopped Semaglutide treatment because of gastrointestinal side effects [15].

CONCLUSION

The results of this review indicated that Glucagon-like peptide-1 analog significantly decreased the risk of non-fatal stroke and its associated risk factors. However, it did not influence the mortality rate or the risk for hospitalization.

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Conflict of Interest

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